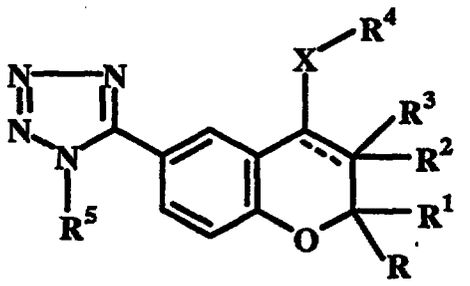
This Sheet Has Been Replaced

BENZOPYRANS

The present invention relates to benzopyrans. More particularly it relates to 6-(tetrazol-5-yl)benzo[b]pyran derivatives and to compositions containing, uses of, processes for the preparation of and intermediates used in the preparation of, such derivatives.

The present derivatives display smooth muscle relaxant activity by a mechanism involving potassium channel opening. They are therefore useful in the curative or prophylactic treatment of diseases associated with the altered tone and/or motility of smooth muscle which can, for example, occur in the lung, bladder, gut, uterus or cardiovascular system. Such diseases include chronic obstructive airways disease, asthma, urinary incontinence, irritable bowel syndrome, diverticular disease, oesophageal achalasia and hypertension. In addition, the present derivatives may be useful in the treatment of peripheral vascular disease, congestive heart failure, pulmonary hypertension, myocardial and cerebral ischaemia, angina, male pattern baldness, cardiac arrhythmia, skeletal muscle fatigue/paralysis (myotonic muscular dystrophy), glaucoma, epilepsy, tinnitus, vertigo and dysmenorrhoea.

The present invention provides compounds of the formula:-



(I)

and the pharmaceutically acceptable salts thereof,
wherein the dashed line represents an optional covalent bond;

This Sheet Has Been Replaced

X is O, NH, S or a direct link;

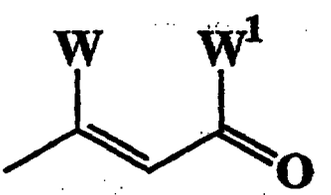
R and R^1 are either each independently selected from H, fluoro(C_1-C_4)alkyl and C_1-C_4 alkyl or taken together represent C_2-C_6 alkylene;

R^2 is H or C_1-C_4 alkyl;

R^3 is hydroxy when the dashed line does not represent a covalent bond and R^3 is absent when the dashed line represents a covalent bond;

R^4 is

(a) , when X is O, a group of the formula:-

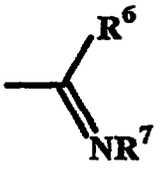


wherein W and W^1 taken together represent C_1-C_4 alkylene, said alkylene being optionally benzo-fused when W and W^1 taken together represent C_2-C_4 alkylene, and optionally substituted, including in the benzo-fused portion, by C_1-C_6 alkyl, hydroxy, -OR^8, halo, -$N(R^8)_2$, -SR^8 or halo(C_1-C_4)alkyl,

(b) , when X is O, NH or S, hydroxyphenyl optionally substituted by C_1-C_6 alkyl, -OR^8, halo, -$N(R^8)_2$, -SR^8 or halo(C_1-C_4)alkyl,

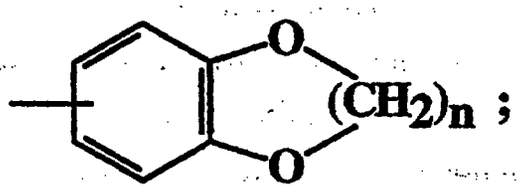
(c) a 4- to 7-membered heterocyclic ring containing either from 1 to 3 N hetero-atoms or one N hetero-atom and one O or one S hetero-atom, said ring being optionally benzo- or C_3-C_7 cycloalkyl-fused and optionally substituted, including in the benzo- or C_3-C_7 cycloalkyl-fused portion, by C_1-C_6 alkyl, hydroxy, hydroxy(C_1-C_4)alkyl, -OR^8, $R^8O(C_1$-$C_4)$alkyl, halo, halo(C_1-C_4)alkyl, -$S(O)_mR^8$, $R^8S(O)_m(C_1$-$C_4)$alkyl, oxo, N-cyanoimino, amino, amino(C_1-C_4)alkyl, -NHR^8, $R^8NH(C_1$-$C_4)$alkyl, -$N(R^8)_2$, $(R^8)_2N(C_1$-$C_4)$alkyl, cyano, cyano(C_1-C_4)alkyl, -CO_2R^8, $R^8O_2C(C_1$-$C_4)$alkyl, -$CONH_2$, $H_2NCO(C_1$-$C_4)$alkyl, -$CONHR^8$, $R^8NHCO(C_1$-$C_4)$alkyl, -$CON(R^8)_2$ or $(R^8)_2NCO(C_1$-$C_4)$alkyl, or, as appropriate, a ring N- or S-oxide derivative of said heterocyclic ring, with the proviso that said heterocyclic ring is linked by a ring carbon atom when X is O, NH or S, or

(d) , when X is NH, a group of the formula:-



wherein R^6 is -OR^8, -NHR^8, -SR^8, -NH(aryl) or -NH(pyridinyl) and R^7 is cyano, nitro or C_2-C_6 alkanoyl;

R^5 is aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said C_1-C_{12} alkyl, C_2-C_{12} alkenyl and C_2-C_{12} alkynyl being optionally substituted by C_4-C_7 cycloalkyl, hydroxy, -OR^8, C_2-C_6 alkanoyloxy, halo, cyano, nitro, amino, -NHR^8,-$N(R^8)_2$, -$S(O)_mR^8$, -$NHSO_2R^8$, -$NHCOR^8$, -COR^8, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -OCO_2R^8, -$CONH(C_1$-$C_6)alkylCO_2R^8$, -$CONR^8(C_1$-$C_6)alkylCO_2R^8$, -CO_2R^8, aryl, aryloxy, arylcarbonyl, arylcarbonyloxy, aryl(C_1-C_6)alkoxy, aryl(C_1-C_6)alkoxycarbonyl, phthalimido, or a group of the formula:-

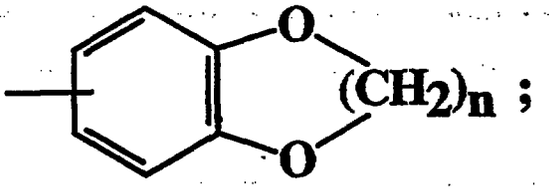


;

R^8 is C_1-C_6 alkyl;

R^9 is indanyl, aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said C_1-C_{12} alkyl, C_2-C_{12} alkenyl and C_2-C_{12} alkynyl being optionally substituted by C_4-C_7 cycloalkyl, hydroxy, -OR^8, C_2-C_6 alkanoyloxy, halo, cyano, nitro, amino, -NHR^8, -$N(R^8)_2$, -$S(O)_mR^8$, -$NHSO_2R^8$, -$NHCOR^8$, -COR^8, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -OCO_2R^8, -$CONH(C_1$-$C_6)alkylCO_2R^8$, -$CONR^8(C_1$-$C_6)alkylCO_2R^8$, -$CO_2(C_1$-C_{12} alkyl), aryl, aryloxy, arylcarbonyl, arylcarbonyloxy, aryl-(C_1-C_6)alkoxy, aryl(C_1-C_6)alkoxycarbonyl, phthalimido, or a group of the formula:-

This Sheet Has Been Replaced



"aryl", used in the definitions of R^5, R^6 and R^9 and in this definition, means phenyl optionally substituted by C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, hydroxy(C_1-C_6)alkyl, -OR^8, $R^8O(C_1$-$C_6)$alkyl, R^8O-(C_1-C_6)alkoxy, $R^8O(C_1$-$C_6)$alkoxy(C_1-C_6)alkyl, halo, halo(C_1-C_6)alkyl, cyano, cyano(C_1-C_6)alkyl, nitro, nitro(C_1-C_6)alkyl, amino, amino(C_1-C_6)alkyl, -NHR^8, $R^8NH(C_1$-$C_6)$alkyl, -$N(R^8)_2$, $(R^8)_2N(C_1$-$C_6)$alkyl, -$S(O)_mR^8$, $R^8S(O)_m(C_1$-$C_6)$ alkyl, -$NHCOR^8$, $R^8CONH(C_1$-$C_6)$alkyl, -COR^8, $R^8CO(C_1$-$C_6)$alkyl, -$CONH_2$, $H_2NCO(C_1$-$C_6)$alkyl, -$CONHR^8$, $R^8NHCO(C_1$-$C_6)$alkyl, -$CON(R^8)_2$, $(R^8)_2NCO$-(C_1-C_6)alkyl, -$CONH(C_1$-$C_6)$alkylCO_2R^8, $R^8O_2C(C_1$-$C_6)$-alkyl$NHCO(C_1$-$C_6)$alkyl, -$CONR^8(C_1$-$C_6)$alkylCO_2R^8, $R^8O_2C(C_1$-$C_6)$alkyl$NR^8CO(C_1$-$C_6)$alkyl, -CO_2R^{9A}, $R^{9A}O_2C(C_1$-$C_6)$alkyl, aryl, aryl(C_1-C_6)alkyl, aryl(C_1-C_6)-alkoxy or aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl;

R^{9A} is indanyl, phenyl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said C_1-C_{12} alkyl, C_2-C_{12} alkenyl and C_2-C_{12} alkynyl being optionally substituted as previously defined for those definitions for R^9 and said phenyl being optionally substituted by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, hydroxy, -OR^8, halo, halo(C_1-C_6)-alkyl, nitro and cyano;

m is 0, 1 or 2; and

n is 1, 2 or 3.

In the above definitions, the term "halo" means fluoro, chloro, bromo or iodo and alkyl, alkenyl and alkoxy groups containing three or more carbon atoms together with alkynyl and alkanoyl groups containing four or more carbon atoms can be straight- or branched-chain.

Preferably the dashed line does not represent a covalent bond.

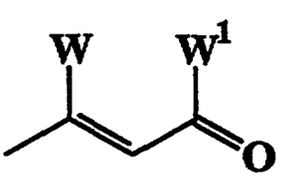
Preferably X is O, NH or a direct link.
Most preferably X is O.

Preferably R and R^1 are each independently selected from H and C_1-C_4 alkyl.
More preferably R and R^1 are both C_1-C_4 alkyl.
Most preferably R and R^1 are both methyl.

Preferably R^2 is H or methyl.
Most preferably R^2 is methyl.

Preferably R^2 is methyl, R^3 is hydroxy and the dashed line does not represent a covalent bond.

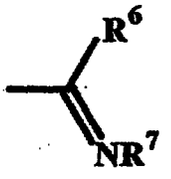
Preferably R^4 is a group of the formula:-



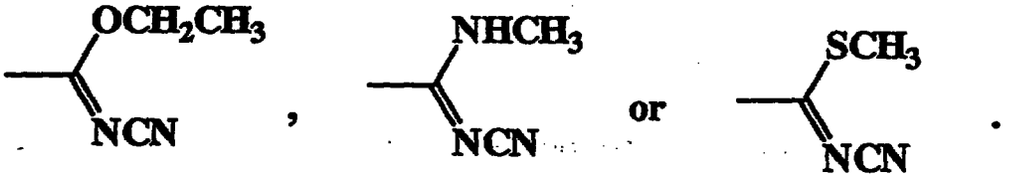
wherein W and W^1 taken together represent C_1-C_4 alkylene, a 6-membered heterocyclic ring containing 1 or 2 nitrogen hetero-atoms and optionally substituted by C_1-C_6 alkyl, hydroxy,

This Sheet Has Been Replaced

halo, C_1-C_4 alkylthio or oxo, or is a group of the formula:-

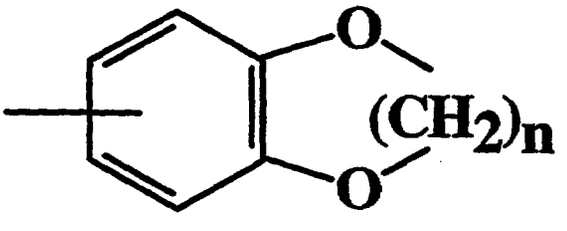


wherein R^6 is -OR^8, -NHR^8 or -SR^8 and R^7 is cyano.
More preferably R^4 is 1-oxocyclopent-2-en-3-yl, 2-oxo-1,2-dihydropyridin-1-yl, 2-oxo-1H-1,2-dihydropyridin-4-yl, 2-oxopiperidin-1-yl, 3-hydroxypyridazin-6-yl, 2-methyl-3-oxopyridazin-6-yl, 4-chloropyrimidin-2-yl, 2-chloropyrimidin-4-yl, 2-methylthiopyrimidin-4-yl or is a group of the formula:-

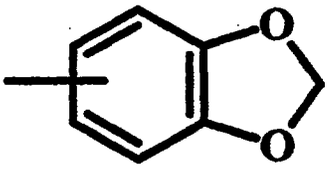


Most preferably R^4 is 3-hydroxypyridazin-6-yl.

Preferably R^5 is aryl or C_1-C_{12} alkyl, said C_1-C_{12} alkyl being optionally substituted by hydroxy, -OR^8, C_2-C_8 alkanoyloxy, amino, -$CONHR^8$, -$CONH(C_1$-$C_6)alkylCO_2R^8$, -CO_2R^9, aryl, aryloxy, arylcarbonyloxy, aryl(C_1-C_6)alkoxy, phthalimido, or a group of the formula:-



More preferably R^5 is phenyl or C_1-C_4 alkyl, said C_1-C_4 alkyl being optionally substituted by hydroxy, methoxy, acetoxy, amino, methylaminocarbonyl, N-(ethoxycarbonylmethyl)carbamoyl, $-CO_2R^9$, phenyl, methylphenyl, methoxyphenyl, hydroxyphenyl, halophenyl, benzyloxyphenyl, phenoxy, benzoyloxy, benzyloxy, phthalimido, or a group of the formula:-



Yet more preferably R^5 is phenyl, methyl, ethyl, n-propyl, 2-hydroxyethyl, 2-methoxyethyl, 2-acetoxyethyl, 2-aminoethyl, 2-(methylaminocarbonyl)ethyl, N-(ethoxycarbonylmethyl)-carbamoylmethyl, ethoxycarbonylmethyl, 3-methoxycarbonyl-prop-1-yl, 3-ethoxycarbonylprop-1-yl, 4-ethoxycarbonylbut-1-yl, 3-vinyloxycarbonylprop-1-yl, 3-(2,2,2-trifluoroethoxycarbonyl)prop-1-yl, 3-(ethoxycarbonyloxymethoxycarbonyl)prop-1-yl, 3-(pivaloyl-oxymethoxycarbonyl)prop-1-yl, 3-phenoxycarbonylprop-1-yl, 3-benzyloxycarbonylprop-1-yl, 3-(5-indanyloxycarbonyl)-prop-1-yl, benzyl, 2-phenylethyl, 3-phenylprop-1-yl, 4-phenylbut-1-yl, 2-(2-methylphenyl)ethyl, 2-(3-methylphenyl)ethyl, 2-(4-methylphenyl)-ethyl, 2-(2-methoxyphenyl)ethyl, 2-(3-methoxyphenyl)-ethyl, 2-(4-methoxyphenyl)ethyl, 2-(4-hydroxyphenyl)ethyl, 2-(4-fluoro-phenyl)ethyl, 2-(4-benzyloxyphenyl)ethyl, 2-phenoxyethyl, 2-benzoyloxyethyl, 2-benzyloxyethyl, 2-phthalimidoethyl or 2-(1,3-benzodioxolan-5-yl)ethyl.

Most preferably R^5 is methyl, ethyl, n-propyl, 3-ethoxycarbonylprop-1-yl, 4-ethoxycarbonylbut-1-yl or 2-phenyl-ethyl.

Preferably R^8 is methyl or ethyl.

Preferably R^9 is indanyl, aryl, C_1-C_{12} alkyl or C_2-C_{12} alkenyl, said C_1-C_{12} alkyl being optionally substituted by halo, C_2-C_6 alkanoyloxy, -OCO_2R^8 or aryl.
More preferably R^9 is indanyl, phenyl, C_1-C_4 alkyl or vinyl, said C_1-C_4 alkyl being optionally substituted by fluoro, pivaloyloxy, ethoxycarbonyloxy or phenyl, as, preferably, is R^{9A}.
Most preferably R^9 is 5-indanyl, phenyl, methyl, ethyl, vinyl, 2,2,2-trifluoroethyl, pivaloyloxymethyl, ethoxycarbonyloxymethyl or benzyl, as, most preferably, is R^{9A}.

Preferably "aryl" means phenyl optionally substituted by C_1-C_6 alkyl, hydroxy, -OR^8, halo or aryl(C_1-C_6)alkoxy.
More preferably "aryl" means phenyl optionally substituted by methyl, hydroxy, methoxy, fluoro or benzyloxy.
Most preferably "aryl" means phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-fluorophenyl or 4-benzyloxyphenyl.

Preferably m is 0.

Preferably n is 1.

The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide,

This Sheet Has Been Replaced

hydroiodide, sulphate, bisulphate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, benzoate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts.

Suitable base salts are formed from bases which form non-toxic salts and examples are the aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and diethanolamine salts.

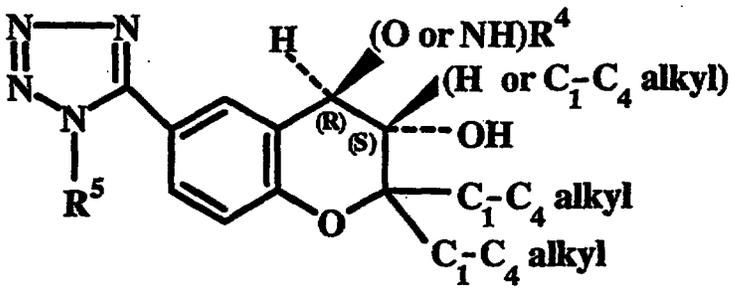
For a review on suitable salts see Berge et al, J. Pharm. Sci., 66, 1-19 (1977).

A compound of the formula (I) may contain one or more asymmetric carbon atoms and/or one or more alkenyl groups and may therefore exist in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of the formula (I) and mixtures thereof, together, where appropriate, with all the tautomeric forms of the compounds of the formula (I).

Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base.

A preferred group of compounds of the formula (I) is where the dashed line does not represent a covalent bond, X is O or NH, R and R^1 are both C_1-C_4 alkyl, R^2 is H or C_1-C_4 alkyl, R^3 is hydroxy and R^4 and R^5 are as previously defined for a compound of the formula (I), and which has the (3S,4R)- stereochemistry in the benzopyran ring, that is a compound of the formula:-

This Sheet Has Been Replaced

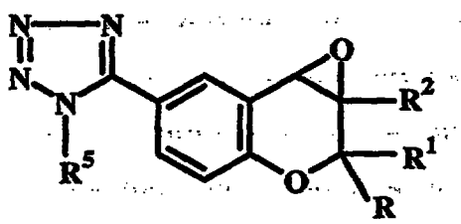


(IA)

The compounds of the formula (I) provided by the invention can be prepared by the following methods:-

This Sheet Has Been Replaced

1) The compounds of the formula (I) wherein the dashed line does not represent a covalent bond; X is O, NH or S, R^4 has the definition (a), (b) or (c) as previously defined for R^4 for a compound of the formula (I) and R, R^1, R^2, R^3 and R^5 are as previously defined for a compound of the formula (I), can be prepared by reacting a compound of the formula:-



(II)

wherein R, R^1, R^2 and R^5 are as defined for this method, with a compound of the formula:-

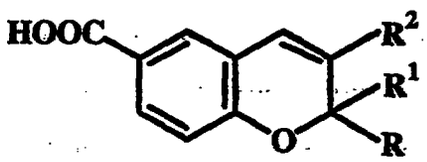
R^4-XH

or, where appropriate, a tautomer thereof,
or, where X is O or S, with a base salt thereof, wherein R^4 and X are as defined for this method. Preferred base salts of the compounds of the formula R^4-XH include the alkali metal salts, e.g. the sodium and potassium salts. If a base salt is used, this may be generated in situ from the corresponding compound of the formula R^4-XH using a suitable base, e.g. sodium hydride.

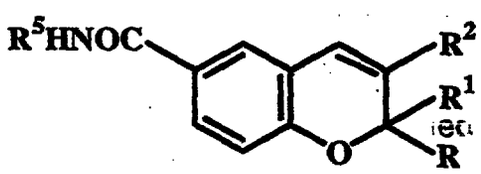
The reaction is typically carried out in a suitable organic solvent, e.g. ethanol or tetrahydrofuran, at from room temperature to, and preferably at, the reflux temperature of the solvent. If a base salt of a compound of the formula R^4-XH is not used, a suitable base catalyst, e.g. pyridine or triethylamine, may also be present.

If a base salt of a compound of the formula R^4-XH wherein X is O and R^4 is as previously defined in definition (a) for R^4 for a compound of the formula (I) is used, the reaction is preferably carried out in the presence of a suitable Lewis acid, e.g. boron trifluoride etherate.

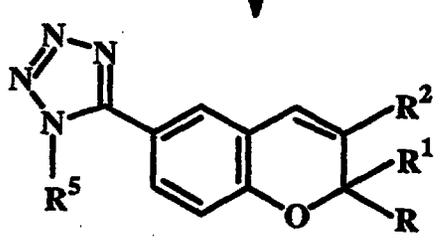
The intermediates of the formula (II) can be prepared by the following route:-



(III)



(IV)



(V)

A compound of the formula (II)

wherein R, R^1, R^2 and R^5 are as defined for this method.

In a typical procedure a carboxylic acid of the formula (III) is converted to an amide of the formula (IV) using a conventional procedure, e.g. by reacting the carboxylic acid with 1,1'-carbonyldiimidazole to first form an imidazolide derivative, followed by reaction of this derivative with an amine of the formula R^5NH_2, wherein R^5 is as defined for this method. Alternatively the carboxylic acid can be converted to the corresponding acid chloride, e.g. using oxalyl chloride in the presence of N,N-dimethylformamide, which can then be reacted with an amine of the formula R^5NH_2 to provide the required amide.

The amide of the formula (IV) is reacted first with phosphorus pentachloride and then with trimethylsilyl azide to form a tetrazole of the formula (V) that can be converted to an epoxide of the formula (II) using sodium hypochlorite in the presence of [(S,S)-1,2-bis(3,5-di-tert-butylsalicylideamino)]-cyclohexane manganese (III) chloride (see J. Amer. Chem. Soc., 113, 7063 (1991)) or by using OXONE™ (potassium peroxymonosulphate).

The intermediates of the formulae (III) and R^4-XH, and the base salts thereof, are either known or may be prepared by conventional techniques.

Alternatively, where R^2 is H, a compound of the formula (V) can be converted to an epoxide of the formula (II) by a two-stage procedure, the first stage involving reacting a compound of the formula (V) with N-bromosuccinimide in aqueous dimethyl sulfoxide to form a 3-bromo-4-hydroxy-2H-benzo[b]pyran derivative and the second stage involving further reacting this bromohydrin derivative with a strong base, e.g. sodium hydride, to form the epoxide.

This Sheet Has Been Replaced

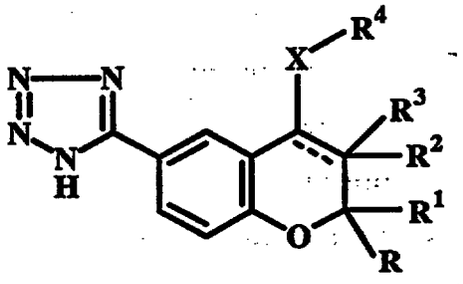


2) The compounds of the formula (I) wherein the dashed line does not represent a covalent bond, X is a direct link, R^4 is an N-linked heterocyclic ring as previously defined in definition (c) for R^4 for a compound of the formula (I), and R, R^1, R^2, R^3 and R^5 are as previously defined for a compound of the formula (I), can be prepared by reacting a compound of the formula (II), wherein R, R^1, R^2 and R^5 are as previously defined for this method, with a 4- to 7-membered ring heterocyclic compound containing at least one N hetero-atom bearing a hydrogen substituent and which otherwise is as defined in this method for R^4, or with a base salt thereof.

In a typical procedure, when a base salt of the heterocyclic compound is not used, the reaction is carried out in the presence of a suitable basic catalyst, e.g. benzyltrimethylammonium hydroxide (TRITON™B) or pyridine, and in a suitable solvent, e.g. dioxan or ethanol, at from room temperature to, and preferably at, the reflux temperature thereof.

When a base salt of the heterocyclic compound is used the preferred base salts include the alkali metal salts, e.g. the sodium and potassium salts. The base salt may be generated in situ by first reacting the heterocyclic compound with a suitable strong base, e.g. sodium hydride, and then allowing the base salt formed to react with a compound of the formula (II).

3) All the compounds of the formula (I) can be prepared by reaction of a compound of the formula:-



(VI),

or a base salt thereof, wherein the dashed line, X, R, R^1, R^2, R^3 and R^4 are as previously defined for a compound of the formula (I), with a compound of the formula R^5Z wherein R^5 is as previously defined for a compound of the formula (I) and Z is a suitable leaving group, e.g. halo (preferably bromo or iodo), methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy.

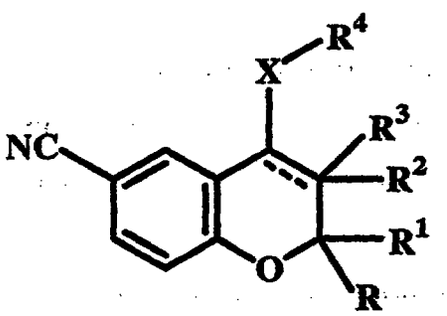
Preferred base salts of the compounds of the formula (VI) include the alkali metal salts, e.g. the sodium salt. The base salt may be generated in situ by reaction of a 1H-tetrazole of the formula (VI) with a suitable base, e.g. sodium hydroxide or sodium t-butoxide.

Where a base salt of a compound of the formula (VI) is not used, the alkylation may be carried out in the presence of bis(tributyl)tin oxide and optionally in a suitable solvent, e.g. acetonitrile or N,N-dimethylformamide, at room temperature.

Alternatively, where a base salt of a compound of the formula (VI) is not used, the alkylation may be carried out in the presence of a suitable acid acceptor, e.g. potassium carbonate, and in a suitable solvent, e.g. acetonitrile.

The compounds of the formula (I) where R^5 is aryl (e.g. phenyl) can be prepared by reacting a base salt, e.g. a sodium salt, of a compound of the formula (VI) with a diaryliodonium halide, e.g. diphenyliodonium chloride where R^5 is phenyl is required. The reaction is typically carried out in a suitable solvent, e.g. t-butanol, and at the reflux temperature thereof.

The intermediate tetrazoles of the formula (VI) can be prepared by reacting a compound of the formula:-



(VII)

wherein the dashed line, X, R, R^1, R^2, R^3 and R^4 are as previously defined for this method, with sodium azide and triethylamine hydrochloride. The reaction is typically carried out in a suitable solvent, e.g. 1-methyl-2-pyrrolidinone, and at an elevated temperature, e.g. ca. 150°C.

This Sheet Has Been Replaced

4) The compounds of the formula (I) wherein the dashed line represents a covalent bond and X, R, R^1, R^2, R^4 and R^5 are as previously defined for a compound of the formula (I), can be prepared by dehydration of a compound of the formula (I) wherein the dashed line does not represent a covalent bond, R^3 is hydroxy, and X, R, R^1, R^2, R^4 and R^5 are as defined for this method.

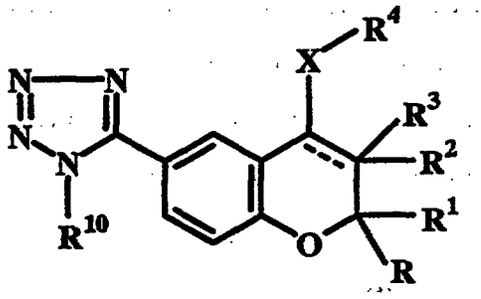
In a typical procedure the dehydration is carried out using a suitable dehydrating agent, e.g. polymer-supported sodium hydroxide, and using a suitable solvent, e.g. anhydrous dioxan, at from room temperature to, and preferably at, the reflux temperature thereof.

5) The compounds of the formula (I) wherein the dashed line does not represent a covalent bond, X is a direct link, R^4 is 2-oxopiperidin-1-yl optionally substituted as previously defined in definition (c) for R^4 for a compound of the formula (I), and R, R^1, R^2, R^3 and R^5 are as previously defined for a compound of the formula (I), can be prepared by reduction of a compound of the formula (I) wherein R^4 is 2-oxopyridin-1-yl, optionally substituted as defined for R^4 for this method and the dashed line, X, R, R^1, R^2, R^3 and R^5 are as defined for this method.

The reduction is typically carried out by catalytic hydrogenation of a compound of the formula (I), e.g. using palladium-on-carbon as a catalyst, in a suitable solvent, e.g. ethanol.

This Sheet Has Been Replaced

6) The compounds of the formula (I) wherein R^5 is aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said alkyl, alkenyl and alkynyl being substituted by $-CO_2R^9$ or by aryl substituted by $-CO_2R^9$ or $R^9O_2C(C_1$-$C_6)$alkyl, and said aryl being substituted by $-CO_2R^9$ or $R^9O_2C(C_1$-$C_6)$alkyl, and the dashed line, X, R, R^1, R^2, R^3, R^4, R^9 and "aryl" are as previously defined for a compound of the formula (I), can be prepared by reaction of a compound of the formula:-



(VIII)

wherein the dashed line, X, R, R^1, R^2, R^3 and R^4 are as defined for this method and R^{10} is aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said alkyl, alkenyl and alkynyl being substituted by $-CO_2H$ or by aryl substituted by $-CO_2H$ or $HO_2C(C_1$-$C_6)$alkyl, and said aryl being substituted by $-CO_2H$ or $HO_2C(C_1$-$C_6)$alkyl, or an activated derivative of such a carboxylic acid, with a compound of the formula R^9OH wherein R^9 is as defined for this method.

The term "activated derivative" includes the corresponding acid halide, e.g. acid chloride, imidazolide and activated ester, e.g. benzotriazol-1-yl ester, derivatives of a carboxylic acid of the formula (VIII).

This Sheet Has Been Replaced

The reaction is typically carried out by reacting a carboxylic acid of the formula (VIII) with oxalyl chloride to form the corresponding acid chloride that may then be reacted with an alcohol of the formula R^9OH, optionally in the presence of a suitable acid acceptor, e.g. pyridine, to provide the required ester.

The reaction may also be carried out using conventional esterification conditions, e.g. by reacting a carboxylic acid of the formula (VIII) with an alcohol of the formula R^9OH in the presence of an acid catalyst.

The reaction can further be carried out by reacting a carboxylic acid of the formula (VIII) with an alcohol of the formula R^9OH in the presence of suitable condensing agent, e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or dicyclohexylcarbodiimide. A variation on this reaction is to first react a carboxylic acid of the formula (VIII) with 1-hydroxybenzotriazole in the presence of a suitable condensing agent to form an activated ester, that can then be reacted with an alcohol of the formula R^9OH to provide the required ester.

The reaction can yet further be carried out under the conditions of the Mitsunobu reaction by reacting a carboxylic acid of the formula (VIII) with an alcohol of the formula R^9OH in the presence of a suitable phosphine, e.g. triphenylphosphine, and a di(C_1-C_4)alkyl azodicarboxylate e.g. diethyl azodicarboxylate.

The carboxylic acid intermediates of the formula (VIII) can be prepared by hydrolysis of a corresponding ester of the formula (I), e.g. a methyl or ethyl ester, using conventional conditions, e.g. using aqueous acid or base.

This Sheet Has Been Replaced

7) The compounds of the formula (I) wherein the dashed line, X, R, R^1, R^2, R^3, R^4 and R^5 are as defined for method (6) and R^9 is vinyl, can be prepared by reaction of a compound of the formula (VIII) wherein the dashed line, X, R, R^1, R^2, R^3 and R^4 are as defined for this method and R^{10} is aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said alkyl, alkenyl and alkynyl being substituted by $-CO_2H$ or by aryl substituted by -COOH or $HO_2C(C_1$-$C_6)$alkyl, and said aryl being substituted by -COOH or $HO_2C(C_1$-$C_6)$alkyl, with a vinyl C_1-C_4 alkanoate, e.g. vinyl acetate, and in the presence of a suitable catalyst, e.g. 1,10-phenanthrolinyl-palladium (II) acetate.

In a typical procedure the reaction is carried out in a suitable solvent, e.g. dichloromethane or tetrahydrofuran, and at an elevated temperature, e.g. at the reflux temperature of the solvent.

8) The compounds of the formula (I) wherein the dashed line, X, R, R^1, R^2, R^3, R^4 and R^5 are as defined for method (6) and R^9 is C_1-C_{12} alkyl optionally substituted as previously defined for the definition of R^9 as C_1-C_{12} alkyl for a compound of the formula (I), can be prepared by reaction of a compound of the formula (VIII), or a base salt thereof, wherein the dashed line, X, R, R^1, R^2, R^3, R^4 and R^{10} are as defined for a compound of the formula (VIII) in method (7), with a compound of the formula:-

$$R^9Z^1$$

wherein Z^1 is a suitable leaving group, e.g. halo, and R^9 is as defined for this method.

This Sheet Has Been Replaced

In a typical procedure a carboxylic acid of the formula (VIII) is reacted with a compound of the formula R^9Z^1 wherein Z^1 is halo, preferably chloro, in the presence of an alkali metal (e.g. cesium) carbonate and in a suitable solvent, e.g. N,N-dimethylacetamide.

Suitable base salts of the compounds of the formula (VIII) are the alkali metal salts, e.g. the caesium, sodium and potassium salts.

For certain compounds of the formula R^9Z^1, the reaction may be conveniently carried out by reaction with a carboxylic acid of the formula (VIII) in the presence of a suitable acid acceptor.

9) The compounds of the formula (I) wherein the dashed line does not represent a covalent bond, X is a direct link, R^4 is a C-linked heterocyclic ring as previously defined in definition (c) for R^4 for a compound of the formula (I), and R, R^1, R^2, R^3 and R^5 are as previously defined for a compound of the formula (I), can be prepared by reacting a compound of the formula (II) wherein R, R^1, R^2 and R^5 are as previously defined for this method, with an organometallic compound of the formula:-

R^4M

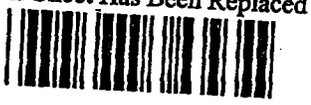
wherein R^4 is a C-linked heterocyclic ring as defined for R^4 for this method and M is a suitable metal, e.g. lithium, sodium or potassium, or metal halide, e.g. a magnesium halide (i.e. a Grignard reagent).

The organometallic compounds of the formula:-

R^4M

wherein M is a suitable metal are preferably generated <u>in situ</u> by deprotonation of the corresponding heterocyclic compound of the formula:-

This Sheet Has Been Replaced



R^4-H

wherein R^4 is as previously defined for this method, with a suitable base, e.g. n- or t-butyl lithium or lithium diisopropylamide.

The organometallic compounds of the formula:-

R^4M

wherein M is a suitable metal halide, e.g. a magnesium halide, can be prepared by treatment of the corresponding organometallic compound of the formula:-

R^4M

wherein M is lithium, in situ with a metal halide, e.g. magnesium bromide.

The reaction is typically carried out under an inert atmosphere of nitrogen or argon and in a suitable solvent, e.g. tetrahydrofuran. The reaction step with the epoxide is typically carried out at from -80°C to the reflux temperature of the solvent, and preferably at from 0°C to room temperature.

10) The compounds of the formula (I) wherein R^5 is C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said alkyl, alkenyl and alkynyl being substituted by C_2-C_6 alkanoyloxy or arylcarbonyloxy, and "aryl", the dashed line, X, R, R^1, R^2, R^3 and R^4 are as previously defined for a compound of the formula (I), can be prepared by reaction of a compound of the formula (I) wherein the dashed line, X, R, R^1, R^2, R^3 and R^4 are as defined for this method and R^5 is C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said alkyl, alkenyl and alkynyl being substituted by hydroxy, either with a C_2-C_6 alkanoic acid or arylcarboxylic acid, or with an activated derivative of either of these carboxylic acids,

wherein "aryl" is as defined for this method.

The term "activated derivative" includes the corresponding acid halide, e.g. acid chloride, acid anhydride, imidazolide and activated ester, e.g. a benzotriazol-1-yl ester, derivatives of the carboxylic acid.

The reaction can be carried out by reacting a C_2-C_6 alkanoyl halide or aroyl halide, e.g. a C_2-C_6 alkanoyl chloride or aroyl chloride, with an alcohol of the formula (I), optionally in the presence of a suitable acid acceptor, e.g. pyridine.

The reaction can also be carried out by reacting an acid anhydride of the formula (C_2-C_6 alkanoyl)$_2$O or (aroyl)$_2$O with an alcohol of the formula (I), optionally in the presence of a suitable acid acceptor, e.g. pyridine.

The reaction can further be carried out by reaction of an alcohol of the formula (I) and an above carboxylic acid under conventional esterification conditions such as in the presence of a suitable condensing agent or under the conditions of the Mitsunobu reaction, using similar procedures to those described in method (6).

11) The compounds of the formula (I) wherein R^5 is aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said alkyl, alkenyl and alkynyl being substituted by -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -$CONH(C_1$-$C_6)alkylCO_2R^8$ or -$CONR^8(C_1$-$C_6)alkylCO_2R^8$, or by aryl substituted by -$CONH_2$, $H_2NCO(C_1$-$C_6)alkyl$, -$CONHR^8$, $R^8NHCO(C_1$-$C_6)alkyl$, -$CON(R^8)_2$, $(R^8)_2NCO(C_1$-$C_6)alkyl$, -$CONH(C_1$-$C_6)alkylCO_2R^8$, $R^8O_2C(C_1$-$C_6)alkylNHCO(C_1$-$C_6)alkyl$, -$CONR^8(C_1$-$C_6)alkylCO_2R^8$ or $R^8O_2C(C_1$-$C_6)alkylNR^8CO(C_1$-$C_6)alkyl$, and said aryl being substituted by -$CONH_2$, $H_2NCO(C_1$-$C_6)alkyl$, -$CONHR^8$, $R^8NHCO(C_1$-$C_6)alkyl$,
-$CON(R^8)_2$, $(R^8)_2NCO(C_1$-$C_6)alkyl$, -$CONH(C_1$-$C_6)alkylCO_2R^8$,

This Sheet Has Been Replaced

$R^8O_2C(C_1\text{-}C_6)alkylNHCO(C_1\text{-}C_6)alkyl$, $-CONR^8(C_1\text{-}C_6)alkylCO_2R^8$ or $R^8O_2C(C_1\text{-}C_6)alkylNR^8CO(C_1\text{-}C_6)alkyl$, and the dashed line, X, R, R^1, R^2, R^3, R^4 and R^5 are as previously defined for a compound of the formula (I), can be prepared by reaction of a compound of the formula (VIII), or an activated derivative thereof, wherein the dashed line, X, R, R^1, R^2, R^3, R^4, R^{10} and the term "activated derivative" are as defined in method (6) for a compound of the formula (VIII), with ammonia or with a compound of the formula R^8NH_2, $(R^8)_2NH$, $R^8O_2C(C_1\text{-}C_6$ alkyl$)NH_2$ or $R^8O_2C(C_1\text{-}C_6$ alkyl$)NHR^8$, wherein R^8 is as defined for this method.

The reaction can be carried out by reacting a carboxylic acid of the formula (VIII) with an above amine in the presence of a suitable condensing agent, e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

The reaction can also be carried out by first reacting a carboxylic acid of the formula (VIII) with 1-hydroxybenzotriazole in the presence of a suitable condensing agent, e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, to form an activated ester, which can then be reacted with an above amine to provide the required amide.

The reaction can further be carried out by first generating the corresponding acid chloride of a carboxylic acid of the formula (VIII), followed by reacting this acid chloride with an above amine to provide the required amide.

The reaction can further be carried out under the conditions of the Mitsunobu reaction (see Method (6)).

12) The compounds of the formula (I) wherein the dashed line, X, R, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined for method (11), can be prepared by reaction of certain compounds of the formula (I) wherein the dashed line, X, R, R^1, R^2, R^3 and R^4 are as defined for this method and R^5 is aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said alkyl, alkenyl and alkynyl being substituted by $-CO_2R^9$ or by aryl substituted by $-CO_2R^9$ or $R^9O_2C(C_1$-$C_6)$alkyl, and said aryl being substituted by $-CO_2R^9$ or $R^9O_2C(C_1$-$C_6)$alkyl, wherein R^9 is a suitable ester-forming group selected from within the definition of R^9 as previously defined for a compound of the formula (I), with ammonia or with a compound of the formula R^6NH_2, $(R^6)_2NH$, $R^6O_2C(C_1$-C_6 alkyl)NH_2 or $R^6O_2C(C_1$-C_6 alkyl)NHR^6, wherein R^6 is as defined for this method.

Examples of suitable ester-forming groups for R^9 for this method are C_1-C_4 alkyl, e.g. methyl and ethyl, phenyl, pentafluorophenyl and p-nitrophenyl.

13) The compounds of the formula (I) wherein R^5 is C_1-C_{12} alkyl substituted by hydroxy, hydroxyphenyl or hydroxy(C_1-C_6)alkylphenyl, and the dashed line, X, R, R^1, R^2, R^3 and R^4 are as previously defined for a compound of the formula (I), can be prepared by hydrogenation of a compound of the formula (I) wherein R^5 is C_1-C_{12} alkyl substituted by benzyloxy, benzyloxyphenyl or benzyloxy(C_1-C_6)alkylphenyl, and the dashed line, X, R, R^1, R^2, R^3 and R^4 are as defined for this method.

In a typical procedure the reaction is carried out in the presence of a palladium-on-carbon catalyst and in a suitable solvent, e.g. ethanol, under pressure and at from room temperature to the reflux temperature of the solvent.

14) The compounds of the formula (I) wherein R^5 is C_1-C_{12} alkyl substituted by amino, and the dashed line, X, R, R^1, R^2, R^3 and R^4 are as previously defined for a compound of the formula (I), can be prepared by reaction of a compound of the formula (I) wherein R^5 is C_1-C_{12} alkyl substituted by phthalimido, and the dashed line, X, R, R^1, R^2, R^3 and R^4 are as defined for this method, with a C_1-C_4 alkylamine (e.g. methylamine) or hydrazine.

The reaction is typically carried out in a suitable solvent, e.g. ethanol, at from room temperature to the reflux temperature of the solvent.

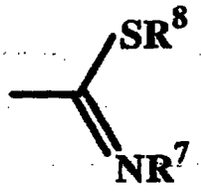
15) The compounds of the formula (I) wherein R^4 is 2-methyl-3-oxopyridazin-6-yl and the dashed line, X, R, R^1, R^2, R^3 and R^5 are as previously defined for a compound of the formula (I), can be prepared by methylation of a compound of the formula (I) wherein R^4 is 3-hydroxypyridazin-6-yl and the dashed line, X, R, R^1, R^2, R^3 and R^5 are as defined for this method.

The reaction is typically carried out using a suitable methylating agent, e.g. dimethyl sulphate, in the presence of a suitable base, e.g. potassium carbonate, and in a suitable solvent, e.g. acetone, at from room temperature to, and preferably at, the reflux temperature of the solvent.

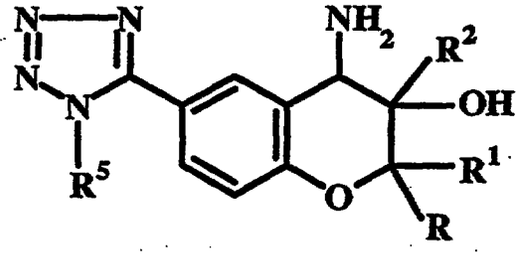
This Sheet Has Been Replaced



16) The compounds of the formula (I) wherein the dashed line does not represent a covalent bond, X is NH, R^4 is a group of the formula:-



and R, R^1, R^2, R^3, R^5, R^7 and R^8 are as previously defined for a compound of the formula (I), can be prepared by reaction of a compound of the formula:-



(IX)

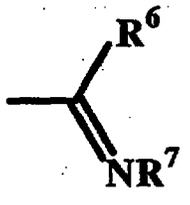
wherein R, R^1, R^2 and R^5 are as previously defined for this method, with a compound of the formula $(R^8S)_2C{=}NR^7$ wherein R^7 and R^8 are as previously defined for this method.

This Sheet Has Been Replaced

In a typical procedure the compounds are heated together in pyridine or ethanol.

The intermediates of the formula (IX) can be prepared by reaction of a compound of the formula (II) wherein R, R^1, R^3 and R^5 are as previously defined for this method with ammonia and in a suitable solvent, e.g. ethanol, at from room temperature to the reflux temperature of the solvent, and preferably at from 50 to 70°C.

17) The compounds of the formula (I) wherein the dashed line does not represent a covalent bond, X is NH, R^4 is a group of the formula:-



wherein R^6 is $-OR^8$, $-NHR^8$, -NH(aryl) or -NH(pyridinyl), and R, R^1, R^2, R^3, R^5, R^7, R^8 and "aryl" are as previously defined for a compound of the formula (I), can be prepared by reaction of a compound of the formula (I) wherein the dashed line, X, R, R^1, R^2, R^3, R^4, R^5, R^7 and R^8 are as defined for method (16), with a suitable base salt of a compound of the formula R^8OH (i.e. an alkoxide derivative), or with a compound of the formula R^8NH_2, (aryl)NH_2 or (pyridinyl)NH_2, wherein "aryl" and R^8 are as defined for this method.

Suitable base salts are the alkali metal salts, e.g. the sodium and potassium salts.

This Sheet Has Been Replaced

18) The compounds of the formula (I) wherein the dashed line does not represent a covalent bond, X is NH, R^4 is a C-linked 4- to 7-membered heterocyclic ring containing from 1 to 3 nitrogen hetero-atoms which is optionally substituted as previously defined in definition (c) for R^4 for a compound of the formula (I), and R, R^1, R^2, R^3 and R^5 are as previously defined for a compound of the formula (I), can be prepared by reaction of a compound of the formula (IX) wherein R, R^1, R^2 and R^5 are as previously defined for this method, with a 4- to 7-membered ring heterocyclic compound containing from 1 to 3 nitrogen hetero-atoms which is substituted on a ring carbon atom by a leaving group, e.g. halo (preferably chloro or bromo) or a group of the formula C_1-C_4 alkyl $S(O)_p$- where p is 0, 1 or 2, and optionally further substituted as previously defined for R^4 for this method.

In a typical procedure the reaction is carried out in the presence of a suitable acid acceptor, e.g. potassium carbonate or diisopropylethylamine, and in a suitable solvent, e.g. N,N-dimethylacetamide or dioxan, at from room temperature to, and preferably at or about, the reflux temperature thereof.

All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products are well known to those skilled in the art with reference to literature precedents and the Examples and Preparations hereto.

This Sheet Has Been Replaced



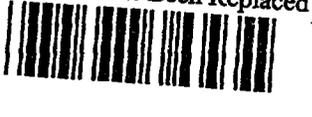
A pharmaceutically acceptable salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or is recovered by evaporation of the solvent.

The compounds of the formula (I) have smooth muscle relaxant activity since they are able to open potassium channels in such tissue. They can be tested for smooth muscle relaxant activity by a method involving measuring the in vitro relaxation of guinea pig tracheal ring preparations as follows:-

Male guinea pigs (500-600g) were killed by a blow to the head and exsanguinated. The trachea was removed, placed in Krebs solution and cleaned. The trachea was slit through the cartilage along it's longitudinal axis and strips consisting of four adjacent cartilage rings were prepared. The strips were each placed in a water-jacketed organ bath (37°C) containing Krebs solution and tied to a force-displacement transducer for the measurement of isometric tension responses. The tissues were equilibrated for 60 minutes under a resting load of 1g and washed every 15 minutes before the start of each experiment.

The composition of the Krebs solution was as follows (millimoles):- NaCl (119); KCl (4.7); $NaHCO_3$ (25); KH_2PO_4 (1.2); $MgSO_4$ (1.2); $CaCl_2$ (2.5); glucose (11), and indomethacin (2.8μM) was added to remove the influence of the endogenous prostanoids. The solution was gassed with 95% O_2 /5% CO_2 and the temperature was kept constant at 37°C.

This Sheet Has Been Replaced



After the equilibration period a priming dose of KCl (20mM) was added to each tissue bath and after a further 20 minutes the tissue was washed. After a further 30 minutes KCl (20mM) was added to contract each tissue. The relaxant action of a compound of the formula (I) was examined when the maintained contractile response had stabilized. The compounds can be added cumulatively (10^{-6}-10^{-5}mol) at 5 minute intervals.

The reversal to pretreatment base line was taken as 100 per cent relaxation in these studies and concentration-relaxation curves were constructed in order to obtain IC_{50} values for potency.

For human use, the compounds of the formula (I) and their salts can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, they can be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents.

They can be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) will be from 0.01 to 20mg/kg (in single or divided doses) and preferably will be from 0.1 to 5mg/kg.

This Sheet Has Been Replaced



Thus tablets or capsules of the compounds will contain from 1mg to 0.5g of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

The compounds of formula (I) can also be administered by inhalation and are conveniently delivered in the form of an aerosol spray presentation from a pressurised container or a nebuliser with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,-3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of formula (I) and a suitable powder base such as lactose or starch.

Aerosol formulations are preferably arranged so that each metered dose or "puff" of aerosol contains from 20µg to 1000µg of a compound of formula (I), or a pharmaceutically acceptable salt thereof, for delivery to the patient. The overall daily dose with an aerosol will be within the range of from 20µg to 10mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

This Sheet Has Been Replaced



Alternatively, the compounds of the formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. For example, they can be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin; or they can be incorporated, at a concentration of from 1 to 10%, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers and preservatives as may be required.

Thus the invention further provides:-

i) a pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier;

ii) a compound of the formula (I), or a pharmaceutically acceptable salt or composition thereof, for use as a medicament;

iii) the use of a compound of the formula (I), or of a pharmaceutically acceptable salt or composition thereof, for the manufacture of a medicament for the curative or prophylactic treatment of angina or a disease associated with the altered tone and/or motility of smooth muscle;

iv) use as stated in (iii) where the disease is chronic obstructive airways disease, asthma, urinary incontinence, irritable bowel syndrome, diverticular disease, oesophageal achalasia or hypertension;

v) a method of treatment of a human to cure or prevent angina or a disease associated with the altered tone and/or motility of smooth muscle which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt or composition thereof;

This Sheet Has Been Replaced

vi) a method as stated in (v) where the disease is chronic obstructive airways disease, asthma, urinary incontinence, irritable bowel syndrome, diverticular disease, oesophageal achalasia or hypertension; and

vii) intermediates of the formulae (II), (V), (VI) or a base salt thereof, (VIII) or an activated derivative thereof, and (IX).

The following Examples illustrate the preparation of the compounds of the formula (I):-

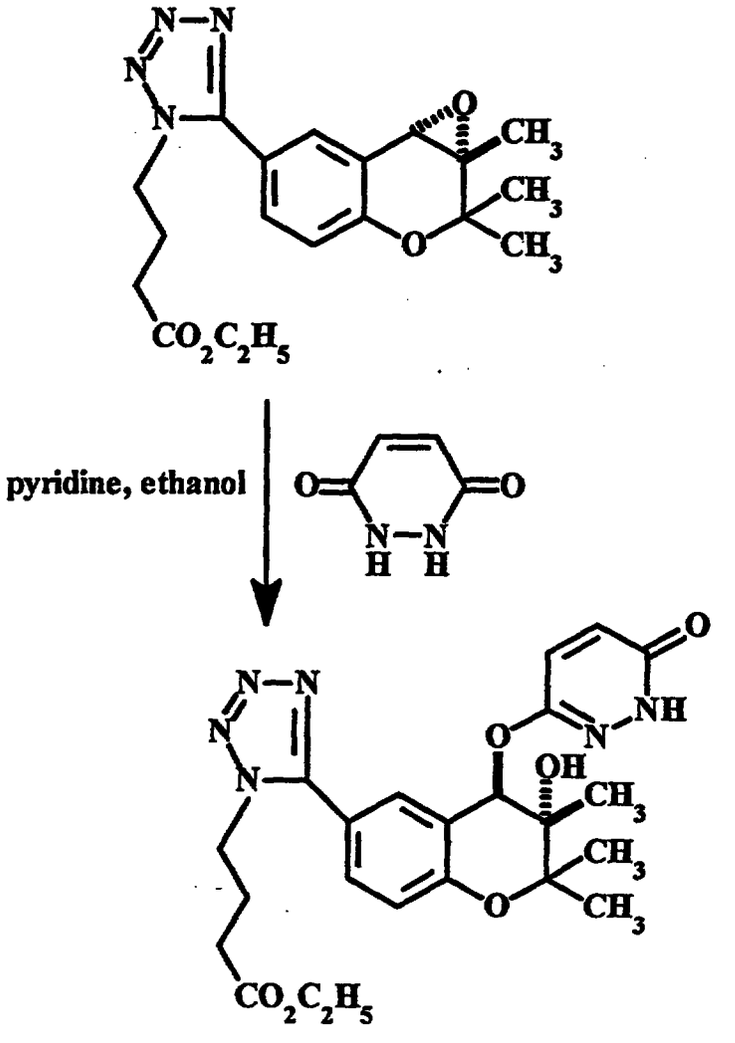
This Sheet Has Been Replaced



This Sheet Has Been Replaced

EXAMPLE 1

(3S,4R)-3,4-Dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran



A mixture containing (3S,4S)-3,4-dihydro-3,4-epoxy-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran (see Preparation 1) (0.5g), 3,6-dihydroxypyridazine (0.23g), pyridine (0.1g) and ethanol (10ml) was heated under reflux for 6 days. On cooling to room temperature the mixture was concentrated in vacuo and the residue azeotroped with dichloromethane (6 x 10ml).

This Sheet Has Been Replaced

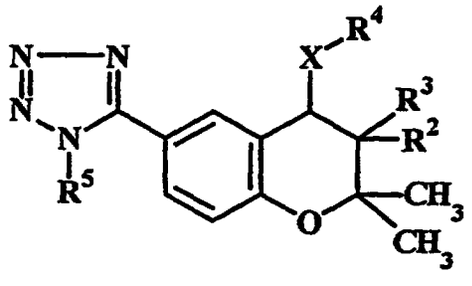


The resulting foam was purified by chromatography on silica eluting with dichloromethane containing methanol (2.5% up to 5%). The product-containing fractions were combined and concentrated in vacuo to give an oil which was azeotroped with hexane to give the title compound as a colourless solid, 0.32g, m.p. 90-110°C.

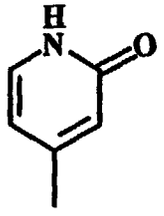
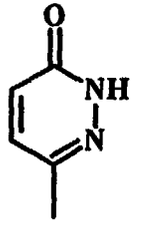
^{1}H-NMR ($CDCl_3$): δ = 7.75(s,1H), 7.60-7.50(dd,1H), 7.15-7.10(d,1H), 7.05-6.95(m,3H), 6.00(s,1H), 4.50-4.40(t,2H), 4.15-4.00(q,2H), 3.55(s,1H), 2.50-2.35(m,2H), 2.30-2.20(m,2H), 1.50(s,3H), 1.45(s,3H), 1.30(s,3H), 1.30-1.20(t,3H) ppm.

EXAMPLES 2 TO 13

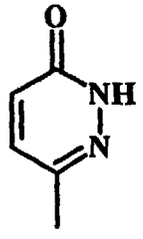
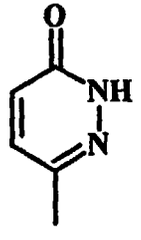
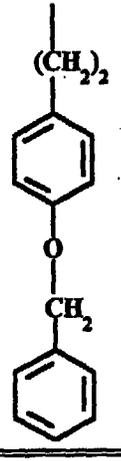
The compounds of the following tabulated Examples of the general formula:-



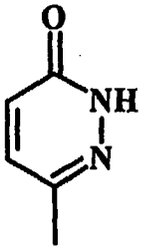
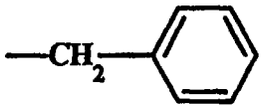
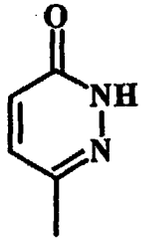
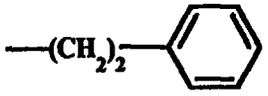
were prepared using similar methods to that used in Example 1 using the appropriate starting materials.

Ex.	Stereo-chem.	X	R^3	R^2	R^4	R^5	Oxirane starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR ($CDCl_3$)[1]
2[2]	3S,4R	O	OH	CH_3		$-(CH_2)_3CO_2C_2H_5$	see Prep. 1	100-107	Found: C,57.39; H,5.98; N,13.77; $C_{24}H_{29}N_5O_6.0.25\ CH_2Cl_2$ requires: C,57.71; H,5.89; N,13.88%. δ=7.60-7.50(m,2H), 7.25-7.20(d,1H), 7.05-6.95(d,1H), 6.35(s,1H), 6.15-6.10(dd,1H), 5.55(s,1H), 4.50-4.40 (t,2H), 4.10-4.00(q,2H), 3.80-3.60(brs,1H), 2.45-2.35(m,2H), 2.30-2.10 (m,2H), 1.55(s,3H), 1.50 (s,3H), 1.35(s,3H), 1.25-1.20(t,3H) ppm.
3[3]	3S,4R	O	OH	CH_3		CH_3	see Prep. 9	249-251	Found: C,55.84; H,5.28; N,21.67; $C_{18}H_{20}N_6O_4$ requires: C,56.24; H,5.24; N,21.86%. δ=7.70-7.60(m,2H), 7.25-7.20(d,1H), 7.00-6.90(m,2H), 5.90(s,1H), 5.35(s,1H), 4.05(s,3H), 1.40(s,3H), 1.35(s,3H), 1.20(s,3H) ppm.

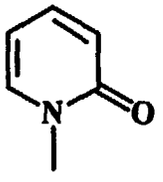
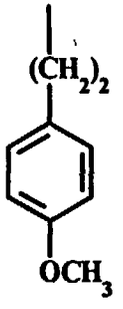
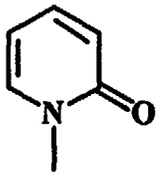
This Sheet Has Been Replaced

Ex.	Stereo-chem.	X	R^3	R^2	R^4	R^5	Oxirane starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR ($CDCl_3$)[1]
4[4]	3S,4R	O	OH	CH_3		$-CH_2CO_2C_2H_5$	see Prep. 12	102-120°C (with foaming)	Found: C,53.55; H,5.22; N,17.42; $C_{21}H_{24}N_6O_6.0.2CH_2Cl_2$ requires: C,53.77; H,5.19; N,17.75%. δ=7.65(s,1H), 7.55-7.45 (dd,1H), 7.15-7.10(d,1H), 7.05-6.90(m,2H), 6.00 (s,1H), 5.15(s,2H), 4.25-4.15(q,2H), 3.65(s,1H), 1.50(s,3H), 1.45(s,3H), 1.30(s,3H), 1.15-1.10 (t,3H) ppm.
5[5]	3S,4R/ 3R,4S	O	OH	CH_3			see Prep. 15	213-218	Found: C,66.22; H,5.73; N,14.16; $C_{32}H_{32}N_6O_6$ requires: C,66.19; H,5.56; N,14.47%. (d_6-DMSO) δ=7.45(s,1H), 7.40-7.25(m,6H), 7.25-7.15(d,1H), 6.90-6.70 (m,6H), 5.90(s,1H), 5.35 (s,1H), 5.00(s,2H), 4.60-4.50(t,2H), 3.05(t,2H), 1.40(s,3H), 1.30(s,3H), 1.20(s,3H) ppm.

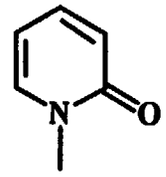
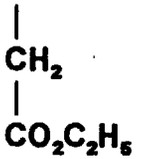
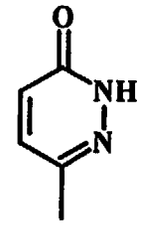
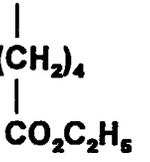
This Sheet Has Been Replaced

Ex.	Stereo-chem.	X	R^3	R^2	R^4	R^5	Oxirane starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR ($CDCl_3$)[1]
6[6]	3S,4R	O	OH	CH_3			see Prep. 18	-	(d_6-DMSO) δ=7.55-7.50 (dd,1H), 7.50(s,1H), 7.30-7.20(m,3H), 7.20-7.15 (d,1H), 7.05-6.95 (m,2H), 6.95-6.85 (m,2H), 5.90 (s,1H), 5.65(s,2H), 5.35 (s,1H), 1.35(s,3H), 1.30 (s,3H), 1.15(s,3H) ppm.
7[7]	3S,4R	O	OH	CH_3			see Prep. 21	-	Found: C,58.49; H,5.19; N,15.93; $C_{25}H_{26}N_6O_4.0.6\ CH_2Cl_2$ requires: C,58.52; H,5.22; N,16.00%. (d_6-DMSO) δ=7.35-7.30 (m,2H), 7.25-7.20 (dd,1H), 7.15-7.05 (m,3H), 6.95-6.80 (m,4H), 5.90(s,1H), 5.70(d,1H), 5.35(s,1H), 4.65(m,2H), 3.10-3.00 (m,2H), 1.40(s,3H), 1.35(s,3H), 1.20(s,3H) ppm.

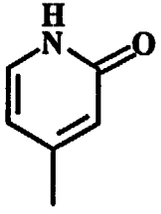
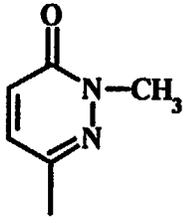
This Sheet Has Been Replaced

Ex	Stereo-chem.	X	R^3	R^2	R^4	R^5	Oxirane starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR($CDCl_3$)[1]
8[8]	3S,4R/ 3R,4S	direct link	OH	H			see Prep. 24	-	δ=7.40-7.35(m,1H), 7.20-7.10(dd,1H), 6.95-6.85 (m,2H), 6.80-6.65(m,5H), 6.35-6.25(d,1H), 6.25-6.15(t,1H), 4.50-4.40 (m,2H), 4.25(d,1H), 3.90-3.85(m,1H), 3.75(s,3H), 3.20-3.00(m,2H), 1.55 (s,3H), 1.40(s,3H) ppm.
9[8]	3S,4R/ 3R,4S	direct link	OH	H		$-(CH_2)_3CO_2C_2H_5$	see Prep. 36	145-147	Found: C,60.56; H,5.92; N,15.33; $C_{23}H_{27}N_5O_5$ requires: C,60.92; H,6.00; N,15.44%. δ=7.65-7.60(d,1H), 7.40-7.35(m,1H); 7.20 (s,1H), 7.10-7.05(d,1H), 7.05-6.95(dd,1H), 6.70-6.65 (d,1H), 6.45-6.35(d,1H), 6.30-6.20(t,1H), 4.50-4.30(m,2H), 4.30(d,1H), 4.15-4.05(q,2H), 3.95-3.90(m,1H), 2.40-2.30 (m,2H), 2.20-2.10(m,2H), 1.55(s,3H), 1.40(s,3H), 1.30-1.20(t,3H) ppm.

This Sheet Has Been Replaced

Ex.	Stereo-chem.	X	R^3	R^2	R^4	R^5	Oxirane starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR ($CDCl_3$)[1]
10[8]	3S,4R/ 3R,4S	direct link	OH	H			see Prep. 72	-	δ=7.55-7.50(dd,1H), 7.45-7.35(m,1H), 7.10 (s,1H), 7.10-7.05(d,1H), 7.00-6.95(dd,1H), 6.70-6.65 (d,1H), 6.40-6.35(d,1H), 6.30-6.20(t,1H), 5.05(s,2H), 4.30-4.10 (q,2H), 4.15-4.10 (m,1H), 3.95-3.85 (m,1H), 1.55(s,3H), 1.40(s,3H), 1.30-1.20(t,3H) ppm.
11[9]	3S,4R	O	OH	CH_3			see Prep. 65	-	Found: C,57.44; H,6.10; N,16.40; $C_{24}H_{30}N_6O_6$ requires: C,57.82; H,6.07; N,16.86%. δ=7.65(d,1H), 7.50-7.40 (dd,1H), 7.10-7.05(d,1H), 7.00-6.90(m,3H), 6.00 (s,1H), 4.40-4.25(t,2H), 4.10-4.00(q,2H), 3.00-2.40 (brs,1H), 2.30-2.20(t,2H), 2.00-1.85(m,2H), 1.65-1.50(m,2H), 1.50(s,3H), 1.45(s,3H), 1.25(s,3H), 1.20-1.15(t,3H) ppm.

This Sheet Has Been Replaced

Ex.	Stereo-chem.	X	R^3	R^2	R^4	R^5	Oxirane starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR ($CDCl_3$)[1]
12[10]	3S,4R	O	OH	CH_3		$-(CH_2)_4CO_2C_2H_5$	see Prep. 65	-	δ=7.55-7.45(m,2H), 7.25-7.20(d,1H), 7.05-6.95 (d,1H), 6.35(s,1H), 6.10-6.05(m,1H), 5.55(s,1H), 4.50-4.00(brs,1H), 4.40-4.30(t,2H), 4.10-4.05 (q,2H), 2.30-2.20(t,2H), 2.15-2.00(m,1H), 2.00-1.85(m,2H), 1.65-1.50 (m,2H), 1.50(s,3H), 1.45(s,3H), 1.35(s,3H), 1.25-1.20(t,3H) ppm.
13[11]	3S,4R	O	OH	CH_3		$-(CH_2)_3CO_2C_2H_5$	see Prep. 1	-	Found: C,57.86; H,6.47; N,16.66; $C_{24}H_{30}N_6O_6$ requires: C,57.82; H,6.07; N,16.86%. δ=7.75(d,1H), 7.60-7.50 (dd,1H), 7.10-6.95(m,3H), 5.95(s,1H), 4.50-4.40 (t,2H), 4.15-4.05(q,2H), 3.75(s,1H), 3.70(s,3H), 2.45-2.35(m,2H), 2.30-2.20(m,2H), 1.50(s,3H), 1.45(s,3H), 1.30(s,3H), 1.30-1.20(t,3H) ppm.

This Sheet Has Been Replaced

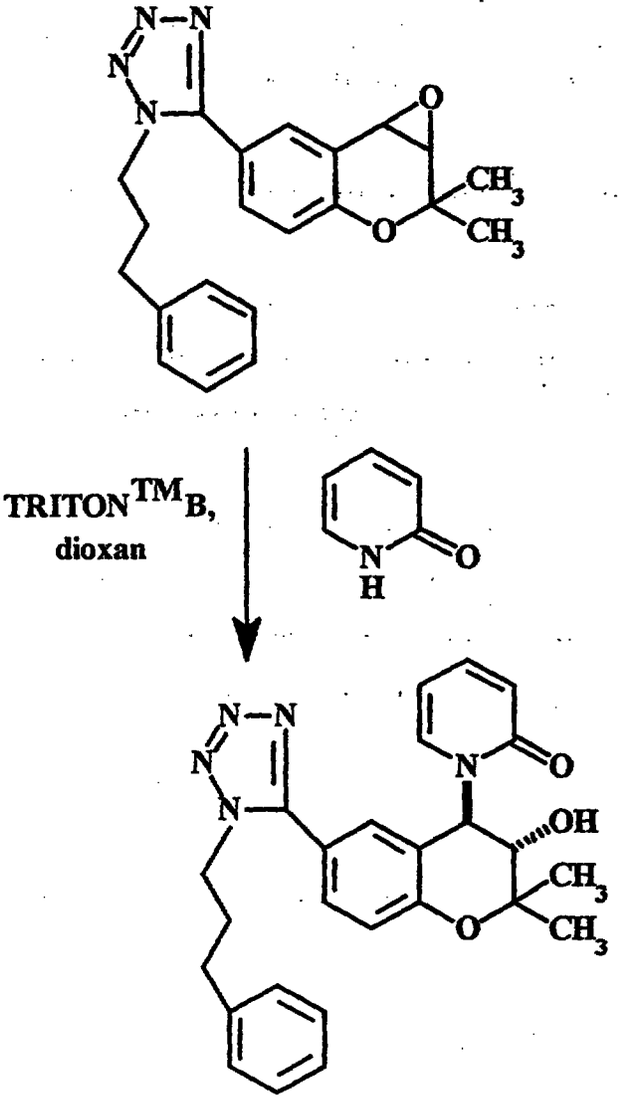
This Sheet Has Been Replaced

1. Except where stated.
2. Eluant for column chromatography was dichloromethane containing methanol (2.5% up to 12%) + 1% concentrated aqueous ammonia.
3. Eluant for column chromatography was dichloromethane containing methanol (5% up to 10%) + concentrated aqueous ammonia (0.25% up to 0.5%). The product obtained by chromatography was triturated with diethyl ether.
4. The product obtained by chromatography was triturated with hexane.
5. Eluant for column chromatography was dichloromethane containing methanol (0% up to 5%). The product obtained by chromatography was triturated with diethyl ether.
6. Eluant for column chromatography was dichloromethane containing methanol (5%). The product obtained by chromatography was triturated with diethyl ether.
7. Eluant for column chromatography was dichloromethane containing methanol (5%). The product obtained by chromatography was triturated with hexane.
8. Eluant for column chromatography was ethyl acetate.
9. Eluant for column chromatography was ethyl acetate. The product obtained by chromatography was triturated with diethyl ether.
10. Eluant for column chromatography was dichloromethane containing methanol (2%) + concentrated aqueous ammonia (0.3%).
11. For the preparation of the 1-methylpyridazin-3,6-dione starting material see J. Org. Chem., 36, 3372 (1971). Eluant for column chromatography was ethyl acetate. The product obtained by chromatography was crystallised from methanol/diethyl ether.

This Sheet Has Been Replaced

EXAMPLE 14

(3S,4R/3R,4S)-3,4-Dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxo-1,2-dihydropyridin-1-yl)-6-(1-[3-phenylprop-1-yl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



(only one stereoisomer shown)

A mixture containing (3S,4S/3R,4R)-3,4-dihydro-2,2-dimethyl-3,4-epoxy-6-(1-[3-phenylprop-1-yl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran (see Preparation 28) (2.6g), 2-hydroxypyridine (2g), benzyltrimethylammonium hydroxide (TRITON™B) (0.5ml of a 40%

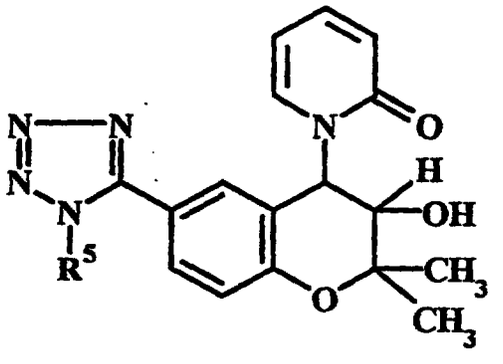
This Sheet Has Been Replaced

solution in methanol) and dioxan (20ml) was heated under reflux for 7 hours then concentrated in vacuo. The residue was purified by chromatography on silica eluting with 1:1 ethyl acetate/dichloromethane. The product-containing fractions were combined and concentrated in vacuo to give the title compound as a foam, 1.8g. Found: C,66.97; H,5.73; N,14.78; $C_{26}H_{27}N_5O_3.0.1\ CH_2Cl_2$ requires: C,67.27; H,5.88; N,15.03%.

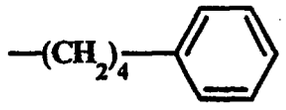
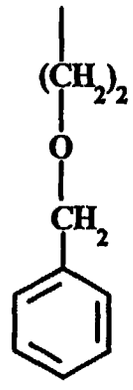
^{1}H-NMR ($CDCl_3$): δ = 7.50-7.45(d,1H), 7.35-7.20(m,4H), 7.10-7.00(m,3H), 6.90-6.85(d,1H), 6.85-6.80(d,1H), 6.40-6.35(d,1H), 6.20-6.10(t,1H), 4.30-4.25(t,2H), 4.25-4.20(m,1H), 3.90-3.85(m,1H), 2.65-2.55(t,2H), 2.30-2.15(m,2H), 1.55(s,3H), 1.40(s,3H) ppm.

EXAMPLES 15 TO 21

The compounds of the following tabulated Examples of the general formula:-



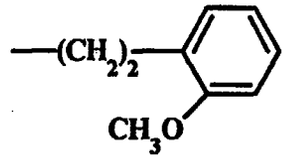
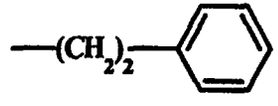
were prepared using similar methods to that used in Example 14 using the appropriate starting materials.

Ex.	Stereo-chem.	R^5	Oxirane starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR($CDCl_3$)
15	3S,4R/ 3R,4S		see Prep. 33	98-103	Found: C,68.55; H,6.45; N,14.50; $C_{27}H_{29}N_5O_3$ requires: C,68.77; H,6.20; N,14.85%. δ=7.55-7.50(d,1H), 7.35-7.10(m,4H), 7.15-7.05(m,4H), 6.95-6.90(d,1H), 6.70-6.65(d,1H), 6.45-6.35(d,1H), 6.20-6.15(t,1H), 4.35-4.25(t,2H), 4.10(d,1H), 3.90-3.85(m,1H), 2.65-2.55(t,2H), 1.95-1.80(m,2H), 1.65-1.50(m,5H), 1.40(s,3H) ppm.
16[1]	3S,4R/ 3R,4S		see Prep. 39	-	δ=7.75-7.70(dd,1H), 7.40-7.20(m,5H), 7.10-7.05(m,2H), 6.95-6.90(d,1H), 6.70-6.60(d,1H), 6.40(d,1H), 6.20-6.15(t,1H), 4.50-4.45(m,2H), 4.40-4.25(ABq,2H), 4.30-4.20(m,1H), 3.95-3.85(m,3H), 1.55(s,3H), 1.40(s,3H) ppm.

This Sheet Has Been Replaced

Ex.	Stereo-chem.	R^5	Oxirane starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR($CDCl_3$)
17[2]	3S,4R/ 3R,4S		see Prep. 43	221-223	Found: C,58.51; H,4.40; N,14.71; $C_{27}H_{24}N_6O_6.0.67\ CH_2Cl_2$ requires: C,58.44; H,4.48; N,14.78%. δ=7.85-7.70(m,4H), 7.50-7.45(d,1H), 7.40-7.35(m,1H), 7.10(s,1H), 7.05-6.95 (d,1H), 6.95-6.90(d,1H), 6.70-6.65(d,1H), 6.35-6.25(m,2H), 4.70-4.60(m,2H), 4.25(d,1H), 4.10-4.00(m,2H), 3.90-3.85 (m,1H), 1.55(s,3H), 1.35(s,3H) ppm.
18[3]	3S,4R/ 3R,4S		see Prep. 49	-	Found: C,65.07; H,5.98; N,13.59; $C_{26}H_{27}N_5O_4.0.4\ CH_3CO_2C_2H_5$ requires: C,65.16; H,5.98; N,13.77%. δ=7.40-7.30(m,1H), 7.20-7.10(m,2H), 7.05-6.90(m,2H), 6.80-6.75(m,3H), 6.50-6.45(d,1H), 6.35-6.25(m,2H), 6.25-6.20 (m,1H), 4.60-4.40(m,2H), 4.25(d,1H), 3.95-3.85(m,1H), 3.75(s,3H), 3.25-3.05(m,2H), 1.55(s,3H), 1.40(s,3H) ppm.

This Sheet Has Been Replaced

Ex.	Stereo-chem.	R^6	Oxirane starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR($CDCl_3$)
19[3]	3S,4R/ 3R,4S		see Prep. 52	-	δ=7.40-7.15(m,3H), 7.00-6.95(d,1H), 6.90(d,1H), 6.80-6.65(m,5H), 6.30(d,1H), 6.20-6.15(t,1H), 4.65-4.45(m,2H), 4.30(d,1H), 3.90-3.85(m,1H), 3.65(s,3H), 3.25-3.05(m,2H), 1.55(s,3H), 1.40(s,3H) ppm.
20[4]	3S,4R/ 3R,4S	$-(CH_2)_2OCH_3$	see Prep. 56	224-226	Found: C,60.60; H,5.87; N,17.51; $C_{20}H_{23}N_5O_4$ requires: C,60.44; H,5.83; N,17.62%. δ=7.75-7.70(dd,1H), 7.45-7.30(m,2H), 7.10-7.05(d,1H), 7.00(dd,1H), 6.70(d,1H), 6.45-6.35(d,1H), 6.30-6.20(t,1H), 4.45-4.35(m,2H), 4.15-4.05(m,1H), 3.95-3.75 (m,3H), 3.15(s,3H), 1.55(s,3H), 1.40(s,3H) ppm.
21[5]	3S,4R/ 3R,4S		see Prep. 62	180-190	Found: C,67.81; H,5.68; N,15.80; $C_{25}H_{25}N_5O_3$ requires: C,67.70; H,5.68; N,15.79%. δ=7.40-7.35(m,1H), 7.25-7.10(m,4H), 6.95-6.90(d,1H), 6.90-6.80(m,3H), 6.70 (d,1H), 6.65(s,1H), 6.30-6.25(d,1H), 6.20-6.15(t,1H), 4.55-4.40(m,2H), 4.20(d,1H), 3.90-3.85(dd,1H), 3.25-3.10(m,2H), 1.55 (s,3H), 1.35(s,3H) ppm.

This Sheet Has Been Replaced

This Sheet Has Been Replaced



1. Eluant for column chromatography was dichloromethane containing methanol (1%).

2. Eluant for column chromatography was ethyl acetate and the product obtained was triturated with diethyl ether.

3. Eluant for column chromatography was ethyl acetate.

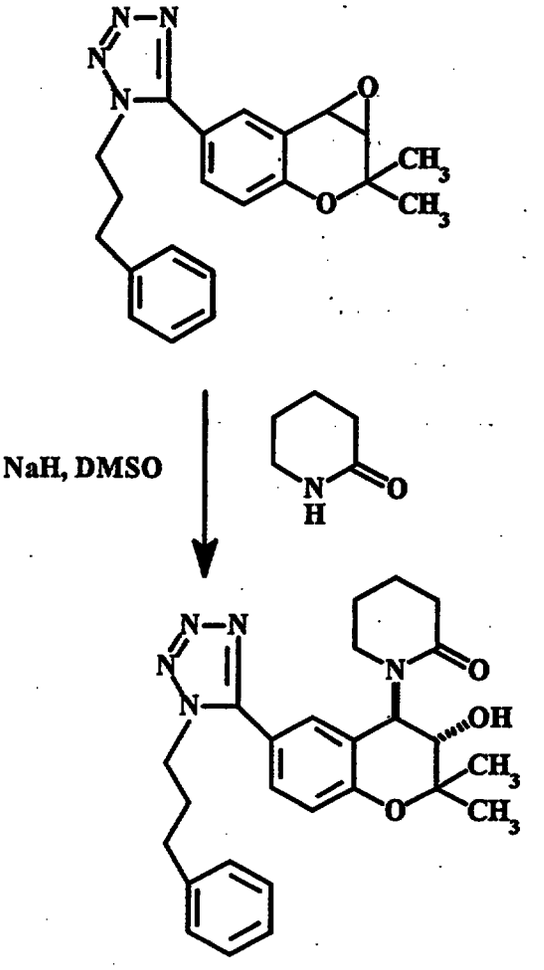
4. Eluant for column chromatography was dichloromethane containing methanol (2.5%) and the product obtained was triturated with diethyl ether.

5. Column chromatography was unnecessary. The reaction mixture was cooled to room temperature, diluted with dichloromethane and washed with water, then dried ($MgSO_4$) and concentrated in vacuo. The resulting solid was crystallised from ethyl acetate to give the product.

This Sheet Has Been Replaced

EXAMPLE 22

(3S,4R/3R,4S)-3,4-Dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-6-(1-[3-phenylprop-1-yl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



(only one stereoisomer shown)

Sodium hydride (0.4g of an 80% dispersion in mineral oil) was added to a solution of δ-valerolactam (1.3g) in dimethyl sulphoxide (DMSO) (10ml), and the mixture was stirred at room temperature for 1 hour. A solution of (3S,4S/3R,4R)-3,4-dihydro-2,2-dimethyl-3,4-epoxy-6-(1-[3-phenylprop-1-yl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran (see Preparation 28) (1.6g) in dimethyl sulphoxide (10ml) was added and the mixture was stirred at room temperature for 16 hours. Water (100ml) was added and the mixture was extracted with ethyl acetate (3 x 50ml). The combined extracts were concentrated in vacuo to give an oil which

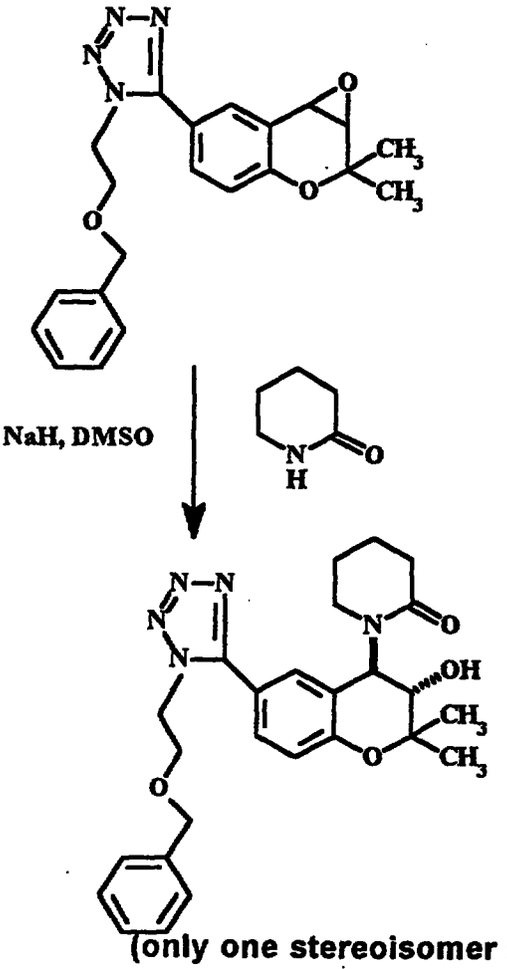
This Sheet Has Been Replaced

was purified by chromatography on silica eluting with dichloromethane containing methanol (2%). The product-containing fractions were combined and concentrated in vacuo to give a foam which was triturated with diethyl ether then diluted with hexane to give the title compound as a solid foam, 0.4g.

^{1}H-NMR ($CDCl_3$): δ=7.40-7.20(m,5H), 7.15-7.10(d,2H), 7.00-6.95(d,1H), 6.05-5.95(d,1H), 3.85-3.80(m,1H), 3.80-3.65(m,2H), 3.45-3.40(m,1H), 3.15-3.00(m,1H), 3.00-2.85(m,1H), 2.75-2.65(m,2H), 2.65-2.55(m,2H), 2.35-2.20(m,2H), 1.90-1.60(m,4H), 1.55(s,3H), 1.35(s,3H) ppm.

EXAMPLE 23

(3S,4R/3R,4S)-6-(1-[2-Benzyloxyethyl]-1H-tetrazol-5-yl)-3,4-dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-2H-benzo[b]pyran



(only one stereoisomer shown)

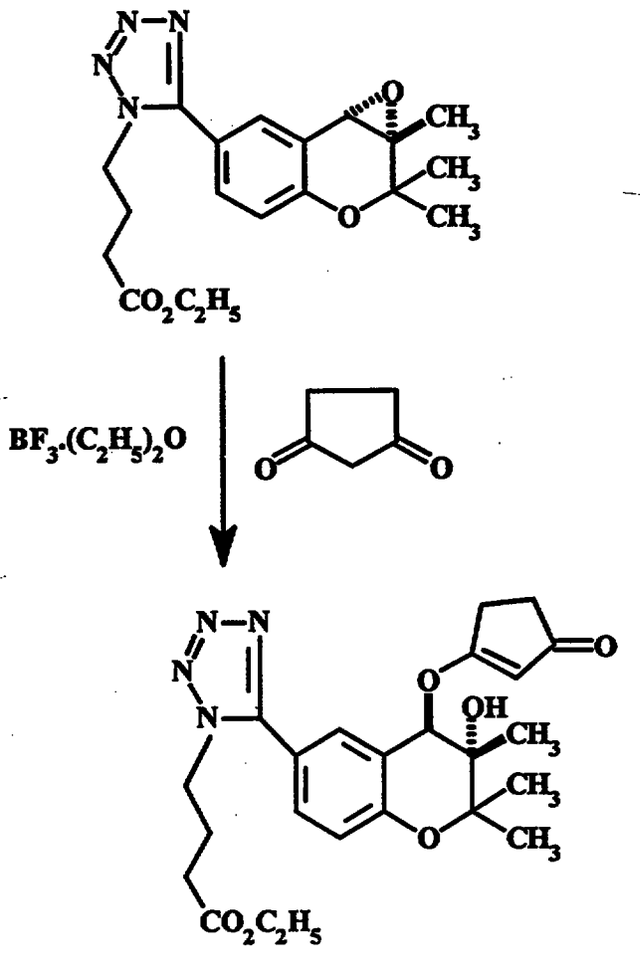
Sodium hydride (0.28g of an 80% dispersion in mineral oil) was added, over 10 minutes, to a solution of 2-oxopiperidine (1.1g) and (3S,4S/3R,4R)-6-(1-[2-benzyloxyethyl]-1H-tetrazol-5-yl)-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2H-benzo[b]pyran (see Preparation 39) (3.2g). When the addition was complete the mixture was stirred at room temperature for 6 hours then poured onto ice (100g). The mixture was extracted with ethyl acetate (2 x 50ml) and the combined extracts were washed with saturated sodium chloride solution (50ml) then concentrated in vacuo. The residue was purified by chromatography on silica eluting with ethyl acetate. The product-containing fractions were combined and concentrated in vacuo to give the title compound as a foam, 1.3g.
Found: C,64.42; H,6.55; N,14.28; $C_{26}H_{31}N_5O_4.0.07\ CH_2Cl_2$ requires: C,64.79; H,6.49; N,14.49%.
^{1}H-NMR ($CDCl_3$): δ=7.70-7.60(d,1H), 7.45(s,1H), 7.35-7.25(m,3H), 7.15-7.10(m,2H), 6.95-6.90(d,1H), 6.05-5.95(d,1H), 4.55-4.45(m,2H), 4.45(s,2H), 4.05-3.95(m,2H), 3.90-3.75(m,1H), 3.40(d,1H), 3.10-2.90(m,2H), 2.60-2.50(m,2H), 1.90-1.65(m,4H), 1.55(s,3H), 1.30(s,3H) ppm.

This Sheet Has Been Replaced



EXAMPLE 24

(3S,4R)-3,4-Dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-4-(1-oxocyclopent-2-en-3-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran



This Sheet Has Been Replaced

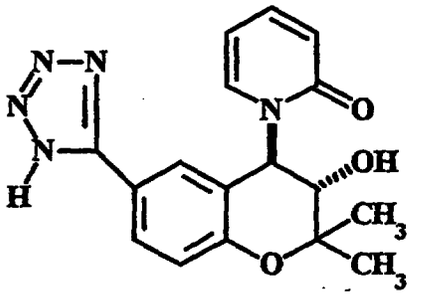
Sodium hydride (0.048g of an 80% dispersion in mineral oil) was added to a solution of cyclopentan-1,3-dione (0.16g) in anhydrous tetrahydrofuran (25ml) and the mixture was stirred at room temperature for 45 minutes. A solution of (3S,4S)-3,4-dihydro-3,4-epoxy-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran (see Preparation 1) (0.5g) in anhydrous tetrahydrofuran (25ml) was added followed by boron trifluoride etherate (0.2ml). The mixture was stirred at room temperature for 2 hours then 10% aqueous sodium bicarbonate (100ml) was added and the mixture

was extracted with ethyl acetate (2 x 50ml). The combined extracts were washed with 1N hydrochloric acid (50ml) and concentrated in vacuo. The residue was purified by chromatography on silica eluting with ethyl acetate containing hexane (50% down to 0%). The product-containing fractions were combined and concentrated in vacuo to give the title compound as a foam, 0.096g. Found: C,59.14; H,6.33; N,11.78; $C_{24}H_{30}N_4O_6.H_2O$ requires: C,59.01; H,6.60; N,11.47%.

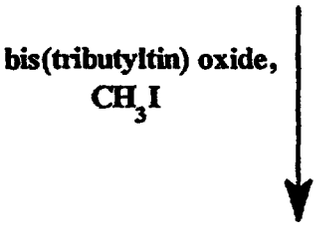
^{1}H-NMR ($CDCl_3$): δ=7.60-7.50(m,2H), 7.05-7.00(d,1H), 5.70(s,1H), 5.35(s,1H), 4.50-4.40(m,2H), 4.10-4.00(m,2H), 2.90(s,1H), 2.85-2.65(m,2H), 2.55-2.30(m,4H), 2.30-2.15(m,2H), 1.50(s,3H), 1.45(s,3H), 1.35(s,3H), 1.30-1.20(t,3H) ppm.

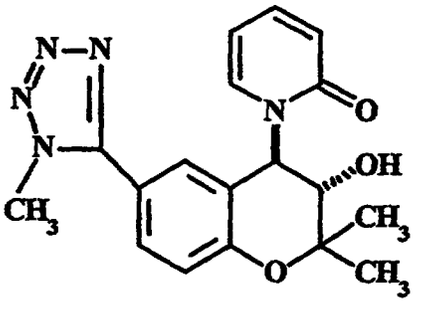
EXAMPLE 25

(3S,4R/3R,4S)-3,4-Dihydro-2,2-dimethyl-3-hydroxy-6-(1-methyl-1H-tetrazol-5-yl)-4-(2-oxo-1,2-dihydropyridin-1-yl)-2H-benzo[b]pyran



This Sheet Has Been Replaced





(only one stereoisomer shown)

A mixture containing (3S,4R/3R,4S)-3,4-dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxo-1,2-dihydropyridin-1-yl)-6-(1H-tetrazol-5-yl)-2H-benzo[b]pyran (see Preparation 59) (0.5g), iodomethane (5ml) and bis-tributyltin oxide (0.9g) was stirred at room temperature for 4 days then partitioned between dichloromethane (50ml) and 10% aqueous sodium hydroxide (50ml). The layers were separated and the dichloromethane solution was washed with water (50ml) then dried ($MgSO_4$) and concentrated in vacuo to give an oil which was triturated with a mixture of hexane (20ml) and ethyl acetate (10ml) to give a solid. The solid was purified by chromatography on silica eluting with dichloromethane containing methanol (1% up to 3%) and acetic acid (1% up to 3%).

The fractions containing the higher Rf product were combined and concentrated in vacuo to give (3S,4R/3R,4S)-3,4-dihydro-2,2-dimethyl-3-hydroxy-6-(2-methyl-1H-tetrazol-5-yl)-4-(2-oxo-1,2-dihydropyridin-1-yl)-2H-benzo[b]pyran, 0.07g.

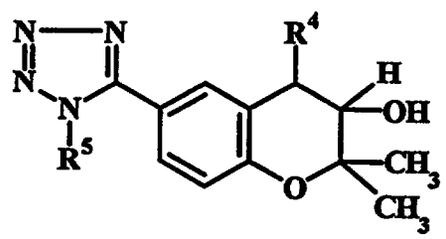
The fractions containing the lower Rf product were combined and concentrated in vacuo to give a solid which was recrystallised from ethanol to give the title compound, 0.2g, m.p. 235-237°C. Found: C,61.36; H,5.21; N,19.62; $C_{18}H_{19}N_5O_3$ requires: C,61.17; N,5.42; N,19.82%. ^{1}H-NMR (d_6-DMSO) [mixture of rotomers]: δ=7.85-7.80(d,0.25H), 7.65-7.60(d,0.5H), 7.60-7.55(d,0.25H), 7.50-7.35(m,2H), 7.15(s,0.25H), 7.10-6.95(m,1.75H), 6.50-6.45(d,0.5H), 6.30-6.15(m,2H), 5.80-5.75(d,1H), 4.95-4.90(d,0.25H), 4.55-4.50(m,0.25H), 4.05-3.95(m,3H), 1.45(s,2H), 1.40(s,1H), 1.25(s,2H), 1.20(s,1H) ppm.

This Sheet Has Been Replaced



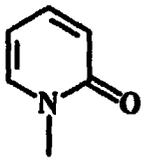
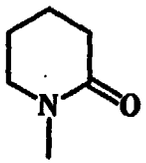
EXAMPLES 26 TO 36

The compounds of the following tabulated Examples of the general formula:-

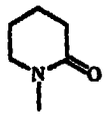
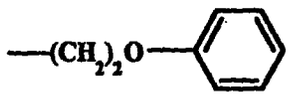
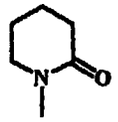
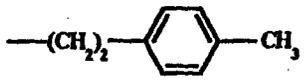


were prepared by similar methods to that used in Example 25 using the appropriate starting materials.

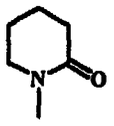
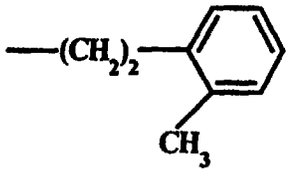
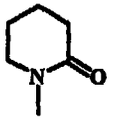
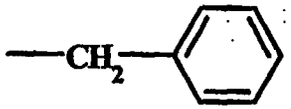
This Sheet Has Been Replaced

Ex.	Stereo-chem.	R^4	R^5	Alkylating agent	Tetrazole starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR ($CDCl_3$)[1]
26[2]	3S,4R/ 3R,4S		$-C_2H_5$	Ethyl iodide	see Prep. 59	226	Found: C,62,19; H,5.79; N,18.79; $C_{19}H_{21}N_5O_3$ requires: C,62.11; H,5.76; N,19.06%. (d_6-DMSO) [mixture of rotomers]: δ=7.85-7.80(d,0.5H), 7.60-7.30 (m,2.5H), 7.10-6.85(m,2H), 6.55-6.45(d,0.5H), 6.30-6.20(m,2H), 5.85-5.75(d,1H), 4.95-4.90(m,0.25H), 4.55-4.45(m,0.25H), 4.35-4.20(m,2H), 4.10-3.95(m,1H), 1.45(s,2H), 1.40(s,1H), 1.30-1.10(m,6H) ppm.
27[3]	3S,4R/ 3R,4S		$-(CH_2)_2CH_3$	n-Propyl iodide	see Prep. 60 and 61	184-185	δ=7.50-7.45(d,1H), 7.35(s,1H), 7.00(d,1H), 6.05-5.95(d,1H), 4.40-4.30(t,2H), 3.90-3.80(d,1H), 3.15-2.95(m,3H), 2.65-2.55 (m,2H), 2.00-1.70(m,5H), 1.55 (s,3H), 1.30(s,3H), 1.00-0.90 (t,3H) ppm.

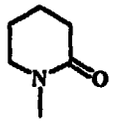
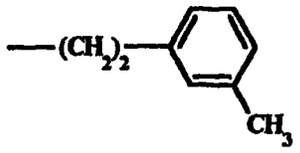
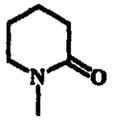
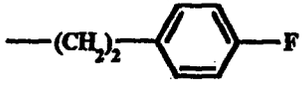
This Sheet Has Been Replaced

Ex.	Stereo-chem.	R^4	R^5	Alkylating agent	Tetrazole starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR ($CDCl_3$)[1]
28[4]	3S,4R/ 3R,4S			2-Phenoxy-ethyl bromide	see Prep. 60 and 61	115-120	Found: C,64.34; H,6.24; N,15.00; $C_{25}H_{29}N_5O_4$ requires: C,64.77; H,6.31; N,15.11%. δ=7.75-7.60(dd,1H), 7.55 (s,1H), 7.35-7.25(m,2H), 7.10-7.00(m,2H), 6.80-6.75 (d,2H), 6.10-6.00(d,1H), 4.85-4.75(m,2H), 4.65-4.45 (m,2H), 3.95-3.85(d,1H), 3.30-3.20(brs,1H), 3.15-3.00(brs,2H), 2.65-2.40 (m,2H), 1.90-1.70(m,4H), 1.60(s,3H), 1.35(s,3H) ppm.
29[5]	3S,4R/ 3R,4S			2-(4-Methyl-phenyl)ethyl bromide	see Prep. 60 and 61	140-146	δ=7.20(s,1H), 7.05-6.95 (m,3H), 6.95-6.85(m,3H), 5.95-5.90(d,1H), 4.60-4.50 (t,2H), 1.85-1.75(m,1H), 1.35-1.30(d,1H), 3.30-3.10 (m,2H), 3.10-2.90(m,2H), 2.60-2.50(m,2H), 2.30 (s,3H), 1.90-1.65(m,4H), 1.55(s,3H) 1.30(s,3H) ppm.

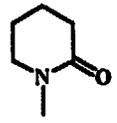
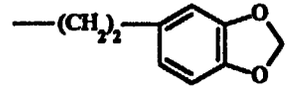
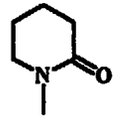
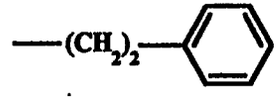
This Sheet Has Been Replaced

Ex.	Stereo-chem.	R^4	R^5	Alkylating agent	Tetrazole starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR ($CDCl_3$)[1]
30[6]	3S,4R/ 3R,4S			2-(2-Methyl-phenyl)ethyl bromide	see Prep. 60 and 61	169-172	Found: C,68.01; H,6.67; N,15.54; $C_{25}H_{31}N_5O_3$ requires: C,67.67; H,6.77; N,15.18%. δ=7.15-6.90(m,5H), 6.90-6.85(d,1H), 6.80-6.75(d,1H), 5.95-5.90(d,1H), 4.65-4.45 (m,2H), 3.85-3.75(m,1H), 3.60-3.55(d,1H), 3.30-3.10 (m,2H), 3.10-2.85(m,2H), 2.60-2.45(m,2H), 2.10 (s,3H), 1.90-1.65(m,4H), 1.50(s,3H), 1.30(s,3H) ppm.
31[7]	3S,4R/ 3R,4S			Benzyl bromide	see Prep. 60 and 61	169-171	Found: C,66.20; H,6.36; N,16.08; $C_{24}H_{27}N_5O_3$ requires: C,66.49; H,6.28; N,16.16%. δ=7.50-7.40(dd,1H), 7.40-7.30(m,3H), 7.25-7.10 (m,3H), 7.00-6.90(d,1H), 6.00-5.90(d,1H), 5.70-5.55 (ABq,2H), 3.85-3.75(d,1H), 3.75-3.60(brs,1H), 3.10-2.95(m,1H), 2.85-2.75 (m,1H), 2.60-2.30(m,2H), 1.80-1.60(m,3H), 1.55 (s,3H), 1.30(s,3H) ppm.

This Sheet Has Been Replaced

Ex.	Stereo-chem.	R^4	R^5	Alkylating agent	Tetrazole starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR ($CDCl_3$)[1]
32[7]	3S,4R/ 3R,4S			2-(3-Methyl-phenyl)ethyl bromide	see Prep. 60 and 61	173-176	δ=7.10-6.95(m,4H), 6.90-6.85(d,1H), 6.75-6.70 (m,2H), 5.95-5.90(d,1H), 4.60-4.50(m,2H), 3.85-3.75 (m,1H), 3.60(d,1H), 3.25-3.10(m,2H), 3.10-2.90 (m,2H), 2.60-2.50(m,2H), 2.25(s,3H), 1.90-1.65 (m,4H), 1.55 (s,3H), 1.30(s,3H) ppm.
33[8]	3S,4R/ 3R,4S			2-(4-Fluoro-phenyl)ethyl iodide[9]	see Prep. 60 and 61	140-144	Found: C,64.85; H,6.10; N,15.18; $C_{25}H_{28}N_6O_3F$ requires: C,64.50; H,6.06; N,15.05%. δ=7.15(d,1H), 7.10-7.05 (dd,1H), 6.95-6.85(m,5H), 6.00-5.90(d,1H), 4.65-4.55 (t,2H), 3.85-3.75(m,1H), 3.35(d,1H), 3.30-3.10 (m,2H), 3.10-3.00(m,1H), 2.95-2.85(m,1H), 2.60-2.55 (m,2H), 1.90-1.65(m,4H), 1.55(s,3H), 1.30(s,3H) ppm.

This Sheet Has Been Replaced

Ex.	Stereo-chem.	R^4	R^5	Alkylating agent	Tetrazole starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR ($CDCl_3$)[1]
34[10]	3S,4R/ 3R,4S			2-Methane-sulphonyloxy -1-(3,4-methylene-dioxyphenyl)-ethane[11]	see Prep. 60 and 61	204-205	δ=7.15(s,1H), 7.15-7.10 (d,1H), 6.90(d,1H), 6.65-6.60(d,1H), 6.40-6.35 (m,2H), 6.00-5.90(m,3H), 4.60-4.50(t,2H), 3.85-3.80(d,1H), 3.30-3.20 (brs,1H), 3.15-2.90 (m,4H), 2.60-2.55(m,2H), 1.90-1.70(m,4H), 1.55 (s,3H), 1.30(s,3H) ppm.
35[12]	3S,4R/ 3R,4S			2-Phenylethyl iodide	see Prep. 60 and 61	105-115	Found: C,67.52; H,6.72; N,15.71; $C_{25}H_{29}N_5O_3$ requires: C,67.09; H,6.53; N,15.65%. δ=7.30-7.15(m,3H), 7.10-6.85(m,5H), 5.95-5.90 (d,1H), 4.65-4.50(m,2H), 3.85-3.75(d,1H), 3.35-3.15 (m,3H), 3.10-2.85(m,2H), 2.60-2.50(m,2H), 1.90-1.65 (m,4H), 1.50(s,3H), 1.30 (s,3H) ppm.

This Sheet Has Been Replaced

Ex.	Stereo-chem.	R^4	R^5	Alkylating agent	Tetrazole starting material ref.	m.p. (°C)	Analysis/^{1}H-NMR ($CDCl_3$)[1]
36[13]	3S,4R/ 3R,4S		CH_3	Methyl iodide	see Prep. 60 and 61	253-254	(d_6-DMSO) δ=7.60(d,1H), 7.30(s,1H), 7.00-6.95(d,1H), 5.80-5.70(m,2H), 5.65-5.60 (brs,1H), 3.75-3.70(d,1H), 3.30(s,1H), 3.20-3.10(m,1H), 2.80-2.70(m,1H), 2.50-2.30 (m,3H), 1.80-1.60(m,4H), 1.45(s,3H), 1.20(s,3H) ppm.

This Sheet Has Been Replaced

This Sheet Has Been Replaced



1. Except where stated.

2. Acetonitrile was used as a solvent for the reaction. Eluant for column chromatography was dichloromethane containing methanol (0% up to 2%) and acetic acid (0% up to 2%). The required compound was the lower Rf. product and it was crystallised from ethyl acetate.

3. Acetonitrile was used as a solvent for the reaction and the mixture was initially sonicated for 30 minutes. Eluant for column chromatography was dichloromethane containing methanol (0% up to 2%) and acetic acid (0% up to 2%).
The corresponding tetrazole 2-alkylated product was obtained as the higher Rf. product from the column. The required compound was obtained as the lower Rf. product and was crystallised from diethyl ether.

4. N,N-Dimethylformamide was used as a solvent for the reaction and ethyl acetate as the extraction solvent in the work-up.
Eluant for column chromatography was toluene containing acetic acid (20% up to 40%). The corresponding tetrazole 2-alkylated product was obtained as the higher Rf. product from the column. The required compound was obtained as the lower Rf. product and was crystallised from ethyl acetate.

5. As footnote (4) except the lower Rf. product from the column was triturated with diethyl ether to provide the required compound.

This Sheet Has Been Replaced

6. As footnote (4) except the lower Rf. product from the column was rechromatographed on silica eluting with dichloromethane containing methanol (5%) to provide the required product after trituration with diethyl ether.

7. As footnote (4) except the required compound, obtained as the lower Rf. product, was crystallised from ethyl acetate/hexane.

8. N,N-Dimethyl formamide was used as a solvent for the reaction. In the work-up reaction the mixture was partitioned between ethyl acetate and 5% aqueous sodium hydroxide, the layers separated and the aqueous layer extracted with ethyl acetate. The combined ethyl acetate extracts were dried ($MgSO_4$) and concentrated in vacuo to give an oil which was purified by chromatography on silica eluting with dichloromethane containing methanol (1% up to 2%) and acetic acid (1% up to 2%). The product-containing fractions were combined and concentrated in vacuo to give an oil which was crystallised from ethyl acetate to give the corresponding tetrazole 2-alkylated product, m.p. 210-212°C. The mother liquors from the crystallisation were concentrated in vacuo to give a gum which was further purified by chromatography on silica eluting with dichloromethane containing methanol (1% up to 2%) and acetic acid (1% up to 2%). The fractions containing the lower Rf product were combined and concentrated in vacuo to give a gum which was crystallised from ethyl acetate/ether to give the required product.

This Sheet Has Been Replaced

9. See Preparation 75.

10. The reaction mixture was sonicated for 24 hours. The corresponding tetrazole 2-alkylated product was obtained as the higher Rf. product from the column. The required product was obtained as the lower Rf. product from the column after trituration with diethyl ether.

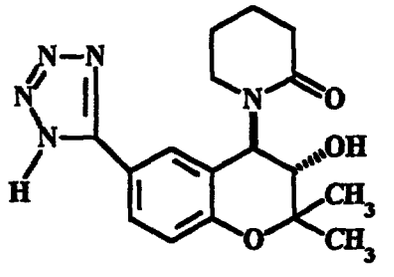
11. See Preparation 70.

12. As footnote (4) except the lower Rf. product from the column was rechromatographed on silica eluting with dichloromethane containing methanol (1.5% up to 5%) and acetic acid (1.5% up to 5%) to provide the required product.

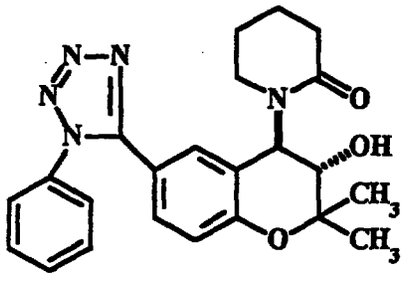
13. The eluant used for column chromatography was toluene containing acetic acid (33% up to 50%). The corresponding tetrazole 2-alkylated product was obtained as the higher Rf. product from the column.
The required product was obtained as the lower Rf. product as a solid.

EXAMPLE 37

(3S,4R/3R,4S)-3,4-Dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-6-(1-phenyl-1H-tetrazol-5-yl)-2H-benzo[b]pyran



1) Sodium t-butoxide
2) $Ph_2I^+Cl^-$



(only one stereoisomer shown)

This Sheet Has Been Replaced



Sodium metal (0.035g) was added to tert-butanol (30ml) and the mixture was heated under reflux for 30 minutes. On cooling to room temperature (3S,4R/3R,4S)-3,4-dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-6-(1H-tetrazol-5-yl)-2H-benzo[b]pyran (see Preparations 60 and 61) (0.5g) was added followed by diphenyliodonium chloride (0.5g) and the mixture was heated under reflux for 10 hours. Sodium hydroxide (0.22g) was added followed by further diphenyliodonium chloride (0.5g) and the mixture was heated under reflux for a further 7 hours. The solution was concentrated in vacuo and the residue was partitioned between dichloromethane (50ml) and 5% aqueous sodium hydroxide (50ml). The layers were separated

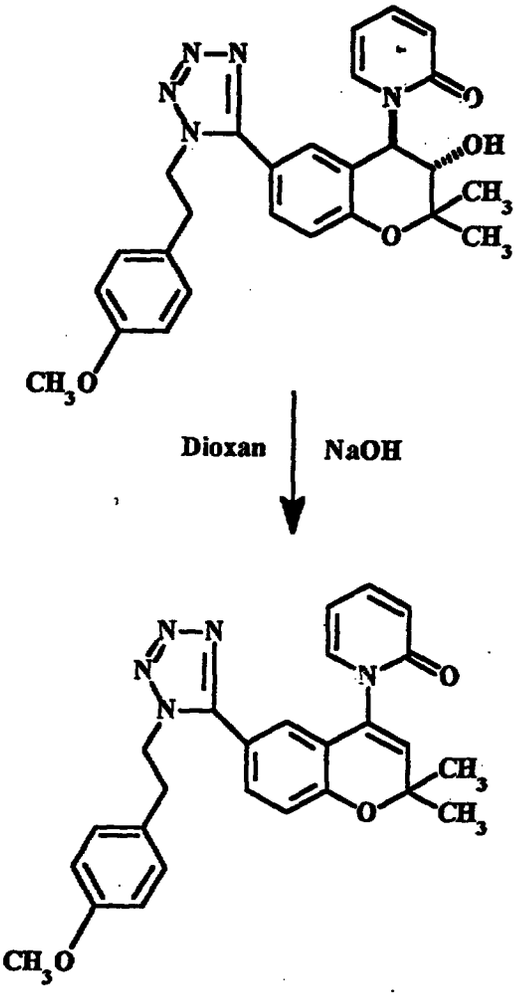
This Sheet Has Been Replaced

and the aqueous layer was extracted with dichloromethane (2 x 50ml). The combined extracts were dried ($MgSO_4$) then concentrated in vacuo to give an oil which was purified by chromatography on silica eluting with dichloromethane containing methanol (1% up to 8%). The product-containing fractions were combined and concentrated in vacuo to give a gum which was triturated with ethyl acetate to give the title compound, 0.005g.

^{1}H-NMR ($CDCl_3$): δ=7.65-7.55(m,3H), 7.50-7.40(m,2H), 7.45-7.25 (m,2H), 6.90-6.80(d,1H), 5.95-5.85(d,1H), 3.85-3.70(m,1H), 3.10-2.90(m,2H), 2.90-2.80(m,1H), 2.60-2.50(m,2H), 1.90-1.60(m,4H), 1.55(s,3H), 1.30(s,3H) ppm.

EXAMPLE 38

2,2-Dimethyl-6-(1-[2-(4-methoxyphenyl)ethyl]-1H-tetrazol-5-yl)-4-(2-oxo-1,2-dihydropyridin-1-yl)-2H-benzo[b]pyran



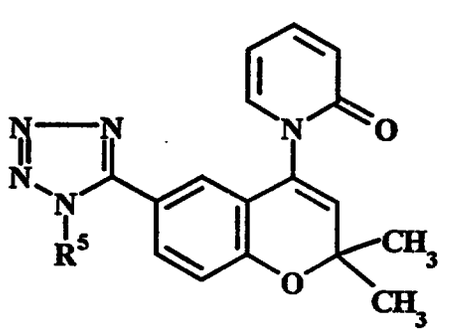
This Sheet Has Been Replaced

A mixture containing (3S,4R/3R,4S)-3,4-dihydro-2,2-dimethyl-3-hydroxy-6-(1-[2-(4-methoxyphenyl)ethyl]-1H-tetrazol-5-yl)-4-(2-oxo-1,2-dihydropyridin-1-yl)-2H-benzo[b]pyran (see Example 8) (0.65g), polymer-supported sodium hydroxide (Merck 1567, 1g) and anhydrous dioxan (30ml) was heated under reflux for 15 minutes. On cooling to room temperature, the mixture was filtered, the dioxan was evaporated in vacuo, the residue was partitioned between water and dichloromethane, the organic layer was separated, concentrated in vacuo and the residue was purified by chromatography on silica eluting with dichloromethane containing methanol (2.5%). The product-containing fractions were combined and concentrated in vacuo to give an oil which was triturated with 2:1 hexane/ethyl acetate to give the title compound as a solid, 0.277g, m.p. 156-158°C. Found: C,68.21; H,5.58; N,15.27; $C_{26}H_{25}N_5O_3$ requires: C,68.56; H,5.53; N,15.37%.

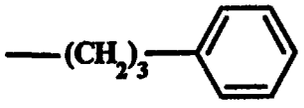
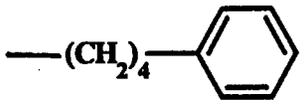
^{1}H-NMR ($CDCl_3$): δ=7.45-7.35(m,1H), 7.25-7.15(dd,1H), 7.00-6.85(m,5H), 6.75-6.70(d,2H), 6.60-6.50(d,1H), 6.30-6.20(t,1H), 5.80(s,1H), 4.60-4.40(m,2H), 3.75(s,3H), 3.20-3.05(m,2H), 1.65(s,3H), 1.55(s,3H) ppm.

EXAMPLES 39 to 46

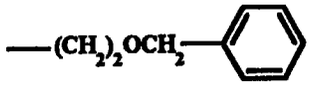
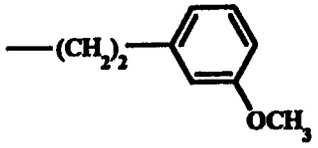
The compounds of the following tabulated Examples of the general formula:-



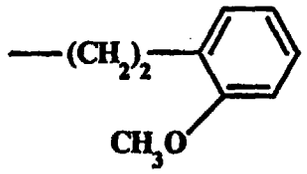
were prepared by similar methods to that of Example 38 using the appropriate starting materials.

Ex.	R^6	Reference for the preparation of the 3,4-dihydro-2H-benzo[b]pyran starting material	m.p. (°C)	Analysis/^{1}H-NMR($CDCl_3$)
39[1]		see Example 14	130-132	Found: C,70.66; H,5.77; N,16.08; $C_{26}H_{25}N_5O_2.0.025\ CH_2Cl_2$ requires: C,70.78; H,5.72; N,15.86%. δ=7.45-7.10(m,8H), 7.00-6.90(m,2H), 6.60-6.50(d,1H), 6.30-6.20(t,1H), 5.80(s,1H), 4.35-4.25(t,2H), 2.75-2.60(m,2H), 2.30-2.15(m,2H), 1.65(s,3H), 1.60(s,3H) ppm.
40[2]		see Example 15	129-131	Found: C,71.37; H,6.00; N,15.20; $C_{27}H_{27}N_5O_2$ requires: C,71.50; H,6.00; N,15.44%. δ=7.50-7.35(m,2H), 7.35-7.10(m,6H), 7.05-6.90(m,2H), 6.60-6.55(d,1H), 6.30-6.20(t,1H), 5.80(s,1H), 4.35-4.25(t,2H), 2.65-2.55(t,2H), 1.95-1.85(m,2H), 1.70-1.50(m,2H), 1.65(s,3H), 1.60(s,3H) ppm.

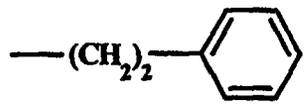
This Sheet Has Been Replaced

Ex.	R^5	Reference for the preparation of the 3,4-dihydro-2H-benzo[b]pyran starting material	m.p. (°C)	Analysis/^{1}H-NMR($CDCl_3$)
41[3]		see Example 16	-	δ=7.70-7.65(d,1H), 7.40-6.90(m,9H), 6.60-6.55(d,1H), 6.15-6.10(t,1H), 5.75(s,1H), 4.60-4.30(m,2H), 4.40(s,2H), 4.00-3.90(m,2H), 1.65(s,3H), 1.55(s,3H) ppm.
42[4]		see Example 18	-	Found: C,67.45; H,5.46; N,14.99; $C_{26}H_{25}N_5O_3$.0.1 CH_2Cl_2 requires: C,67.56; H,5.47; N,15.09%. δ=7.45-7.35(m,1H), 7.20-7.10(m,2H), 6.95-6.90(m,1H), 6.90-6.85(m,2H), 6.75-6.70(dd,1H), 6.60-6.50(m,3H), 6.30-6.20(t,1H), 5.80(s,1H), 4.60-4.45(m,2H), 3.70(s,3H), 3.25-3.10(m,2H), 1.65(s,3H), 1.55(s,3H) ppm.

This Sheet Has Been Replaced

Ex.	R^5	Reference for the preparation of the 3,4-dihydro-2H-benzo[b]pyran starting material	m.p. (°C)	Analysis/^{1}H-NMR($CDCl_3$)
43[4]		see Example 19	-	δ=7.45-7.35(m,1H), 7.35-7.15(m,2H), 7.10-7.05(dd,1H), 6.95-6.85(m,3H), 6.85-6.75(m,2H), 6.65-6.55(d,1H), 6.30-6.20(m,1H), 5.80(s,1H), 4.60-4.50(m,2H), 3.70(s,3H), 3.25-3.10(t,2H), 1.65(s,3H), 1.60(s,3H) ppm.
44[5]	$-CH_2CH_2OCH_3$	see Example 20	141-144	Found: C,63.57; H,5.72; N,18.35; $C_{20}H_{21}N_5O_3$ requires: C,63.31; N,5.72; H,18.46%. δ=7.70-7.65(dd,1H), 7.50-7.40(m,1H), 7.30-7.20(m,2H), 7.05-6.95(d,1H), 6.65-6.55(d,1H), 6.30-6.20(t,1H), 5.75(s,1H), 4.55-4.35(m,2H), 3.90-3.80(m,2H), 3.15(s,3H), 1.65(s,3H), 1.60(s,3H) ppm.

This Sheet Has Been Replaced

Ex.	R^6	Reference for the preparation of the 3,4-dihydro-2H-benzo[b]pyran starting material	m.p. (°C)	Analysis/^{1}H-NMR($CDCl_3$)
45[6]	CH_3	see Example 25	205-210	Found: C,64.48; H,5.09; N,20.57; $C_{18}H_{17}N_5O_2$ requires: C,64.46; H,5.11; N,20.88%. δ=7.55-7.40(m,2H), 7.25-7.20(d,1H), 7.05-7.00(m,2H), 6.65-6.60(d,1H), 6.30-6.25(t,1H), 5.80(s,1H), 4.05(s,3H), 1.65(s,3H), 1.60(s,3H) ppm.
46[4]		see Example 21	-	δ=7.45-7.35(m,1H), 7.30-7.20(m,5H), 7.10-6.95(m,3H), 6.90(d,1H), 6.55-6.50(d,1H), 6.25-6.20(t,1H), 5.80(s,1H), 4.60-4.40(m,2H), 3.30-3.10(m,2H), 1.65(s,3H), 1.55(s,3H) ppm.

This Sheet Has Been Replaced

1. The required product was obtained after trituration with diethyl ether.

2. The reaction mixture was cooled to room temperature and the dioxan removed in vacuo to give the required compound as an oil which crystallised on standing.

3. The required product was obtained after trituration with hexane.

4. The required product was obtained as a foam after the column fractions had been concentrated in vacuo.

5. The reaction mixture was cooled to room temperature, the solvent removed in vacuo and the residue partitioned between dichloromethane and water. The organic layer was separated and concentrated in vacuo to give an oil which afforded the required product after trituration with diethyl ether.

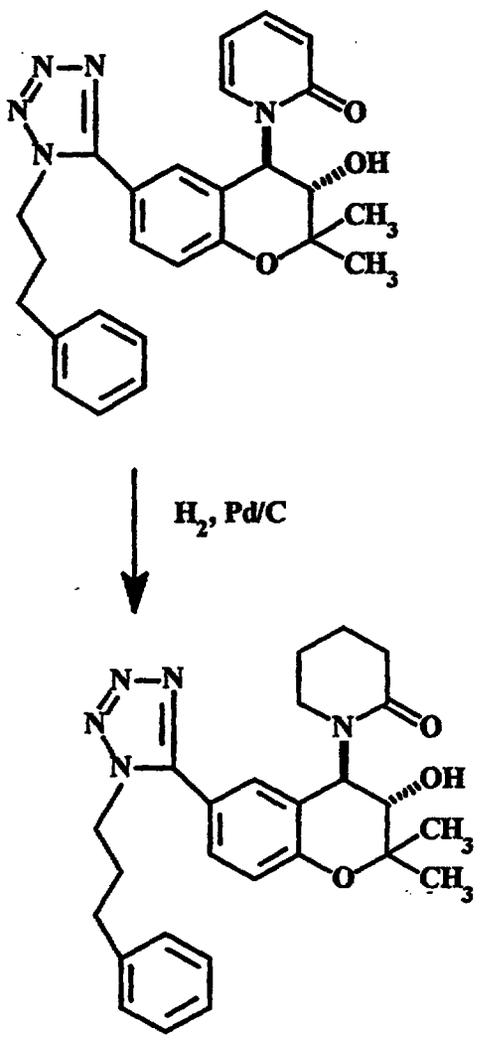
6. The hot reaction mixture was filtered, cooled and concentrated in vacuo. The residue was crystallised from ethyl acetate to provide the required product.

This Sheet Has Been Replaced



EXAMPLE 47

(3S,4R/3R,4S)-3,4-Dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-6-(1-[3-phenylprop-1-yl)-1H-tetrazol-5-yl)-2H-benzo[b]pyran



This Sheet Has Been Replaced



(only one stereoisomer shown)

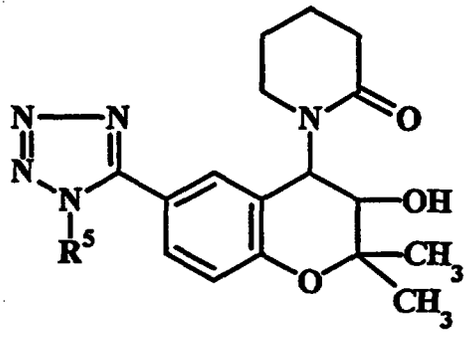
A mixture containing (3S,4R/3R,4S)-3,4-dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxo-1,2-dihydropyridin-1-yl)-6-(1-[3-phenylprop-1-yl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran (see Example 14) (0.8g), 10% palladium-on-carbon (0.1g) and ethanol (40ml) was hydrogenated at 50 psi (345kPa) for 24 hours. A further batch of 10% palladium-on-carbon (0.1g) was added and the hydrogenation continued for a further 24 hours. The mixture was filtered through a cellulose-based filter aid

and the filtrate concentrated in vacuo to give a solid which was triturated with diethyl ether to give the title compound as a colourless solid, 0.66g, m.p. 115-122°C. Found: C,66.19; H,7.25; N,13.96; $C_{26}H_{31}N_5O_3.C_2H_5OH$ requires: C,66.25; H,7.35; N,13.80%.

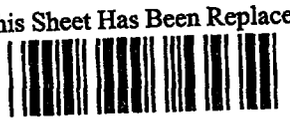
^{1}H-NMR ($CDCl_3$): δ=7.40-7.20(m,5H), 7.15-7.10(d,2H), 7.00-6.95(d,1H), 6.05-5.95(d,1H), 3.85-3.80(m,1H), 3.80-3.65(m,2H), 3.45-3.40(m,1H), 3.15-3.00(m,1H), 3.00-2.85(m,1H), 2.75-2.65(m,2H), 2.65-2.55(m,2H), 2.35-2.20(m,2H), 1.90-1.60(m,4H), 1.55(s,3H), 1.35(s,3H) ppm.

EXAMPLES 48 to 57

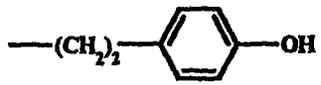
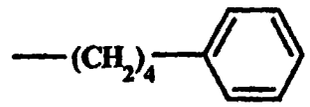
The compounds of the following tabulated Examples of the general formula:-



This Sheet Has Been Replaced



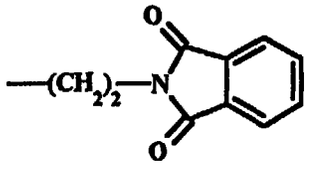
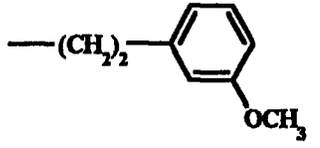
were prepared by similar methods to that of Example 47 using the appropriate starting materials.

Ex.	Stereo-chem.	R^6	Reference for the preparation of the pyridone starting material	m.p. (°C)	Analysis/^{1}H-NMR($CDCl_3$)
48[2]	3S,4R/ 3R,4S		see Example 72	217-220	Found: C,64.28; H,6.45; N,14.84; $C_{25}H_{29}N_5O_4$ requires: C,64.78; H,6.31; N,15.11%. (d_6-DMSO): δ=9.20(s,1H), 7.35-7.30 (d,1H), 7.15(s,1H), 6.95-6.90(d,1H), 6.75-6.70(d,2H), 6.55-6.50(d,2H), 5.75-5.70(d,1H), 6.60-5.55(d,1H), 4.65-4.45(m,2H), 3.70-3.65(m,1H), 3.15-3.10(m,1H), 3.00-2.85(m,2H), 2.70-2.60(m,1H), 2.40-2.30(m,2H), 1.75-1.60(m,3H), 1.45(s,3H), 1.15(s,3H) ppm.
49[2]	3S,4R/ 3R,4S		see Example 15	167-169	Found: C,68.18; H,6.98; N,14.69; $C_{27}H_{33}N_5O_3$ requires: C,68.19; H,6.99; N,14.73%. δ=7.45-7.10(m,5H), 7.10-7.05(d,2H), 7.00-6.95(d,1H), 6.00-5.95(d,1H), 4.40-4.30(t,2H), 3.90-3.75(d,1H), 3.50-3.40(brs,1H), 3.10-2.90(m,2H), 2.65-2.50(m,4H), 2.00-1.50(m,8H), 1.55(s,3H), 1.30(s,3H) ppm.

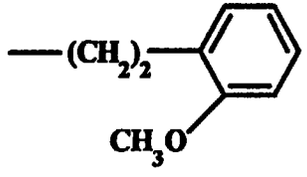
This Sheet Has Been Replaced

Ex.	Stereo-chem.	R^5	Reference for the preparation of the pyridone starting material	m.p. (°C)	Analysis/^{1}H-NMR($CDCl_3$)
50[2]	3S,4R/ 3R,4S	$-(CH_2)_3CO_2C_2H_5$	see Example 9	-	Found: C,60.06; H,6.37; N,15.02; $C_{23}H_{31}N_5O_5$ requires: C,60.38; H,6.83; N,15.31%. δ=7.55-7.45(d,1H), 7.40(s,1H), 7.05-6.95(d,1H), 6.05-5.95((d,1H), 4.50-4.40(t,2H), 4.15-4.05(q,2H), 3.90-3.80(m,1H), 3.40(s,1H), 3.10-2.90(m,2H), 2.65-2.50(m,2H), 2.45-2.35(m,2H), 2.30-2.20(m,2H), 1.95-1.70(m,4H), 1.50(s,3H), 1.30(s,3H), 1.30-1.20(t,3H) ppm.
51[2]	3S,4R/ 3R,4S	$-CH_2CO_2C_2H_5$	see Example 10	-	δ=7.50-7.45(d,1H), 7.30(s,1H), 7.00-6.95(d,1H), 5.95-5.90(d,1H), 5.20-5.05(ABq,2H), 4.35-4.25(q,2H), 3.85-3.80(d,1H), 3.50-3.40(brs,1H), 3.15-3.05(m,1H), 2.95-2.90(m,1H), 2.60-2.50(m,2H), 1.95-1.60(m,4H), 1.50(s,3H), 1.30-1.20(m,6H) ppm.

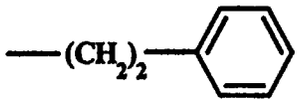
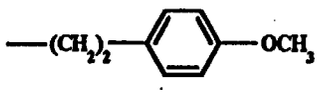
This Sheet Has Been Replaced

Ex.	Stereo-chem.	R^5	Reference for the preparation of the pyridone starting material	m.p. (°C)	Analysis/^{1}H-NMR($CDCl_3$)
52[2,3]	3S,4R/ 3R,4S		see Example 17	-	(d_6-DMSO): δ=7.85-7.70(m,4H), 7.30-7.25(d,1H), 7.20(s,1H), 6.70-6.65 (d,1H), 5.70-5.60(d,1H), 5.55(d,1H), 4.75-4.55(m,2H), 3.90-3.75(m,2H), 3.70-3.60(m,1H), 3.20-3.10(m,1H), 2.75-2.65(m,1H), 2.50-2.30(m,2H), 1.80-1.50(m,4H), 1.40(s,3H), 1.10(s,3H) ppm.
53[2]	3S,4R/ 3R,4S		see Example 18	195-197	Found: C,65.31; H,6.53; N,14.56; $C_{26}H_{31}N_5O_4$.0.1 $(C_2H_5)_2O$ requires: C,65.38; H,6.65; N,14.44%. δ=7.15-7.10(m,1H), 7.05-6.95(m,2H), 6.90-6.85(d,1H), 6.75-6.70(dd,1H), 6.50-6.45(d,1H), 6.40(s,1H), 5.95-5.90(d,1H), 4.65-4.50(m,2H), 3.85-3.75(m,1H), 3.70(s,3H), 3.35-3.30(m,1H), 3.30-3.10(m,2H), 3.05-2.85(m,2H), 2.60-2.50(m,2H), 1.90-1.70(m,4H), 1.55(s,3H), 1.30(s,3H) ppm.

This Sheet Has Been Replaced

Ex.	Stereo-chem.	R^5	Reference for the preparation of the pyridone starting material	m.p. (°C)	Analysis/^{1}H-NMR($CDCl_3$)
54[2,4]	3S,4R/ 3R,4S		see Example 19	190-192	Found: C,65.26; H,6.66; N,14.63; $C_{26}H_{31}N_5O_4$.0.125 $(C_2H_5)_2O$ requires: C,65.37; H,6.67; N,14.38%. δ=7.25-7.15(m,1H), 7.15-7.10(m,2H), 6.90-6.70(m,4H), 5.95-5.90(d,1H), 4.70-4.45(m,2H), 3.85-3.75(m,1H), 3.70(s,3H), 3.50-3.40(m,1H), 3.25-3.10(m,2H), 3.05-2.90(m,2H), 2.60-2.50(m,2H), 1.90-1.70(m,4H), 1.55(s,3H), 1.30(s,3H) ppm.
55[2]	3S,4R/ 3R,4S	$-CH_2CH_2OCH_3$	see Example 20	200-202	Found: C,59.69; H,6.76; N,17.29; $C_{20}H_{27}N_5O_4$ requires: C,59.83; H,6.78; N,17.44%. δ=7.65-7.60(d,1H), 7.50(s,1H), 7.00-6.95(d,1H), 6.05-5.95(d,1H), 4.55-4.40(m,2H), 3.95-3.90(t,2H), 3.90-3.80(d,1H), 3.45-3.35(brs,1H), 3.30(s,3H), 3.10-2.90(m,2H), 2.65-2.50(m,2H), 1.90-1.65(m,4H), 1.55(s,3H), 1.30(s,3H) ppm.

This Sheet Has Been Replaced

Ex.	Stereo-chem.	R^5	Reference for the preparation of the pyridone starting material	m.p. (°C)	Analysis/^{1}H-NMR($CDCl_3$)
56[2,5]	3S,4R/ 3R,4S		see Example 21	168-170	Found: C,66.98; H,6.52; N,15.56; $C_{25}H_{29}N_5O_3$ requires: C,67.09; H,6.53; N,15.65%. δ=7.30-7.15(m,3H), 7.10-6.85(m,5H), 5.95-5.90(d,1H), 4.65-4.50(m,2H), 3.85-3.75(m,1H), 3.65(d,1H), 3.30-3.15(m,2H), 3.10-2.95(m,1H), 2.95-2.85(m,1H), 2.60-2.50(t,2H), 1.90-1.60(m,4H), 1.50(s,3H), 1.30(s,3H) ppm.
57[2,6]	3S,4R/ 3R,4S		see Example 8	178-180	Found: C,63.92; H,6.54; N,14.41; $C_{26}H_{31}N_5O_4.0.5\ H_2O$ requires: C,64.18; H,6.63; N,14.39%. δ=7.15(s,1H), 7.10-7.00(dd,1H), 6.90-6.80(m,3H), 6.80-6.70(d,2H), 6.00-5.90(d,1H), 4.60-4.50(t,2H), 3.90-3.75(m,1H), 3.80(s,3H), 3.50-3.45(d,1H), 3.25-3.10(m,2H), 3.10-2.90(m,2H), 2.60-2.50(t,2H), 1.90-1.65(m,4H), 1.50(s,3H), 1.30(s,3H) ppm.

This Sheet Has Been Replaced

This Sheet Has Been Replaced

1. Except where stated.

2. Hydrogenation carried out at 50°C.

3. The reaction mixture was filtered, the filtrate concentrated in vacuo and the solid obtained triturated with hot methanol, filtered and dried to provide the required product.

4. The filtrate obtained after passage through the cellulose-based filter aid was concentrated in vacuo to give an oil which was purified by chromatography on silica eluting with dichloromethane containing methanol (2.5%). The product-containing fractions were combined and concentrated in vacuo to give a foam which was triturated with diethyl ether to give the required product as a solid.

5. The required product was obtained after recrystallisation of the crude product from ethyl acetate.

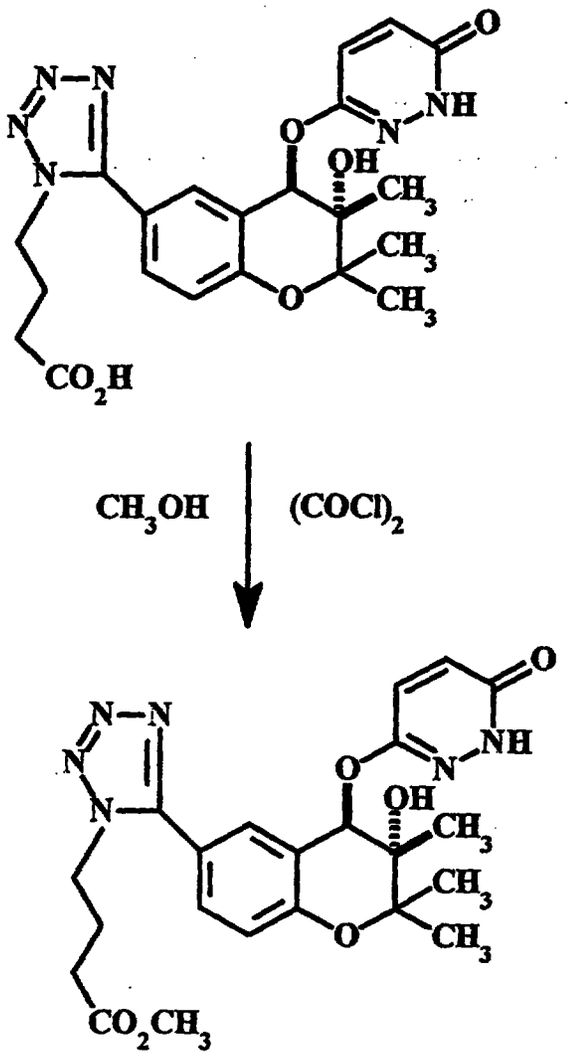
6. After the hydrogenation the reaction mixture was filtered through a cellulose-based filter aid and the filtrate concentrated in vacuo to give a gum which was azeotroped with dichloromethane to give a foam. The foam was taken up in ethyl acetate whereupon a solid precipitated which was purified further by chromatography on silica eluting with dichloromethane containing methanol (5%). The product-containing fractions were combined and concentrated in vacuo to give a gum which was azeotroped with dichloromethane to give a foam. The foam was crystallised from ethyl acetate to give a solid which was further

This Sheet Has Been Replaced

purified by chromatography on silica eluting with ethyl acetate containing dichloromethane (20% down to 0%). The product-containing fractions were combined and concentrated in vacuo to give a gum which was azeotroped with dichloromethane. The resulting solid was triturated with diethyl ether and dried to give the required product as a solid.

EXAMPLE 58

(3S,4R)-3,4-Dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-6-(1-[3-methoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran

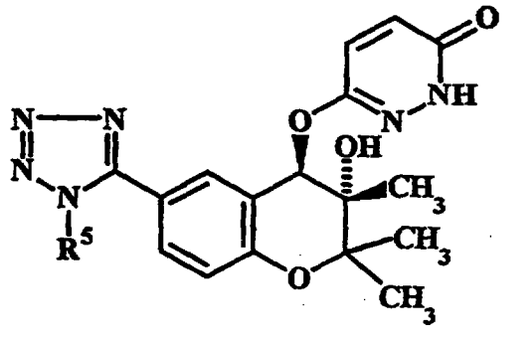


This Sheet Has Been Replaced

Oxalyl chloride (10 drops) was added to a solution of (3S,4R)-6-(1-[3-carboxyprop-1-yl]-1H-tetrazol-5-yl)-3,4-dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran (see Preparation 48) (0.15g) in anhydrous tetrahydrofuran (5ml). After 10 minutes the mixture was concentrated in vacuo and the residue azeotroped with anhydrous dichloromethane (3 x 5ml). Dichloromethane (4ml) was added followed by methanol (0.5ml). After 15 minutes the solution was concentrated in vacuo and the residue purified by chromatography on silica eluting with dichloromethane containing methanol (2.5% up to 5%). The product-containing fractions were concentrated in vacuo to give an oil which was triturated with hexane to give the title compound as a foam, 0.13g.
^{1}H-NMR ($CDCl_3$): δ=7.75(s,1H), 7.60-7.55(dd,1H), 7.15-7.10(d,1H), 7.05-6.95(m,2H), 6.00(s,1H), 4.50-4.40(m,2H), 3.65(s,3H), 3.55-3.30(brs,1H), 2.50-2.40(m,2H), 2.30-2.20(m,2H), 1.50(s,3H), 1.45(s,3H), 1.30(s,3H) ppm.

EXAMPLES 59 to 61

The compounds of the following tabulated Examples of the general formula:-



were prepared by similar methods to that of Example 58 using the appropriate starting materials.

Ex.	R^6	m.p. (°C)	Analysis/^{1}H-NMR($CDCl_3$)
59[1]	$-(CH_2)_3-CO_2CH_2CF_3$	-	Found: C,50.08; H,4.66; N,14.94; $C_{23}H_{25}F_3N_6O_6.0.2\ CH_2Cl_2$ requires: C,50.16; H,4.61; N,15.13%. δ=7.70(s,1H), 7.65-7.55(dd,1H), 7.15-7.10(d,1H), 7.10-6.95(m,2H), 6.05(s,1H), 4.50-4.35(m,4H), 3.45(s,1H), 2.60-2.50(m,2H), 2.35-2.20(m,2H), 1.50(s,3H), 1.45(s,3H), 1.30(s,3H) ppm.
60[2]		-	δ=10.95-10.85(brs,1H), 7.80-7.75(d,1H), 7.65-7.55(dd,1H), 7.45-7.30(m,5H), 7.20-7.15(d,1H), 7.10-7.00(m,2H), 6.05(s,1H), 5.10(s,2H), 4.55-4.45(m,2H), 3.40(s,1H), 2.55-2.50(m,2H), 2.40-2.25(m,2H), 1.55(s,3H), 1.50(s,3H), 1.35(s,3H) ppm.
61[3]		-	Found: C,63.04; H,5.62; N,14.43; $C_{30}H_{32}N_6O_6$ requires: C,62.92; H,5.63; N,14.68%. δ=11.00-10.90(brs,1H), 7.70(d,1H), 7.55-7.50(dd,1H), 7.15-7.10(d,1H), 7.10-7.05(d,1H), 7.00-6.90(m,2H), 6.85(s,1H), 6.75-6.70(dd,1H), 5.95(s,1H), 4.55-4.45(t,2H), 3.45-3.40(s,1H), 2.90-2.80(m,4H), 2.70-2.60(t,2H), 2.40-2.25(m,2H), 2.10-2.00(m,2H), 1.45(s,3H), 1.40(s,3H), 1.30(s,3H) ppm.

This Sheet Has Been Replaced

This Sheet Has Been Replaced

1. Pyridine was added together with 2,2,2-trifluoroethanol. No trituration with hexane was carried out.

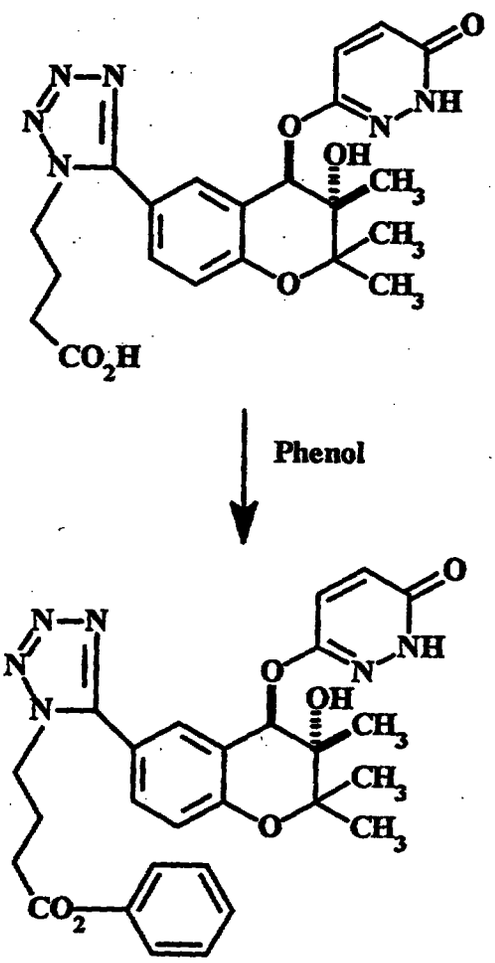
2. Pyridine was added together with benzyl alcohol. The product obtained from the column was triturated with diethyl ether to provide the required product.

3. Pyridine was added together with 5-indanol. No trituration with hexane was carried out.

This Sheet Has Been Replaced

EXAMPLE 62

(3S,4R)-3,4-Dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-6-(1-[3-phenoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



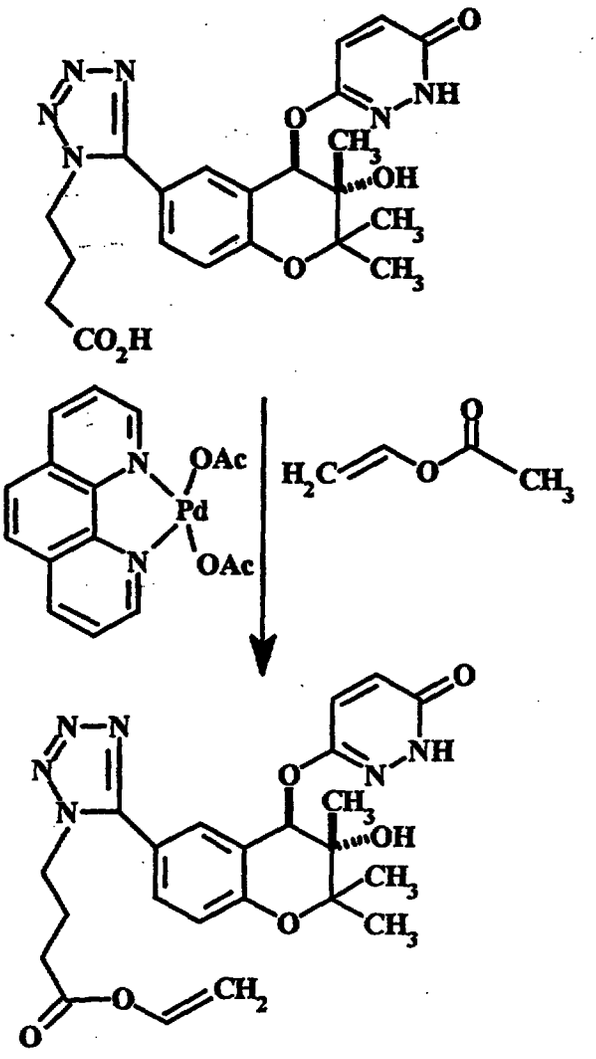
This Sheet Has Been Replaced

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.092g) was added to a solution of (3S,4R)-6-(1-[3-carboxyprop-1-yl]-1H-tetrazol-5-yl)-3,4-dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran (see Preparation 48) (0.2g) and triethylamine (0.05g) in anhydrous dichloromethane (5ml) and the mixture was stirred at room temperature for 1.75 hours. Phenol (0.06g) was added and the mixture was stirred at room temperature for 18 hours then concentrated in vacuo. The residue was purified by chromatography on silica eluting with dichloromethane containing methanol (2.5% up to 5%). The product-containing fractions were combined and concentrated in vacuo to give the title compound as a foam, 0.042g.

^{1}H-NMR ($CDCl_3$): δ=7.75(d,1H), 7.80-7.75(dd,1H), 7.40-7.30(m,2H), 7.30-7.20(m,1H), 7.10-6.90(m,5H), 5.95(s,1H), 4.55-4.50(m,2H), 3.50(brs,1H), 2.75-2.65(m,2H), 2.40-2.30(m,2H), 1.50(s,3H), 1.45(s,3H), 1.30(s,3H) ppm.

EXAMPLE 63

(3S,4R)-3,4-Dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-6-(1-[3-vinyloxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



This Sheet Has Been Replaced

A mixture containing (3S,4R)-6-(1-[3-carboxyprop-1-yl]-1H-tetrazol-5-yl)-3,4-dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran (see Preparation 48) (0.5g), vinyl acetate (5ml), 1,10-phenanthrolinylpalladium(II) acetate (see Tetrahedron, 28, 233(1972)) (0.05g), dichloromethane (10ml) and anhydrous tetrahydrofuran (10ml) was heated under reflux for 2 days. The mixture was concentrated in vacuo and the residue was purified by chromatography on silica eluting with ethyl acetate. The product-containing fractions were combined and concentrated in vacuo to give the title compound as a foam, 0.18g. Found: C,57.07; H,5.48; N,17.24; $C_{22}H_{26}N_6O_6$ requires: C,57.25; H,5.43; N,17.42%.

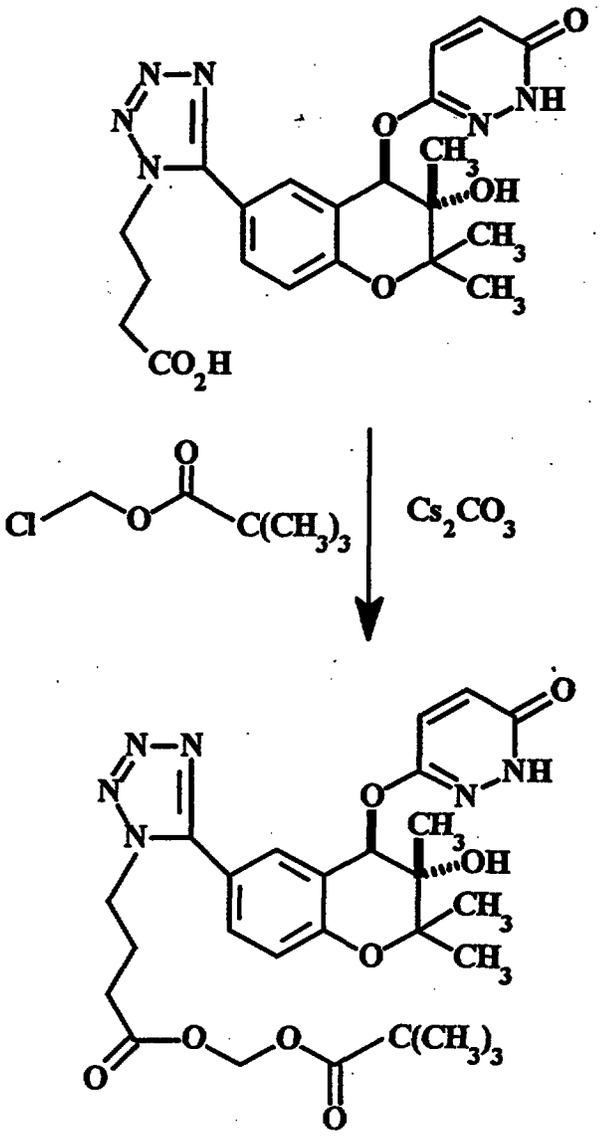
^{1}H-NMR ($CDCl_3$): δ=11.30-11.25(brs,1H), 7.75(d,1H), 7.65-7.55(dd,1H), 7.25-7.10(m,2H), 7.10-7.00(m,2H), 6.05(s,1H), 4.95-4.85(dd,1H), 4.65-4.60(dd,1H), 4.55-4.45(t,2H), 3.60(brs,1H), 2.60-2.50(t,2H), 2.40-2.25(m,2H), 1.60(s,3H), 1.50(s,3H), 1.35(s,3H) ppm.

This Sheet Has Been Replaced



EXAMPLE 64

(3S,4R)-3,4-Dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-6-(1-[3-(pivaloyloxymethoxycarbonyl)prop-1-yl]-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



This Sheet Has Been Replaced

Cesium carbonate (0.18g) was added to a solution of (3S,4R)-6-(1-[3-carboxyprop-1-yl]-1H-tetrazol-5-yl)-3,4-dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran (see Preparation 48) (0.5g) in anhydrous N,N-dimethylacetamide (20ml) and the mixture was stirred with heating until an almost homogeneous solution was obtained. On cooling to room temperature pivalic acid chloromethyl ester (0.18ml) was added and the mixture was stirred at room temperature for 3 days then concentrated in vacuo and the residue partitioned between dichloromethane (100ml) and ice-cold 1M hydrochloric acid (50ml). The layers were separated, the dichloromethane layer dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography on silica eluting with ethyl acetate. The product-containing fractions were combined and concentrated in vacuo to give the title compound as a foam, 0.39g, m.p. 90-100°C. Found: C,56.87; H,6.06; N,14.76; $C_{27}H_{34}N_6O_8$ requires: C,56.83; H,6.00; N,14.73%.

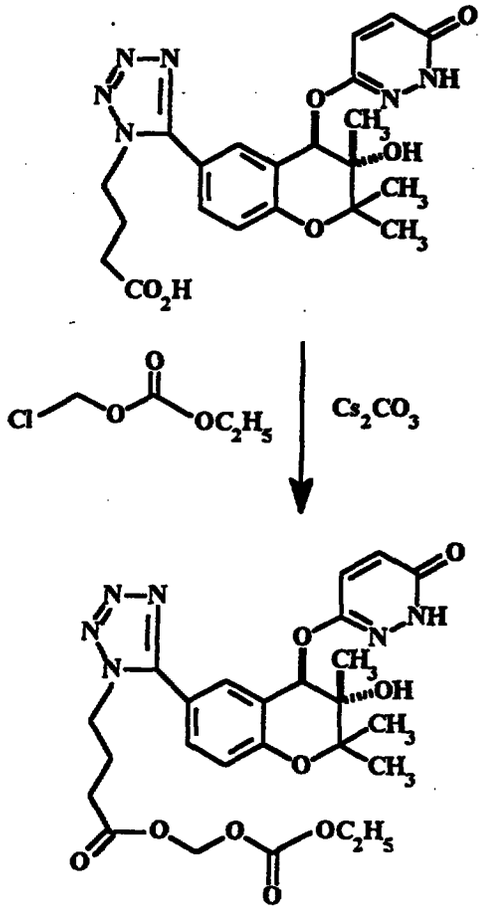
^{1}H-NMR ($CDCl_3$): δ=11.30-11.25(brs,1H), 7.70(d,1H), 7.55-7.45(dd,1H), 7.15-7.10(d,1H), 7.00-6.90(m,2H), 6.00(s,1H), 5.70-5.65(ABq,2H), 4.50-4.40(t,2H), 3.60-3.55(brs,1H), 2.50-2.40(m,2H), 2.25-2.15(m,2H), 1.50(s,3H), 1.45(s,3H), 1.30(s,3H), 1.15(s,9H) ppm.

This Sheet Has Been Replaced



EXAMPLE 65

(3S,4R)-3,4-Dihydro-6-(1-[3-(ethoxycarbonyloxy-methoxycarbonyl)prop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran



This Sheet Has Been Replaced

Cesium carbonate (0.18g) was added to a solution of (3S,4R)-6-(1-[3-carboxyprop-1-yl]-1H-tetrazol-5-yl)-3,4-dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran (see Preparation 48) (0.5g) in anhydrous N,N-dimethylacetamide (20ml) and the mixture was stirred with heating until an almost homogeneous solution was obtained. On cooling to room temperature chloromethyl ethyl carbonate (see Preparation 77) (0.17g) was added and the mixture was stirred at room temperature for 24 hours then partitioned between diethyl ether (100ml) and ice-cold 1M hydrochloric acid (50ml). The layers were separated, the ethereal layer washed with water (50ml) and saturated aqueous sodium chloride solution (50ml), then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography on silica eluting with dichloromethane containing methanol (0% up to 6%). The product-containing fractions were combined and concentrated in vacuo to give the title compound, 0.06g. Found: C,53.84; H,5.55; N,14.97; $C_{25}H_{30}N_6O_9$ requires: C,53.76; H,5.41; N,15.05%.

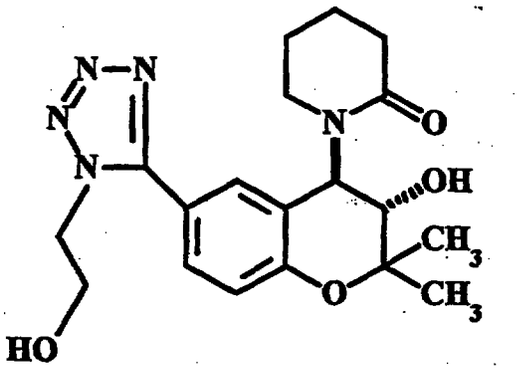
^{1}H-NMR ($CDCl_3$): δ=11.65-11.55(brs,1H), 7.70(d,1H), 7.60-7.55(dd,1H), 7.20-7.15(d,1H), 7.10-6.95(m,2H), 6.10(s,1H), 5.70(s,2H), 4.50-4.40(t,2H), 4.30-4.20(q,2H), 3.80(brs,1H), 2.55-2.45(m,2H), 2.30-2.20(m,2H), 1.55(s,3H), 1.50(s,3H), 1.35-1.25(m,6H) ppm.

This Sheet Has Been Replaced

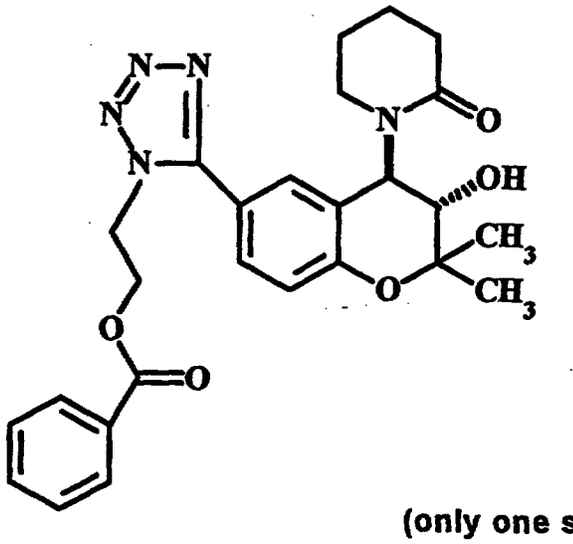


EXAMPLE 66

(3S,4R/3R,4S)-6-(1-[2-Benzoyloxyethyl]-1H-tetrazol-5-yl)-3,4-dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-2H-benzo[b]pyran



pyridine | PhCOCl



(only one stereoisomer shown)

This Sheet Has Been Replaced

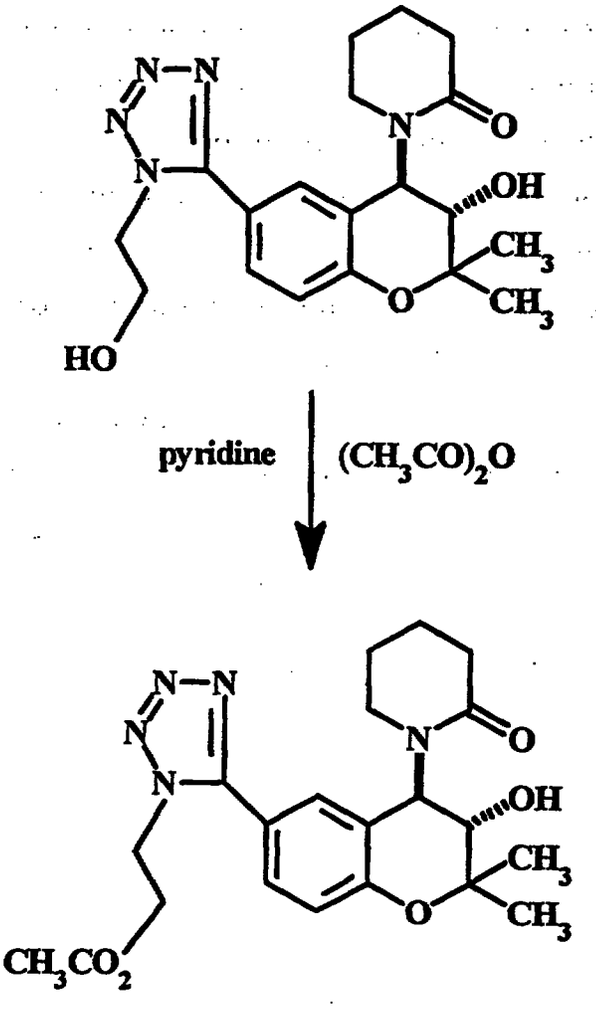
A mixture containing (3S,4R/3R,4S)-3,4-dihydro-2,2-dimethyl-3-hydroxy-6-(1-[2-hydroxyethyl]-1H-tetrazol-5-yl)-4-(2-oxopiperidin-1-yl)-2H-benzo[b]pyran (see Example 71) (0.211g), benzoyl chloride (0.078g) and pyridine (1ml) was shaken in a vial for 30 minutes. The mixture was added to water (5ml) and extracted with ethyl acetate (3 x 5ml). The combined ethyl acetate extracts were concentrated in vacuo to give a colourless solid which was purified by chromatography on silica eluting with dichloromethane containing methanol (5%). The product-containing fractions were combined and concentrated in vacuo to give the title compound as a solid, 0.115g, m.p. 233-236°C. Found: C,63.31; H,5.63; N,14.21; $C_{26}H_{29}N_5O_5$ requires: C,63.53; H,5.95; N,14.25%. ^{1}H-NMR ($CDCl_3$): δ=7.85-7.80(d,2H), 7.60-7.55(m,1H), 7.50-7.35(m,4H), 6.90(d,1H), 5.95-5.90(d,1H), 4.90-4.65(m,4H), 3.85-3.75(m,1H), 3.40(d,1H), 3.10-2.90(m,2H), 2.60-2.50(m,2H), 1.90-1.70(m,4H), 1.50(s,3H), 1.25(s,3H) ppm.

This Sheet Has Been Replaced



EXAMPLE 67

(3S,4R/3R,4S)-6-(1-[2-Acetyloxyethyl]-1H-tetrazol-5-yl)-3,4-dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-2H-benzo[b]pyran



This Sheet Has Been Replaced

(only one stereoisomer shown)

A mixture containing (3S,4R/3R,4S)-3,4-dihydro-2,2-dimethyl-3-hydroxy-6-(1-[2-hydroxyethyl]-1H-tetrazol-5-yl)-4-(2-oxopiperidin-1-yl)-2H-benzo[b]pyran (see Example 71) (0.2g), acetic anhydride (0.047g) and pyridine (2ml) was shaken in a vial for 30 minutes. The mixture was added to water (5ml) and extracted with ethyl acetate (3 x 5ml). The combined extracts were concentrated in vacuo to give a foam which was purified by chromatography on silica eluting with dichloromethane containing methanol (5%). The product-containing fractions were combined and concentrated in vacuo to give the title compound as a foam, 0.117g. Found: C,56.05; H,5.90; N,15.18; $C_{21}H_{27}N_5O_6.0.33CH_2Cl_2$ requires: C,55.96; H,6.09; N,15.29%.

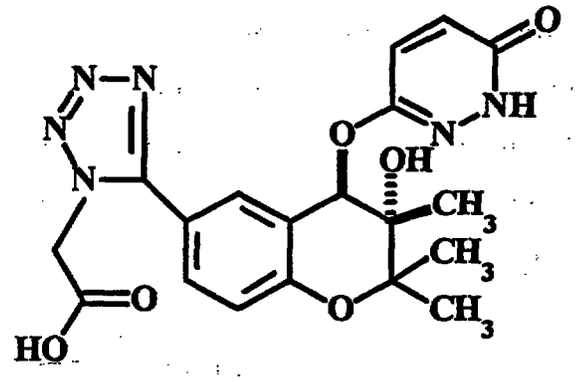
^{1}H-NMR ($CDCl_3$): δ=7.55-7.45(d,1H), 7.35(s,1H), 7.05-6.95(d,1H), 6.05-5.95(d,1H), 4.70-4.60(m,2H), 4.55-4.45(m,2H), 3.90-3.80(m,1H), 3.35-3.30(d,1H), 3.15-2.90(m,2H), 2.60-2.50(m,2H), 1.90(s,3H), 1.95-1.70(m,4H), 1.55(s,3H), 1.30(s,3H) ppm.

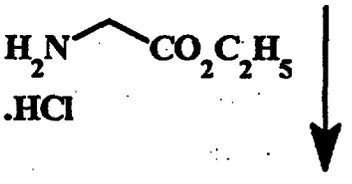
This Sheet Has Been Replaced

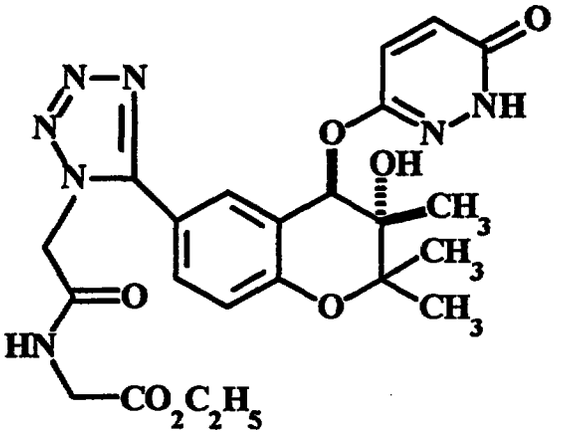


EXAMPLE 68

(3S,4R)-3,4-Dihydro-6-(1-[N-(ethoxycarbonylmethyl)carbamoyl-methyl]-1H-tetrazol-5-yl)-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran







This Sheet Has Been Replaced

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.192g) was added to a solution of (3S,4R)-6-(1-carboxymethyl-1H-tetrazol-5-yl)-3,4-dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran (see Preparation 69) (0.214g), N-methylmorpholine (0.162g), 1-hydroxybenzotriazole (0.068g) and ethyl glycinate hydrochloride (0.084g) in anhydrous dichloromethane (5ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 3 days. The mixture was concentrated in vacuo and the residue partitioned between ethyl acetate (30ml) and water (30ml). The layers were separated and the ethyl acetate layer was washed with saturated aqueous sodium chloride solution (30ml) then dried ($MgSO_4$) and concentrated in vacuo to give the title compound, 0.09g, m.p. 130-140°C.

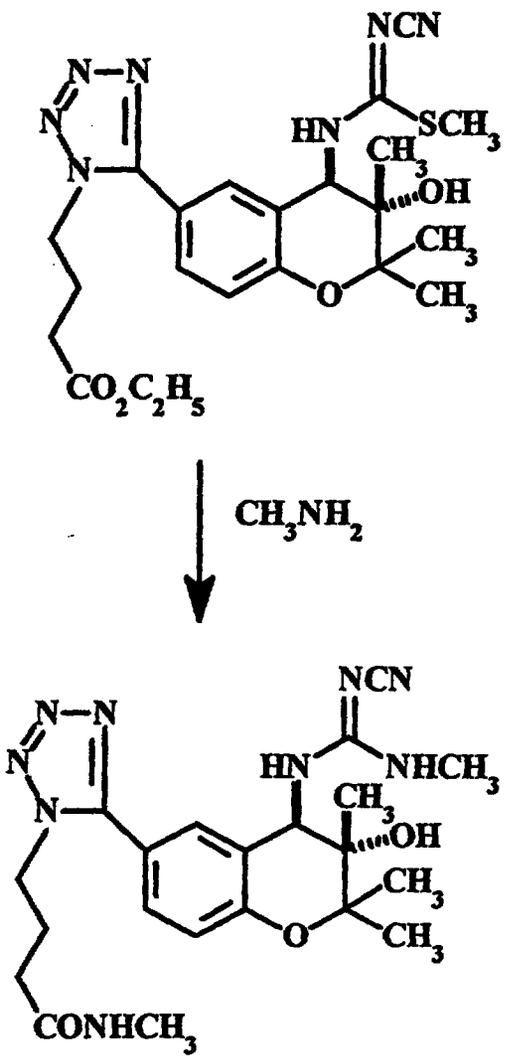
^{1}H-NMR ($CDCl_3$): δ=11.85-11.60(brs,1H), 7.85(s,1H), 7.80-7.60(m,2H), 7.15-7.10(d,1H), 7.05-6.95(m,2H), 5.95(s,1H), 5.30-5.10(ABq,2H), 4.25-4.10(q,2H), 4.10-4.00(d,2H), 2.20-1.70(brs,1H), 1.55(s,3H), 1.50(s,3H), 1.35(s,3H), 1.30-1.20(t,3H) ppm.

This Sheet Has Been Replaced



EXAMPLE 69

(3S,4R)-4-(2-Cyano-3-methylguanidino)-3,4-dihydro-3-hydroxy-6-(1-[3-(N-methylcarbamoyl)prop-1-yl]-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



This Sheet Has Been Replaced

A mixture of (3S,4R)-4-(3-cyano-2-methylisothioureido)-3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-2,2,3-trimethyl-2H-benzo[b]pyran (see Example 75) (0.2g) and methylamine (2ml of a 33% solution in industrial methylated spirit) was allowed to stand at room temperature for 4 hours. Further methylamine (2ml of a 33% solution in industrial methylated spirit) was added and the mixture was allowed to stand for a further 3 days. The solvent was removed in vacuo and the resulting foam was purified by chromatography on silica eluting with dichloromethane containing methanol (5% up to 10%). The product-containing fractions were combined and concentrated in vacuo to give the title compound as a solid, 0.15g, m.p. 143-146°C.

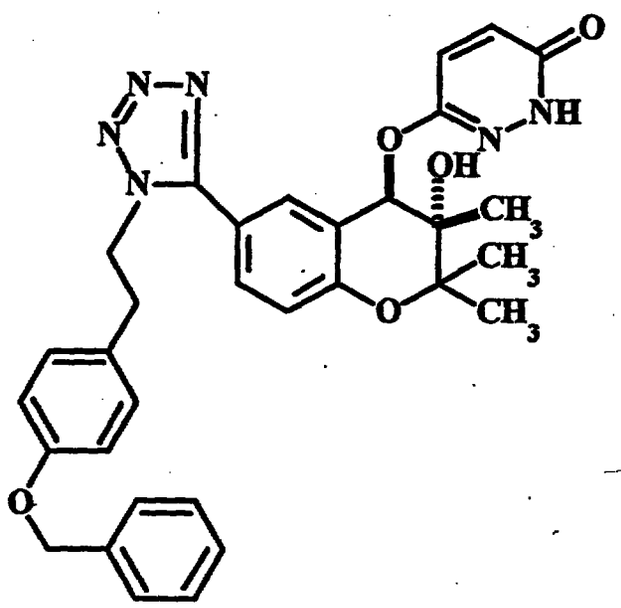
^{1}H-NMR (d_6-DMSO): δ=7.75-7.65(m,1H), 7.55-7.45(m,2H), 7.30-7.25(brs,1H), 6.95-6.85(m,2H), 5.40-5.15(brm,2H), 4.45-4.35(m,2H), 2.80(d,3H), 2.10-1.95(m,4H), 1.40(s,3H), 1.30(s,3H), 1.05(s,3H) ppm.

This Sheet Has Been Replaced

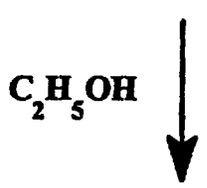


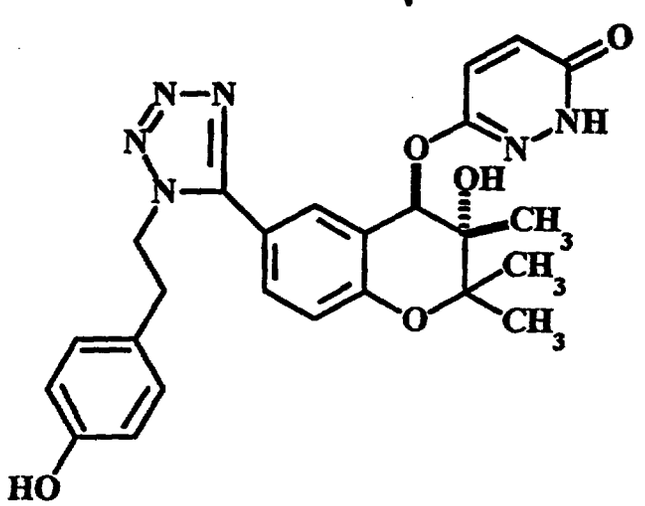
EXAMPLE 70

(3S,4R/3R,4S)-3,4-Dihydro-3-hydroxy-6-(1-[2-(4-hydroxyphenyl)ethyl]-1H-tetrazol-5-yl)-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran



This Sheet Has Been Replaced





(only one stereoisomer shown)

A mixture containing (3S,4R/3R,4S)-6-(1-[2-(4-Benzyloxyphenyl)-ethyl]-1H-tetrazol-5-yl)-3,4-dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran (see Example 5) (0.35g), 10% palladium-on-carbon (0.05g) and ethanol (50ml) was hydrogenated at 50°C and 345kPa (50 psi) for 2 hours. The mixture was filtered through a cellulose based filter aid and the filtrate was concentrated in vacuo to give a foam which was purified by chromatography on silica eluting with ethyl acetate containing methanol (4%) and concentrated aqueous ammonia (0.5%). The product-containing fractions were combined and concentrated in vacuo to give a gum which was triturated with diethyl ether to give the title compound as a colourless foam, 0.15g, m.p. 120-160°C (with foaming).

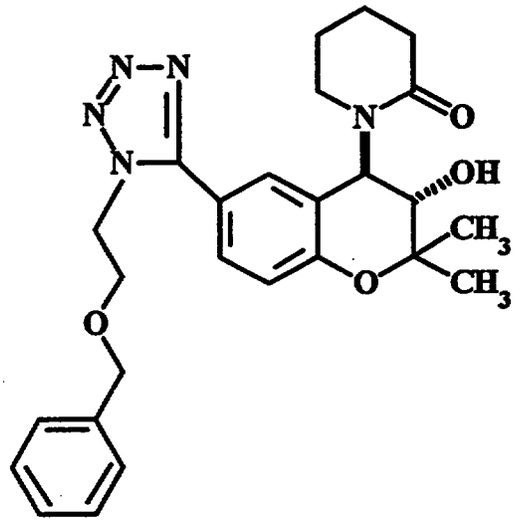
^{1}H-NMR (d_6-DMSO): δ=9.25-9.10(brs,1H), 7.45(s,1H), 7.35-7.30(d,1H), 7.25-7.20(d,1H), 6.95-6.85(m,2H), 6.75-6.65(d,2H), 6.55-6.45(d,2H), 5.90(s,1H), 5.40-5.30(brs,1H), 4.55-4.45(t,2H), 2.95-2.85(t,2H), 1.40(s,3H), 1.30(s,3H), 1.20(s,3H) ppm.

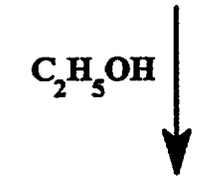
This Sheet Has Been Replaced

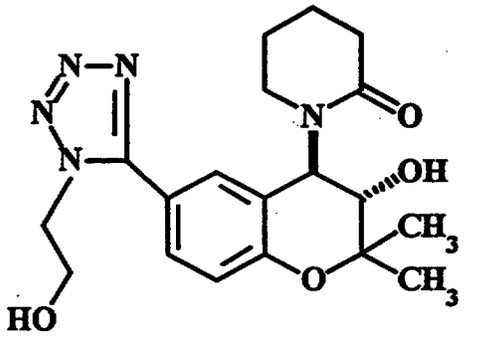


EXAMPLE 71

(3S,4R/3R,4S)-3,4-Dihydro-2,2-dimethyl-3-hydroxy-6-(1-[2-hydroxyethyl]-1H-tetrazol-5-yl)-4-(2-oxopiperidin-1-yl)-2H-benzo[b]pyran







(only one stereoisomer shown)

This Sheet Has Been Replaced

A mixture containing (3S,4R/3R,4S)-6-(1-[2-benzyloxyethyl]-1H-tetrazol-5-yl)-3,4-dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-2H-benzo[b]pyran (see Example 23) (0.67g), 10% palladium-on-carbon (0.2g) and ethanol (50ml) was hydrogenated at 345kPa (50 psi) and 50°C for 16 hours. The catalyst was filtered off and the filtrate was concentrated in vacuo to give a foam which was purified by chromatography on silica eluting with dichloromethane containing methanol (5%). The product-containing fractions were combined and concentrated in vacuo to give a foam which was triturated with diethyl ether to give the title compound as a solid, 0.45g, m.p. 217-219°C. Found: C,59.00; H,6.47; N,17.87; $C_{19}H_{25}N_5O_4$ requires: C,58.90; H,6.50; N,18.08%.

^{1}H-NMR ($CDCl_3$): δ=7.55-7.50(d,1H), 7.45(s,1H), 6.85-6.80(d,1H), 5.85-5.75(d,1H), 4.70-4.60(t,1H), 4.40(d,1H), 4.35-4.25(m,2H), 4.05-3.90(m,2H), 3.70-3.65(m,1H), 3.10-3.00(m,1H), 2.85-2.75(m,1H), 2.50-2.30(m,2H), 1.80-1.45(m,4H), 1.40(s,3H), 1.15(s,3H) ppm.

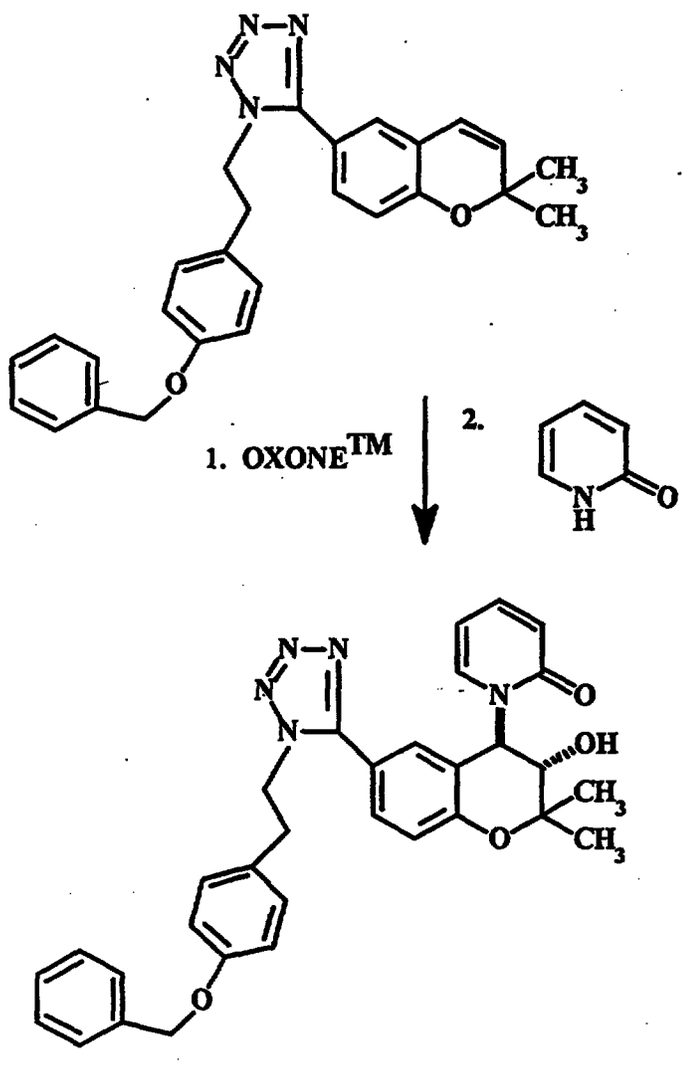
This Sheet Has Been Replaced



EXAMPLE 72

(3S,4R/3R,4S)-6-(1-[2-(4-Benzyloxyphenyl)ethyl]-1H-tetrazol-5-yl)-3,4-dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxo-1,2-dihydropyridin-1-yl)-2H-benzo[b]pyran

This Sheet Has Been Replaced



(only one stereoisomer shown)

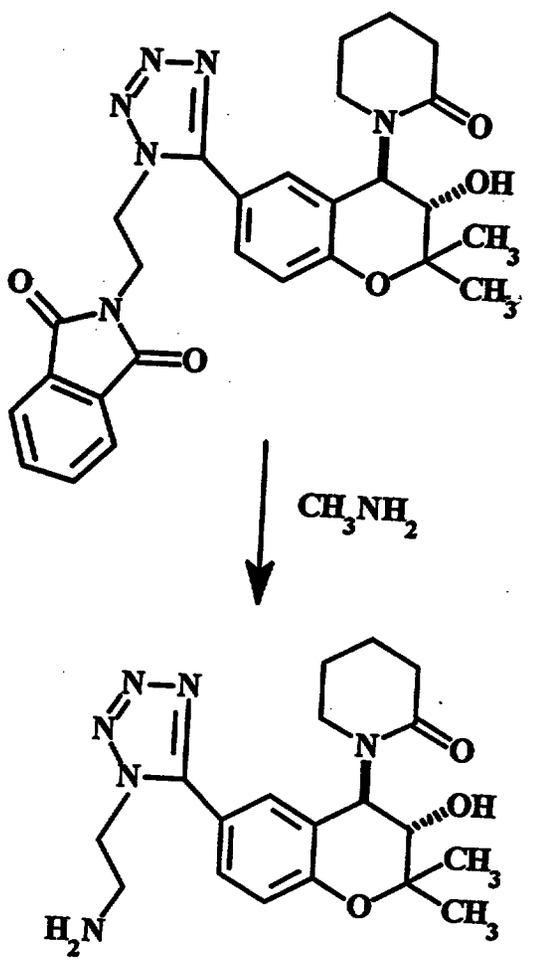
This Sheet Has Been Replaced

A solution of OXONE (trade mark) (4.2g) in water (20ml) was added, over 1 hour, to a stirred mixture of 6-(1-[2-(4-benzyloxyphenyl)ethyl]-1H-tetrazol-5-yl)-2,2-dimethyl-2H-benzo[b]pyran (see Preparation 31) (3g), sodium hydrogen carbonate (3.5g), water (20ml) and acetone (60ml). When the addition was complete the mixture was stirred at room temperature for a further 1 hour. The acetone was evaporated in vacuo and the resulting aqueous mixture was extracted with dichloromethane (2 x 100ml). The dichloromethane solution was dried (Na_2SO_4) then concentrated in vacuo to the give the crude epoxide intermediate as a foam, 3.2g. The foam was dissolved in anhydrous dioxan (20ml) then 2-hydroxypyridine (2g) and benzyltrimethylammonium hydroxide (0.5ml of a 40% solution in methanol) were added. The mixture was heated under reflux for 4 hours then allowed to stand at room temperature for 16 hours. Water (100ml) was added and the mixture extracted with dichloromethane (3 x 50ml). The combined dichloromethane extracts were washed with water (50ml) and concentrated in vacuo to give a solid which was purified by column chromatography on silica eluting with dichloromethane containing methanol (2.5%). The product-containing fractions were combined and concentrated in vacuo to give the title compound as a foam, 2.5g. Found: C,67.84; H,5.27; N,11.97; $C_{32}H_{31}N_5O_4.H_2O$ requires: C,67.71; H,5.86; N,12.34%.

^{1}H-NMR ($CDCl_3$): δ=7.50-7.25(m,6H), 7.20-7.15(d,1H), 7.00-6.75(m,6H), 6.70-6.65(d,1H), 6.35-6.30(d,1H), 6.20-6.15(t,1H), 5.05(s,2H), 4.50-4.40(m,2H), 4.20(d,1H), 3.90-3.85(dd,1H), 3.20-3.00(m,2H), 1.55(s,3H), 1.40(s,3H) ppm.

EXAMPLE 73

(3S,4R/3R,4S)-6-(1-[2-Aminoethyl]-1H-tetrazol-5-yl)-3,4-dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-2H-benzo[b]pyran



This Sheet Has Been Replaced

(only one stereoisomer shown)

A mixture of (3S,4R/3R,4S)-3,4-dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-6-(1-[2-phthalimidoethyl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran (see Example 52) (0.5g) and methylamine (10ml of a 33% solution in industrial methylated spirit) was stirred at room temperature for 24 hours. The solvent was evaporated in vacuo and the residue was azeotroped twice with dichloromethane to give a solid which was purified by chromatography on silica eluting with dichloromethane containing methanol (1.25%). The product-containing fractions were combined and concentrated in vacuo to give the title compound as a foam, 0.34g.

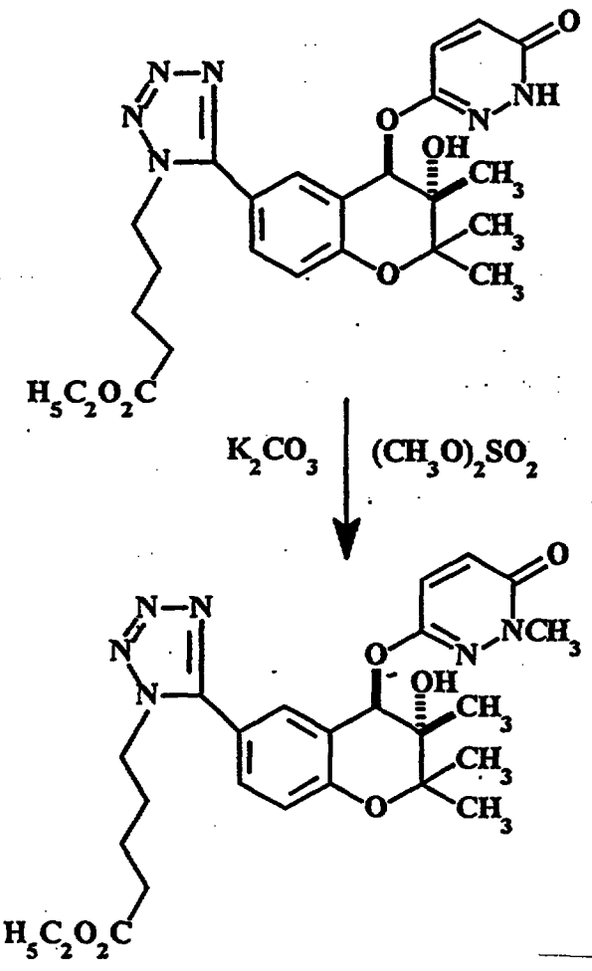
^{1}H-NMR ($CDCl_3$): δ=7.60-7.55(d,1H), 7.50(s,1H), 7.00-6.95(d,1H), 6.00-5.90(d,1H), 4.45-4.35(m,2H), 3.90-3.80(d,1H), 3.35-3.25(m,2H), 3.15-3.05(m,1H), 3.05-2.90(m,1H), 2.60-2.50(m,2H), 1.90-1.60(m,5H), 1.55(s,3H), 1.30(s,3H) ppm.

This Sheet Has Been Replaced



EXAMPLE 74

(3S,4R)-3,4-Dihydro-6-(1-[4-ethoxycarbonylbut-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-4-(2-methyl-3-oxopyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran



This Sheet Has Been Replaced

A mixture containing (3S,4R)-3,4-dihydro-6-(1-[4-ethoxycarbonylbut-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-4-(3-hydroxy-pyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran (see Example 11) (0.25g), dimethyl sulfate (0.34ml), anhydrous potassium carbonate (0.51g) and acetone (10ml) was heated under reflux for 4 hours. On cooling to room temperature the mixture was concentrated in vacuo and the residue partitioned between ethyl acetate (50ml) and water (50ml).

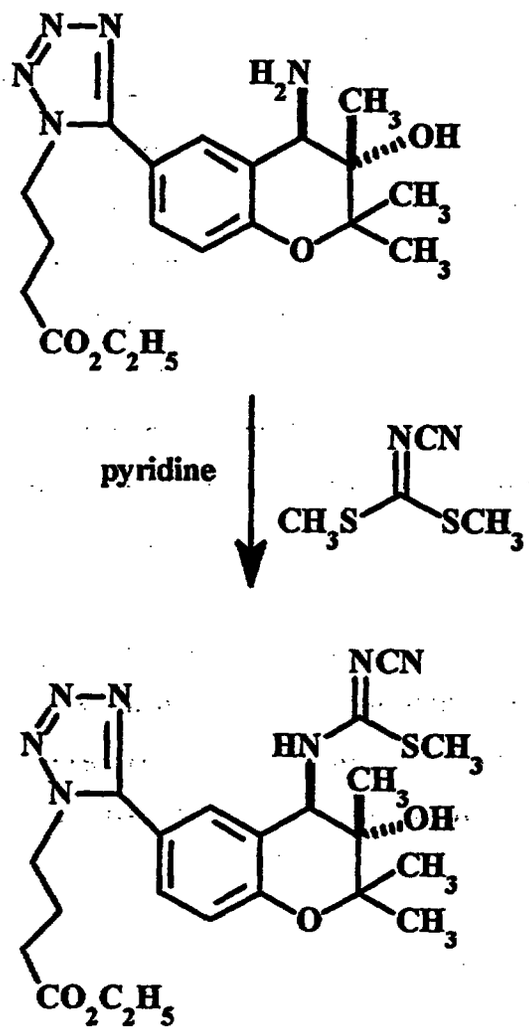
The ethyl acetate layer was washed with saturated aqueous sodium chloride (50ml), dried ($MgSO_4$) and concentrated in vacuo to give an oil which was purified by chromatography on silica eluting with ethyl acetate. The product-containing fractions were combined and concentrated in vacuo to give the title compound as a gum, 0.015g.
^{1}H-NMR ($CDCl_3$): δ=7.65(d,1H), 7.45-7.40(dd,1H), 7.10-6.90(m,3H), 5.95(s,1H), 4.40-4.30(t,2H), 4.10-4.00(q,2H), 3.80-3.70(brs,1H), 3.65(s,3H), 2.30-2.20(t,2H), 1.95-1.85(m,2H), 1.60-1.50(m,2H), 1.45(s,3H), 1.40(s,3H), 1.25(s,3H), 1.25-1.15(t,3H) ppm.

This Sheet Has Been Replaced



EXAMPLE 75

(3S,4R)-4-(3-Cyano-2-methylisothioureido)-3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-2,2,3-trimethyl-2H-benzo[b]pyran



This Sheet Has Been Replaced

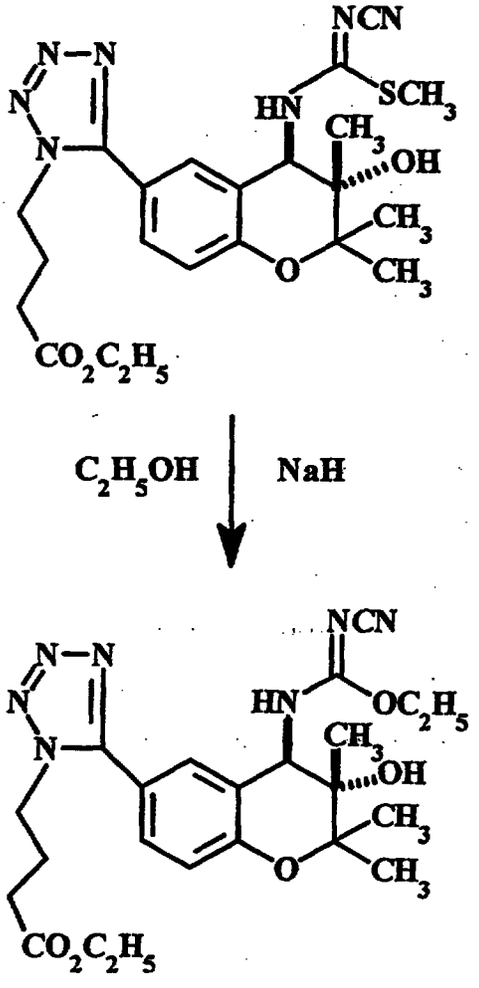
A mixture containing (3S,4R)-4-amino-3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-2,2,3-trimethyl-2H-benzo[b]pyran (see Preparation 55) (1.2g), dimethyl N-cyanodithioiminocarbonate (0.7g) and pyridine (10ml) was heated at 75°C for 18 hours then concentrated in vacuo to give a gum which was stirred in dichloromethane containing methanol (2.5%) (20ml). The resulting solid was filtered off and dried in vacuo to give the title compound, 0.85g, m.p. 225-227°C. Found: C,54.13; H,5.91; N,19.81; $C_{22}H_{29}N_7O_4S$ requires: C,54.20; H,6.00; N,20.11%.

^{1}H-NMR (d_6-DMSO): δ=8.45-8.30(brs,1H), 7.60-7.55(d,1H), 7.40(s,1H), 7.00-6.90(d,1H), 5.50-5.40(brs,1H), 5.35(s,1H), 4.50-4.40(t,2H), 4.00-3.90(q,2H), 2.70-2.60(brs,3H), 2.40-2.30(t,2H), 2.15-2.00(m,2H), 1.40(s,3H), 1.30(s,3H), 1.10(s,3H), 1.15-1.05(t,3H) ppm.

This Sheet Has Been Replaced

EXAMPLE 76

(3S,4R)-4-(3-Cyano-2-ethylisoureido)-3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-2,2,3-trimethyl-2H-benzo[b]pyran



This Sheet Has Been Replaced

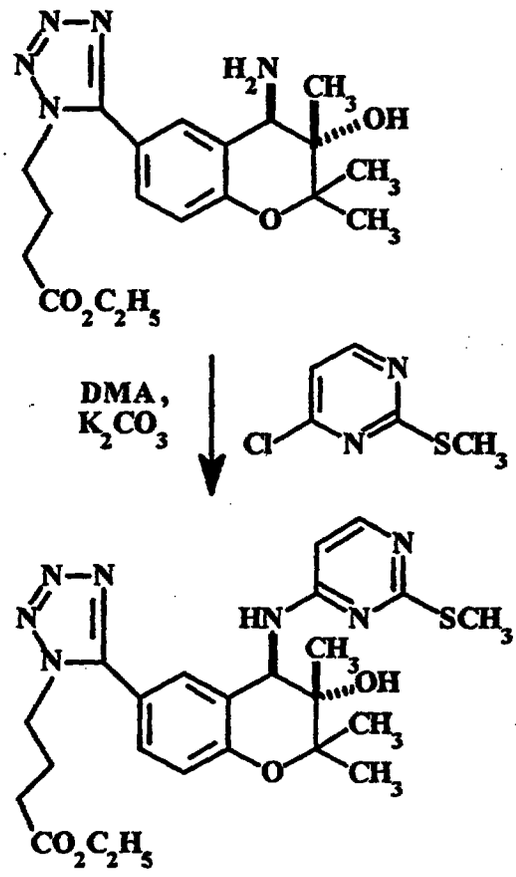
Sodium hydride (0.03g of an 80% dispersion in mineral oil) was added to ethanol (4ml). After 5 minutes (3S,4R)-4-(3-cyano-2-methylisothioureido)-3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-2,2,3-trimethyl-2H-benzo[b]pyran (see Example 75) (0.2g) was added and the mixture was allowed to stand at room temperature for 16 hours. The solution was acidified to pH 3 with 2N hydrochloric acid and then was concentrated in vacuo. The residue was purified by chromatography on silica eluting with dichloromethane containing methanol (2.5%). The product-containing fractions were combined and concentrated in vacuo to give an oil which was triturated with hexane to give the title compound as a foam, 0.09g. Found: C,57.00; H,6.46; N,19.48; $C_{23}H_{31}N_7O_6$.0.1 hexane requires: C,57.35; H,6.60; N,19.83%.

^{1}H-NMR ($CDCl_3$): δ=7.55-7.45(m,2H), 7.05-6.95(d,1H), 6.55-6.45(d,1H), 5.30-5.15(m,1H), 4.60-4.45(m,1H), 4.45-4.25(m,3H), 4.15-4.05(m,2H), 2.55-2.30(m,3H), 2.20-2.10(m,2H), 1.50(s,3H), 1.45(s,3H), 1.40-1.30(t,3H), 1.25(s,3H), 1.30-1.20(t,3H) ppm.

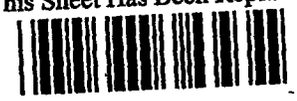


EXAMPLE 77

(3S,4R)-3,4-Dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-4-(2-methylthiopyrimidin-4-yl)amino-2,2,3-trimethyl-2H-benzo[b]pyran



This Sheet Has Been Replaced



A mixture containing (3S,4R)-4-amino-3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-2,2,3-trimethyl-2H-benzo[b]pyran (see Preparation 55) (0.6g), 4-chloro-2-methylthiopyrimidine (0.5g), anhydrous potassium carbonate (0.7g) and anhydrous dimethylacetamide (5ml) was heated at 120°C for 24 hours. On cooling to room temperature water (10ml) was added and the mixture was extracted with ethyl acetate (2 x 50ml). The extracts were combined and washed with water (50ml) then concentrated in vacuo to give an oil which was purified by chromatography on silica eluting with dichloromethane containing ethyl acetate (40%). The product-containing fractions were combined and concentrated in vacuo to give a foam which was further purified by chromatography on silica eluting with dichloromethane containing isopropanol (3.3%). The product-containing fractions were combined and concentrated in vacuo to give an oil which was triturated with hexane to give the title compound as a foam, 0.077g, m.p. 115-130°C.

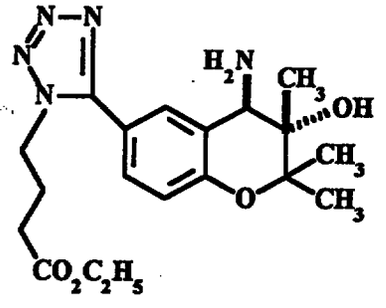
^{1}H-NMR ($CDCl_3$): δ=7.95-7.90(d,1H), 7.65(s,1H), 7.55-7.45(dd,1H), 7.05-6.95(d,1H), 6.95-6.85(m,1H), 6.00-5.80(brm,1H), 4.65-4.40(m,2H), 4.15-4.05(m,2H), 2.55(s,3H), 2.50-2.40(m,2H), 2.30-2.10(m,2H), 1.60(s,3H), 1.55(s,3H), 1.30(s,3H), 1.30-1.20(t,3H) ppm.

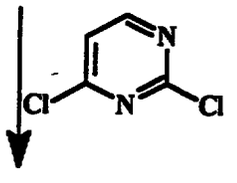
This Sheet Has Been Replaced

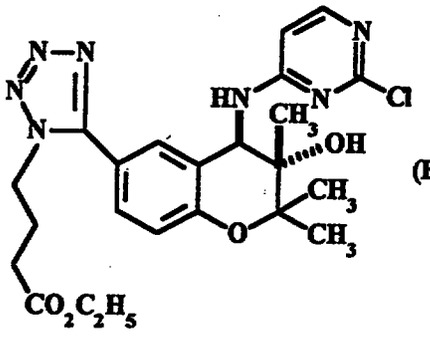


EXAMPLE 78

(3S,4R)-4-(2-Chloropyrimidin-4-yl)amino- and (3S,4R)-4-(4-Chloropyrimidin-2-yl)amino-3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-2,2,3-trimethyl-2H-benzo[b]pyran (Examples 78A and 78B respectively)

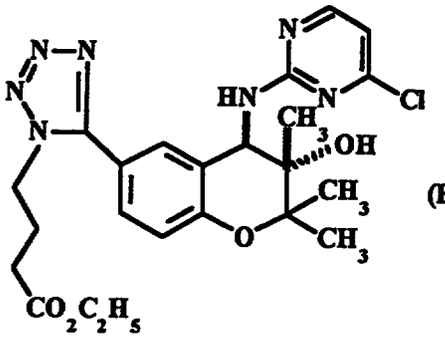






(Example 78A)

+



(Example 78B)

This Sheet Has Been Replaced

A mixture containing (3S,4R)-4-amino-3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-2,2,3-trimethyl-2H-benzo[b]pyran (see Preparation 55) (0.5g), 2,4-dichloropyrimidine (0.383g), diisopropylethylamine (0.33g) and dioxan (10ml) was heated under reflux for 18 hours. The mixture was concentrated in vacuo and the residue purified by chromatography on silica eluting with dichloromethane containing ethyl acetate (40%). This first gave, after combination and evaporation of the appropriate fractions, an oil which was triturated with hexane to give the 4-chloropyrimidinyl title compound, Example 78B, as a foam, 0.12g.

^{1}H-NMR ($CDCl_3$): δ=8.15-8.10(d,1H), 7.70(s,1H), 7.55-7.50(dd,1H), 7.05-7.00(d,1H), 6.70-6.65(d,1H), 6.30-6.25(d,1H), 5.50-5.45(d,1H), 4.60-4.45(m,2H), 4.20-4.00(m,2H), 2.50-2.40(m,2H), 2.25-2.10(m,2H), 1.55(s,3H), 1.50(s,3H), 1.30-1.15(t,3H), 1.25(s,3H) ppm.

Further elution of the column with ethyl acetate containing dichloromethane (20%) gave, after combination and evaporation of the appropriate fractions, an oil which was triturated with diethyl ether to give the 2-chloropyrimidinyl title compound, Example 78A, as a foam, 0.34g.

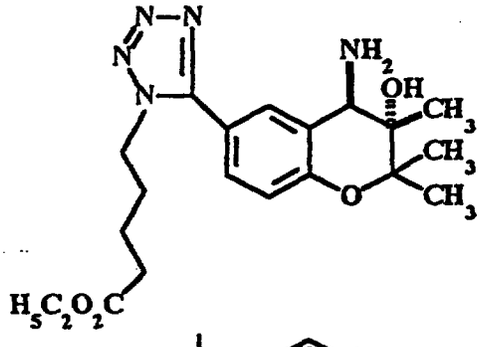
^{1}H-NMR ($CDCl_3$): δ=8.10-8.05(d,1H), 7.60(s,1H), 7.35-7.30(d,1H), 7.15-7.00(brs,1H), 6.95-6.85(m,2H), 5.65-5.50(brm,1H), 5.30-5.20(brs,1H), 4.55-4.25(m,2H), 4.10-3.90(m,2H), 2.45-2.30(m,2H), 2.15-2.05(m,2H), 1.55(s,3H), 1.50(s,3H), 1.25(s,3H), 1.30-1.10(t,3H) ppm.

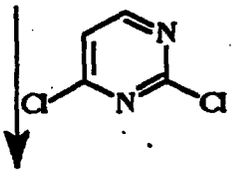
This Sheet Has Been Replaced



EXAMPLE 79

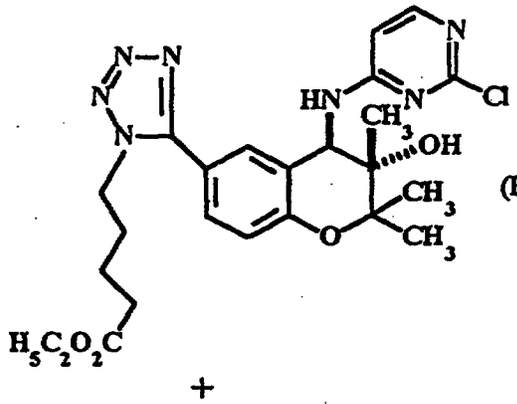
(3S,4R)-4-(2-Chloropyrimidin-4-yl)amino- and (3S,4R)-4-(4-Chloropyrimidin-2-yl)amino-3,4-dihydro-6-(1-[4-ethoxycarbonylbut-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-2,2,3-trimethyl-2H-benzo[b]pyran (Examples 79A and 79B respectively





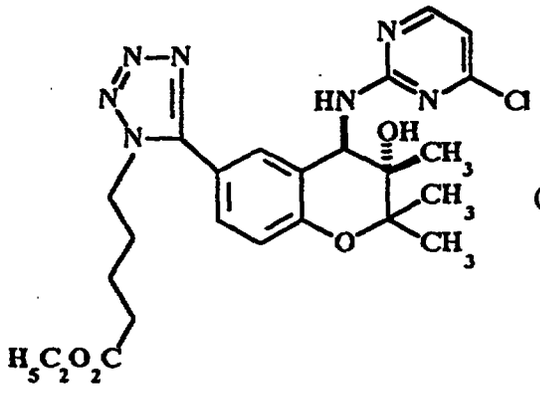
This Sheet Has Been Replaced





(Example 79A)

+



(Example 79B)

A mixture containing (3S,4R)-4-amino-3,4-dihydro-6-(1-[4-ethoxycarbonylbut-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-2,2,3-trimethyl-2H-benzo[b]pyran (see Preparation 68) (0.36g), 2,4-dichloropyrimidine (0.26g), diisopropylethylamine (0.225g) and dioxan (5ml) was heated at 95°C for 20 hours. On cooling to room temperature the mixture was poured into water (20ml) and extracted with ethyl acetate (3 x 20ml). The combined ethyl acetate extracts were washed with water (50ml) then dried ($MgSO_4$) and concentrated in vacuo to give a gum which was purified by chromatography on silica eluting with 1:1 ethyl acetate/hexane. The fractions containing the higher Rf product were combined and concentrated in vacuo to give the 4-chloropyrimidinyl title compound, Example 79B, 0.076g.
^{1}H-NMR ($CDCl_3$): δ=8.10(d,1H), 7.70(s,1H), 7.45-7.40(dd,1H), 7.00-6.95(d,1H), 6.65-6.60(d,1H), 6.20-6.00(brs,1H), 5.50-5.40(d,1H), 4.40-4.35(t,2H), 4.10-3.95(m,3H), 2.30-2.20(m,2H), 1.95-1.85(m,2H), 1.60-1.40(m,2H), 1.50(s,3H), 1.45(s,3H), 1.25-1.15(m,6H) ppm.

The fractions containing the lower Rf product were combined and concentrated in vacuo to give the 2-chloropyrimidinyl title compound, Example 79A, 0.18g.
^{1}H-NMR ($CDCl_3$): δ=8.05-8.00(d,1H), 7.55(s,1H), 7.30-7.25(d,1H), 7.10-7.00(brs,0.5H), 6.90(d,1H), 6.85(d,1H), 5.65-5.50(brs,1H), 5.10-4.95(brs,0.5H), 4.45-4.25(m,2H), 4.15-4.00(m,3H), 2.25-2.10(m,2H), 1.95-1.75(m,2H), 1.60-1.20(brm,2H), 1.50(s,3H), 1.45(s,3H), 1.25-1.15(m,6H) ppm.

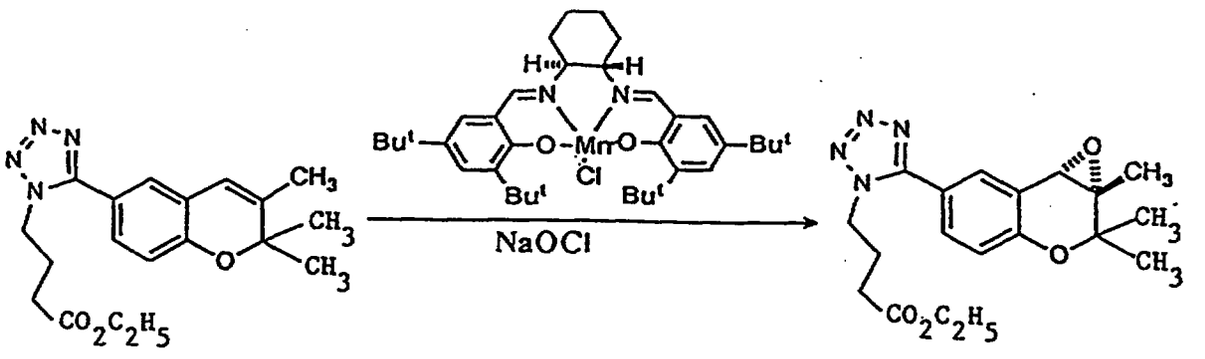
The following Preparations illustrate the preparation of certain starting materials used in the preceding Examples:-

This Sheet Has Been Replaced



PREPARATION 1

(3S,4S)-3,4-Dihydro-3,4-epoxy-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



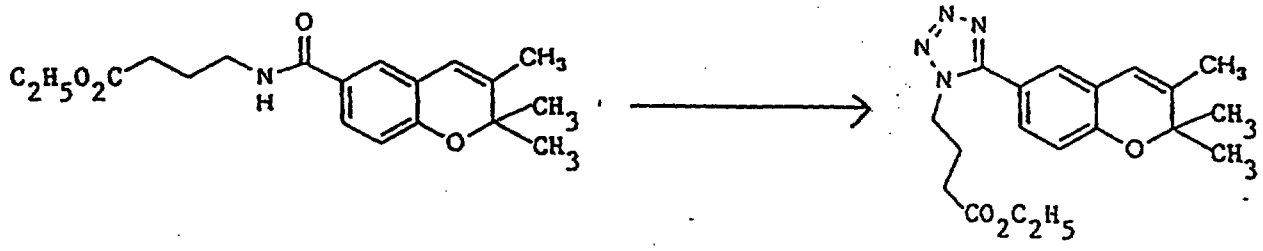
A solution of the compound of Preparation 2 (2g) and [(S,S)-1,2-bis(3,5-di-*tert*-butylsalicylideamino]cyclohexane manganese III chloride (see J. Amer. Chem. Soc., 1991, *113*, 7063) (0.23g) in dichloromethane (7ml) was added to a stirred solution of commercial bleach (21ml of a 3M solution) at 0°C. The mixture was stirred at 0°C for 7 hours then diluted with dichloromethane (20ml). The layers were separated and the dichloromethane solution was washed with water (20ml) then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with dichloromethane containing methanol (2.5%). The product-containing fractions were combined and concentrated *in vacuo*, to give the title compound as a red/brown oil, 0.99g, optical purity 97% by chiral HPLC.

^{1}H-NMR ($CDCl_3$): δ = 7.75 (s,1H), 7.60-7.55 (dd,1H), 7.00-6.95 (d,1H), 4.55-4.45 (t,2H), 4.15-4.05 (q,2H), 3.95(s,1H), 2.45-2.35 (m,2H), 2.30-2.20 (m,2H), 1.60 (s,3H), 1.55 (s,3H), 1.30 (s,3H), 1.30-1.20 (t,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 2

6-(1-[3-Ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



Phosphorus pentachloride (1.8g) was added to a solution of the compound of Preparation 3 (2.4g) in chloroform (30ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (1.4g) was added and the mixture was stirred at room temperature for 16 hours. Water (20ml) was added and the mixture was stirred vigorously. The layers were separated and the chloroform solution was concentrated *in vacuo* to give an orange oil which was purified by chromatography on silica eluting with dichloromethane containing ethyl acetate (5%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a pale yellow oil, 2.04g.

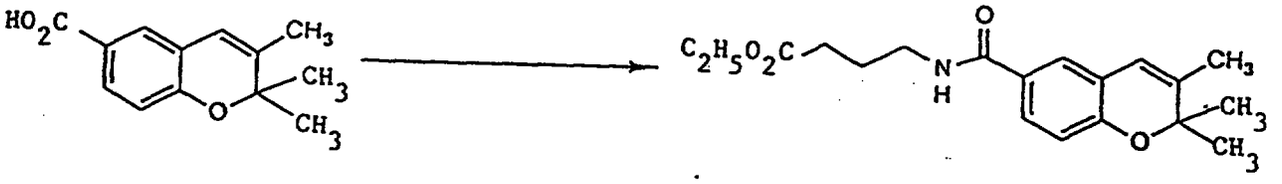
^{1}H-NMR ($CDCl_3$): δ = 7.40-7.35 (dd,1H), 7.30 (d,1H), 6.90-6.85 (d,1H), 6.15-6.10 (d,1H), 4.55-4.45 (m,2H), 4.15-4.05 (m,2H), 2.45-2.30 (m,2H), 2.30-2.20 (m,2H), 1.85 (s,3H), 1.45 (s,6H), 1.25-1.20 (t,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 3

6-(N-[3-Ethoxycarbonyl]prop-1-yl)carbamoyl-2,2,3-trimethyl-2H-benzo[b]pyran



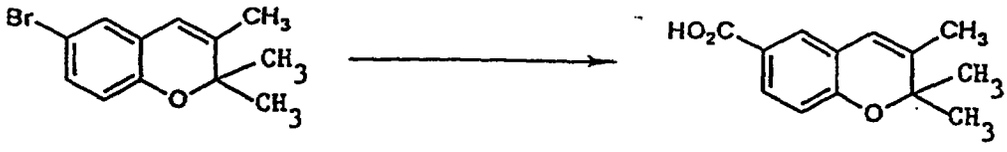
A mixture of the compound of Preparation 4 (2g) and 1,1'-carbonyldiimidazole (1.6g) was stirred in dichloromethane (50ml) for 30 minutes. Triethylamine (1.4g) and ethyl 4-aminobutanoate hydrochloride (2.3g) were added and the mixture was stirred at room temperature for 5 days then washed with water (100ml) and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with dichloromethane containing methanol (1.25%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a yellow oil, 2.4g.

^{1}H-NMR ($CDCl_3$): δ = 7.50-7.45 (dd,1H), 7.35 (d,1H), 6.80-6.75 (d,1H), 6.45-6.35 (m,1H), 6.10 (s,1H), 4.15-4.05 (q,2H), 3.50-3.40 (q,2H), 2.45-2.35 (t,2H), 2.00-1.90 (m,2H), 1.85 (s,3H), 1.40 (s,6H), 1.25-1.20 (t,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 4

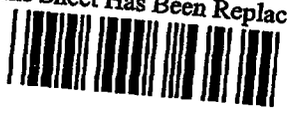
2,2,3-Trimethyl-2H-benzo[b]pyran-6-carboxylic acid



n-Butyllithium (81ml of a 2.5M solution in hexane) was added dropwise to a solution of the compound of Preparation 5 (47g) in anhydrous tetrahydrofuran (250ml) at -70°C. When the addition was complete the mixture was stirred at -70°C for 15 minutes then carbon dioxide pellets were added at such a rate that the temperature of the reaction mixture did not exceed -60°C. When the addition of pellets was no longer exothermic the mixture was allowed to warm to room temperature. Water (50ml) was added and the tetrahydrofuran evaporated *in vacuo*. Further water (500ml) was added and the solution was brought to pH 14 by the addition of 10% aqueous sodium hydroxide solution. The aqueous mixture was extracted with diethyl ether then acidified to pH 1 by the addition of concentrated hydrochloric acid. The resulting solid was filtered off, washed with water, dissolved in dichloromethane (500ml), the organic layer was separated from the residual water, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting solid was triturated with hexane to give the title compound as a colourless solid, 31g, m.p. 169-171°C. Found: C, 71.22; H, 6.72; $C_{13}H_{14}O_3$ requires: C, 71.55; H, 6.47%.

^{1}H-NMR ($CDCl_3$): δ = 7.90-7.80 (d,1H), 7.65 (s,1H), 6.85-6.75 (d,1H), 6.10 (s,1H), 1.85 (s,3H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced



PREPARATION 5

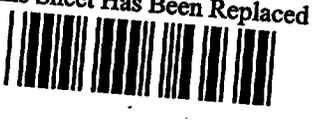
6-Bromo-2,2,3-trimethyl-2H-benzo[b]pyran



Sodium borohydride (24g) was added in portions to a solution of the compound of Preparation 6 (or Preparation 78) (164g) in ethanol (700ml) and the resulting mixture was stirred at room temperature for 1.5 hours then concentrated *in vacuo*. Water (500ml) was added and the mixture was cooled to 0°C then acidified to pH 1 with concentrated hydrochloric acid. The mixture was extracted with diethyl ether (2x500ml) and the combined ether extracts were washed with water (500ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a red oil. The oil was dissolved in toluene (2 litres), *para*-toluenesulphonic acid (22g) was added and the mixture was heated under reflux using Dean-Stark apparatus for 30 minutes. Further *para*-toluenesulphonic acid (5g) was added and heating was continued for 1 hour. On cooling to room temperature, the mixture was washed with 10% aqueous sodium hydroxide (500ml) and water (500ml) then concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with hexane containing dichloromethane (20%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a red oil, 130g.

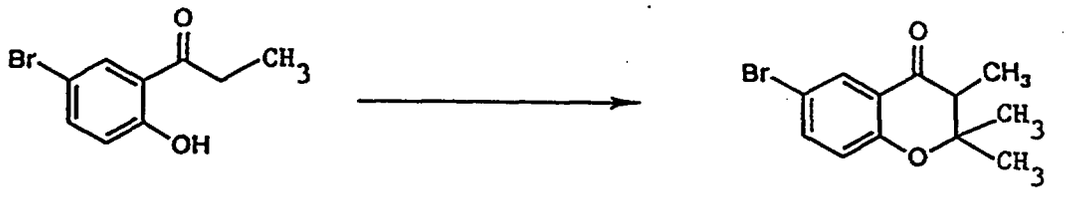
^{1}H-NMR ($CDCl_3$): δ = 7.15-7.10 (dd,1H), 7.00 (s,1H), 6.65-6.60 (d,1H), 6.00 (s,1H), 1.85 (s,3H), 1.60 (s,6H) ppm.

This Sheet Has Been Replaced



PREPARATION 6

6-Bromo-2,3-dihydro-2,2,3-trimethyl-4H-benzo[b]pyran-4-one



A mixture of the compound of Preparation 7 (255g), pyrrolidine (109ml) and toluene (800ml) was heated under reflux in a Dean-Stark apparatus for 22 hours. Acetone (125ml) was added and heating was continued for 24 hours. Further portions of acetone (125ml) were added after 24 and 48 hours and heating was continued for a total of 6 days. The mixture was concentrated *in vacuo* and the residue was taken up in diethyl ether (1250ml). The ethereal solution was washed with 2N hydrochloric acid (800ml), 2N sodium hydroxide (3x300ml) and brine (2x400ml) then dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a dark oil, 164.5g.

^{1}H-NMR ($CDCl_3$): δ = 7.95 (d,1H), 7.55-7.50 (dd,1H), 6.85-6.80 (d,1H), 2.75-2.65 (q,1H), 1.45 (s,3H), 1.25 (s,3H), 1.20-1.15 (d,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 7

4-Bromo-2-propanoylphenol



A mixture of the compound of Preparation 8 (230g) and aluminium chloride (300g) was heated with stirring until the reaction temperature was approximately 80°C, whereupon an exothermic reaction took place which raised the temperature of the mixture to 110°C. The reaction mixture was stirred at 110°C for 20 minutes then the temperature was increased to 140°C for 20 minutes and, finally, the mixture was heated at 160°C for 1 hour. On cooling to room temperature the mixture was treated with ice (1kg), and extracted with dichloromethane (3x500ml). The dichloromethane extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a dark oil which crystallised on standing, 223g.

^{1}H-NMR ($CDCl_3$): δ = 7.85 (d,1H), 7.55-7.50 (dd,1H), 6.90-6.85 (d,1H), 3.10-2.95 (q,2H), 1.25-1.20 (t,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 8

4-Bromophenyl propanoate



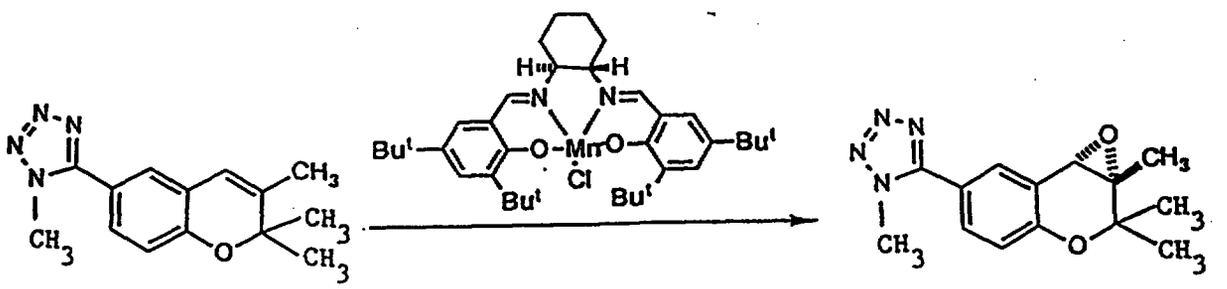
Triethylamine (219ml) was added to a solution of 4-bromophenol (259g) and 4-dimethylaminopyridine (1.5g) in dichloromethane (1000ml) at 0°C at such a rate that the temperature did not rise above 20°C. When the addition was complete propionyl chloride (137ml) was added in portions over 1 hour such that the temperature did not rise above 20°C. Finally, the mixture was stirred at room temperature for 2 hours. Water (700 ml) was added and the layers were separated. The dichloromethane solution was washed with brine (500ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as an oil, 344g.

^{1}H-NMR ($CDCl_3$): δ = 7.45-7.40 (d,2H), 6.95-6.90 (d,2H), 2.60-2.45 (q,2H), 1.25-1.15 (t,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 9

(3S,4S)-3,4-Dihydro-3,4-epoxy-6-(1-methyl-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



A solution of the compound of Preparation 10 (2.5g) and [(S,S)-1,2-bis(3,5-di-*tert*-butylsalicylideamino]cyclohexane manganese III chloride (see J. Amer. Chem. Soc., 1991, *113*, 7063) (0.4g) in dichloromethane (15ml) was added to a stirred solution of commercial bleach (36ml of a 0.55M solution) at 0°C. The mixture was allowed to warm to room temperature and was stirred for 20 hours then extracted with dichloromethane (3x25ml). The combined dichloromethane extracts were concentrated *in vacuo* to give an oil which was purified by chromatography on silica eluting with dichloromethane containing ethyl acetate (5% up to 10%). The product-containing fractions were combined and concentrated *in vacuo* to give a foam which was further purified by chromatography on silica eluting with dichloromethane containing methanol (2.5%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a foam, 1.0g.

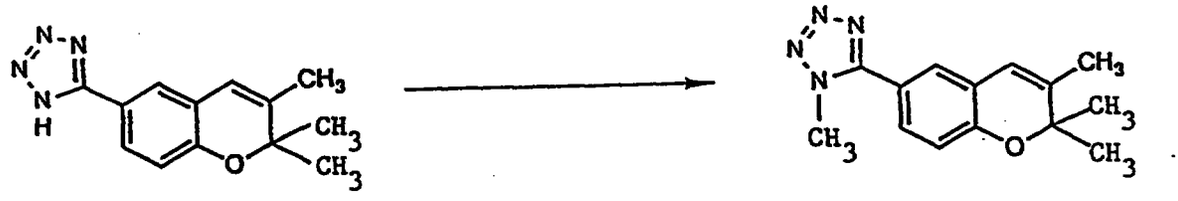
^{1}H-NMR ($CDCl_3$): δ = 7.75 (d,1H), 7.60-7.55 (dd,1H), 7.00-6.95 (d,1H), 4.15 (s,3H), 3.75 (s,1H), 1.65 (s,3H), 1.55 (s,3H), 1.30 (s,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 10

6-(1-Methyl-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



A mixture of the compound of Preparation 11 (4g), bis(tributyltin) oxide (9.8g) and iodomethane (40ml) was stirred at room temperature for 16 hours. The iodomethane was evaporated *in vacuo* and the residue was triturated with hexane containing ethyl acetate (20%). The resulting solid was filtered off and dried to give the title compound, 2.9g, m.p. 127-130°C.

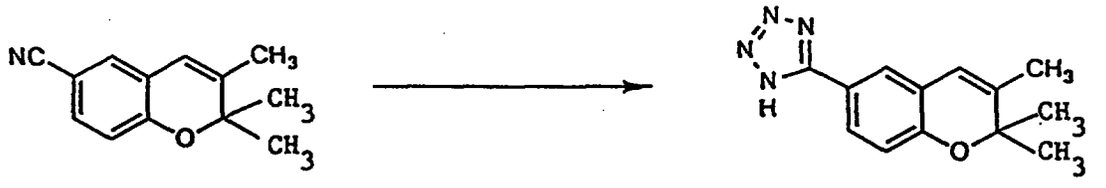
^{1}H-NMR ($CDCl_3$): δ = 7.45-7.35 (dd,1H), 7.30 (d,1H), 6.90-6.85 (d,1H), 6.15 (s,1H), 4.15 (s,3H), 1.85 (s,3H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced



PREPARATION 11

6-(1H-Tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



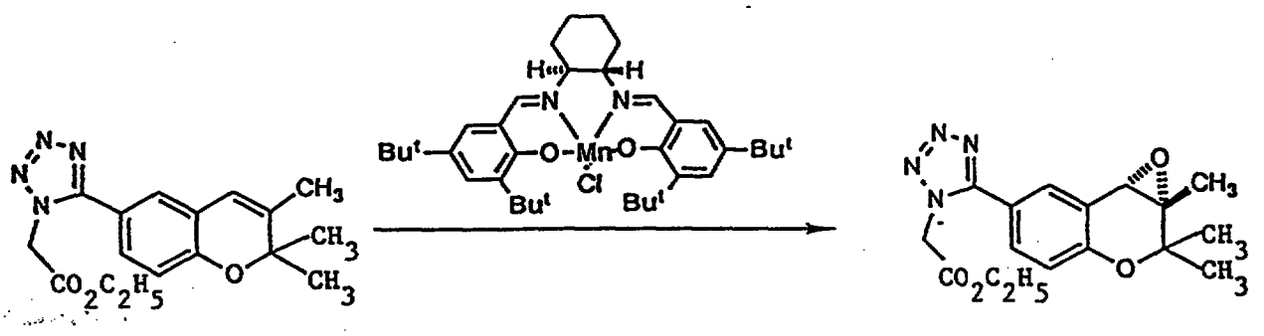
A mixture of 6-cyano-2,2,3-trimethyl-2*H*-benzo[b]pyran (see J. Med. Chem., **1991**, *34*, 3074) (4g), sodium azide (4.0g), triethylamine hydrochloride (4.2g) and 1-methyl-2-pyrrolidinone (40ml), was heated at 150°C for 1 hour. On cooling to room temperature water (200ml) was added and the mixture was brought to pH 14 by the addition of solid sodium hydroxide. The solution was extracted with ethyl acetate (200ml) then acidified to pH 3-4 with concentrated hydrochloric acid to give a solid which was filtered off, washed with water and dried to give the title compound, 4.5g, m.p. 179-181°C. Found: C, 64.58; H, 5.81; N, 23.46; $C_{13}H_{14}N_4O$ requires: C, 64.45; H, 5.82; N, 23.13%.

^{1}H-NMR ($CDCl_3$): δ = 7.70-7.65 (dd,1H), 7.60 (d,1H), 6.80-6.75 (d,1H), 6.05 (s,1H), 1.80 (s,3H), 1.35 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 12

(3S,4S)-3,4-Dihydro-3,4-epoxy-6-(1-ethoxycarbonylmethyl-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran

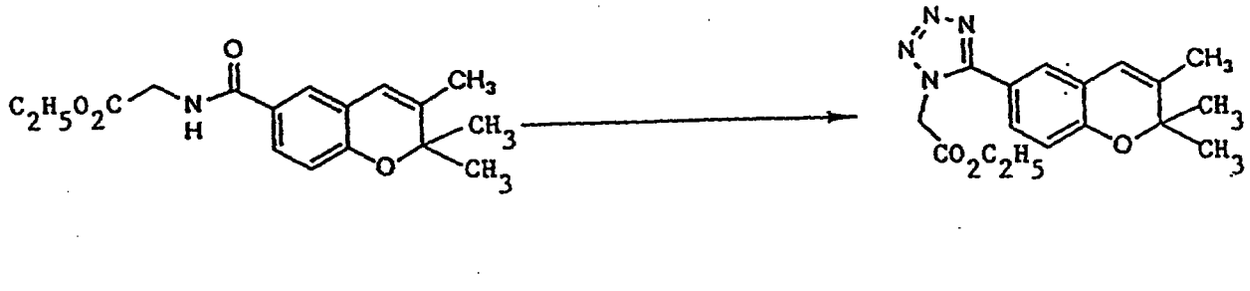


A solution of the compound of Preparation 13 (1.77g) and [(S,S)-1,2-bis(3,5-di-*tert*-butylsalicylideamino]cyclohexane manganese III chloride (see J. Amer. Chem. Soc., 1991, *113*, 7063) (0.23g) in dichloromethane (7ml) was added to a stirred solution of commercial bleach (21ml of a 3M solution) at 0°C. The mixture was allowed to warm to room temperature and stirred for 16 hours. Dichloromethane (50ml) was added and the mixture was filtered through a cellulose-based filter aid. The layers were separated and the dichloromethane solution was concentrated *in vacuo* to give a dark oil which was purified by chromatography on silica eluting with dichloromethane containing methanol (1.25%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a tan foam, 1.03g. ^{1}H-NMR ($CDCl_3$): δ = 7.65 (d,1H), 7.50-7.45 (dd,1H), 6.95-6.90 (d,1H), 5.15 (s,2H), 4.30-4.20 (q,2H), 3.70 (s, 1H), 1.60 (s,3H), 1.55 (s,3H), 1.30 (s,3H), 1.30-1.25 (t,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 13

6-(1-Ethoxycarbonylmethyl-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



Phosphorus pentachloride (1.7g) was added to a solution of the compound of Preparation 14 (2.34g) in chloroform (30ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (1.33g) was added and the mixture was stirred at room temperature for 16 hours. Water (20ml) was added and the mixture was stirred vigorously for 15 minutes. The layers were separated and the chloroform solution was concentrated *in vacuo* to give an orange oil which was purified by chromatography on silica eluting with dichloromethane containing ethyl acetate (5%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as an oil, 1.77g.

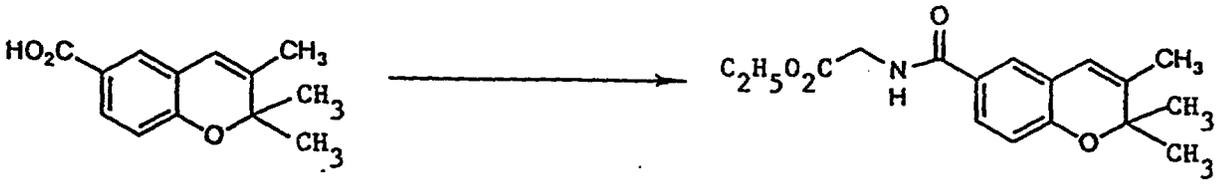
^{1}H-NMR ($CDCl_3$): δ = 7.30-7.20(m,2H), 6.90-6.85(d,1H), 6.10(s,1H), 5.15(s,2H), 4.30-4.20(quartet,2H), 1.90(s,3H), 1.45(s,6H), 1.30-1.20(t,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 14

6-(N-Ethoxycarbonylmethyl)carbamoyl-2,2,3-trimethyl-2H-benzo[b]pyran



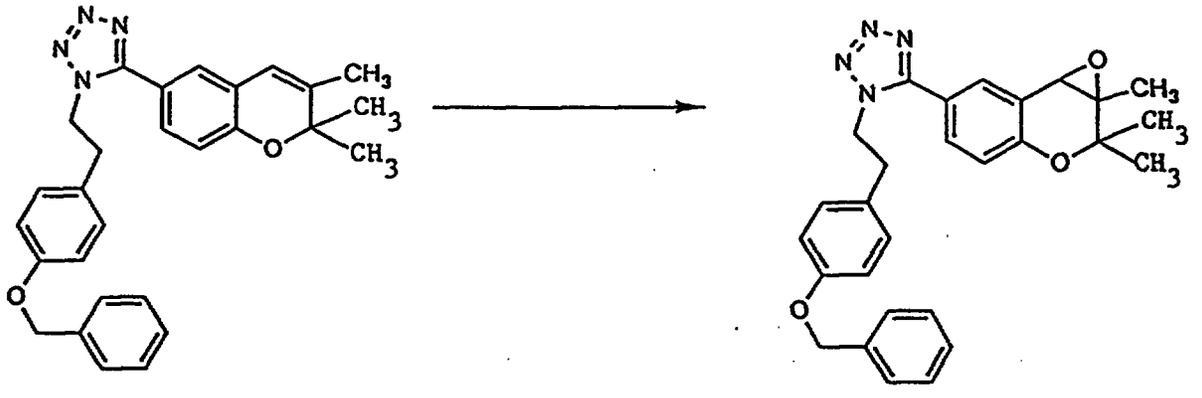
A mixture of the compound of Preparation 4 (2g) and 1,1'-carbonyldiimidazole (1.6g) in dichloromethane (50ml) was stirred at room temperature for 30 minutes. Triethylamine (1.1g) and ethyl glycinate hydrochloride (1.4g) were added and the mixture was stirred at room temperature for 16 hours then washed with water (100ml) and concentrated *in vacuo*. The residual red oil was purified by chromatography on silica eluting with dichloromethane containing methanol (1.25%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as an oil, 2.34g. ^{1}H-NMR ($CDCl_3$): δ = 7.55-7.50 (dd,1H), 7.40 (d,1H), 6.80-6.75 (d,1H), 6.55-6.50 (brs,1H), 6.10 (s,1H), 4.30-4.15 (m,4H), 1.85 (d,3H), 1.40 (s,6H), 1.35-1.30 (t,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 15

(3R,4R/3S,4S)-6-(1-[2-(4-Benzyloxyphenyl)ethyl]-1H-tetrazol-5-yl)-3,4-dihydro-3,4-epoxy-2,2,3-trimethyl-2H-benzo[b]pyran



A solution of OXONE™ (3.7g) in water (17ml) was added, over 2 hours, to a stirred mixture of the compound of Preparation 16 (2.7g), sodium hydrogen carbonate (3g), water (17ml) and acetone (52ml). When the addition was complete the mixture was stirred at room temperature for a further 1.5 hours. The acetone was evaporated *in vacuo* and the resulting aqueous mixture was partitioned between water (50ml) and dichloromethane (100ml). The layers were separated and the dichloromethane layer was dried (Na_2SO_4), filtered through a cellulose-based filter aid and concentrated *in vacuo* to give the title compound as a yellow foam, 2.2g.

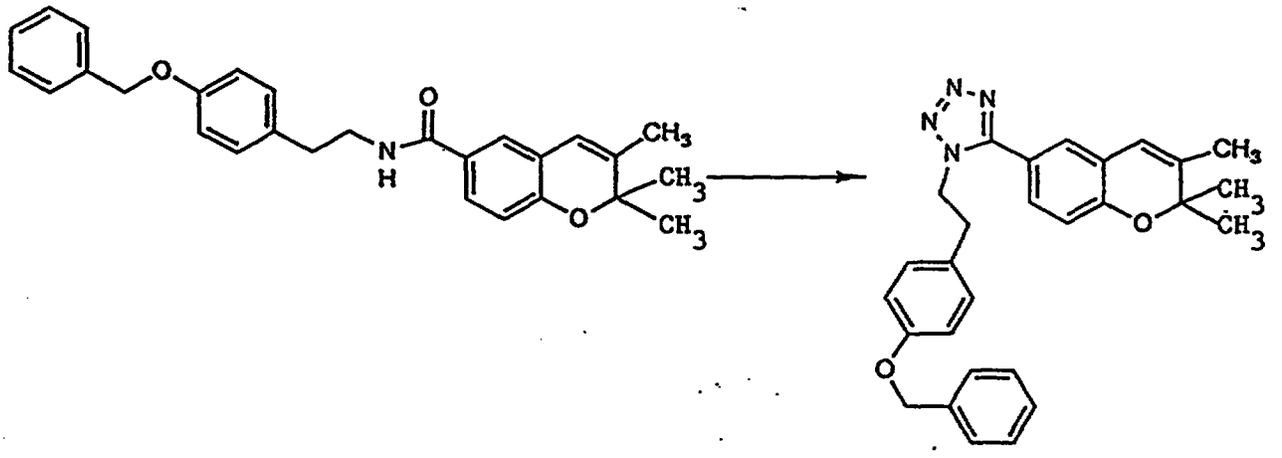
^{1}H-NMR ($CDCl_3$): δ = 7.50-7.30 (m,6H), 7.15-7.05 (m,2H), 6.85-6.80 (m,4H), 5.10-4.95 (m,2H), 4.60-4.45 (m,2H), 3.40 (s,1H), 3.20-3.15 (t,2H), 1.55 (s,3H), 1.50 (s,3H), 1.25 (s,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 16

6-(1-[2-(4-Benzyloxyphenyl)ethyl]-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



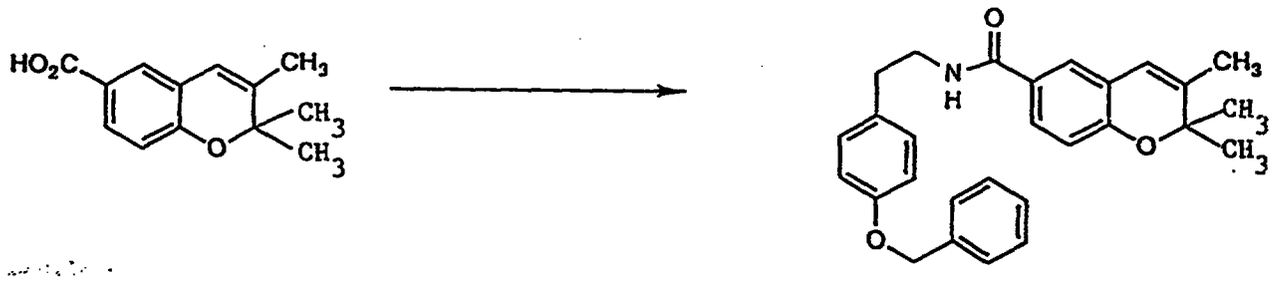
Phosphorus pentachloride (1.2g) was added to a solution of the compound of Preparation 17 in chloroform (30ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (1g) was added and the mixture was stirred at room temperature for 16 hours. Water (20ml) was added and the mixture was stirred vigorously for 15 minutes. The layers were separated and the chloroform solution was dried ($MgSO_4$) then concentrated *in vacuo* to give the title compound as an orange oil, 2.7g.

^{1}H-NMR ($CDCl_3$): δ = 7.45-7.25 (m,6H), 7.00-6.95 (dd,1H), 6.90-6.75 (m,5H), 6.05 (s,1H), 5.00 (s,2H), 4.60-4.50 (t,2H), 3.25-3.15 (t,2H), 1.85 (s,3H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 17

6-(N-[2-(4-Benzyloxyphenyl)ethyl]carbamoyl)-2,2,3-trimethyl-2H-benzo[b]pyran



A mixture of the compound of Preparation 4 (1.5g) and 1,1'-carbonyldiimidazole (1.17g) in dichloromethane (40ml) was stirred at room temperature for 30 minutes. 2-(4-Benzyloxyphenyl)ethylamine (2.2g) was added and the mixture was stirred at room temperature for 3 days then diluted with dichloromethane (100ml) and washed successively with 10% aqueous sodium hydroxide (100ml) and 2N hydrochloric acid (2 x 100ml). The dichloromethane layer was concentrated *in vacuo* and the residue was purified by chromatography on silica eluting with dichloromethane containing methanol (1%). The product-containing fractions were combined and concentrated *in vacuo* to give a foam which was azeotroped with dichloromethane to give the title compound as a pale yellow solid, 2.2g.

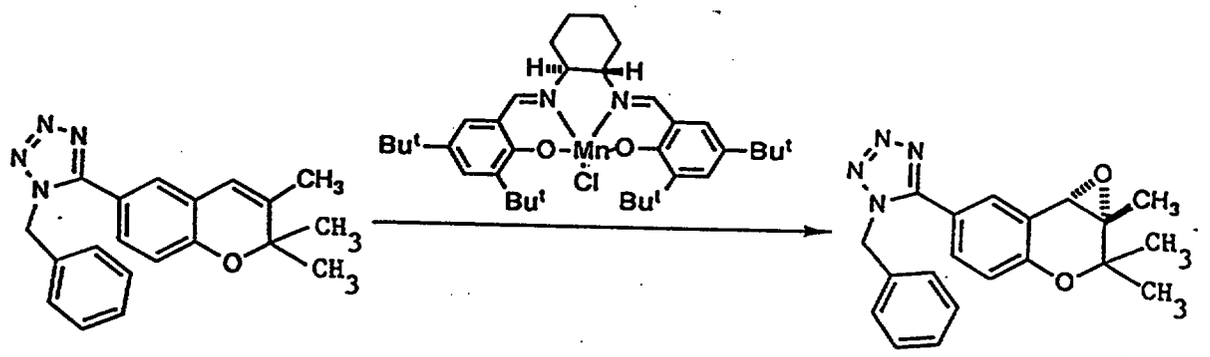
^{1}H-NMR ($CDCl_3$): δ = 7.50-7.30 (m,7H), 7.20-7.10 (d,2H), 6.95-6.90 (d,2H), 6.75-6.70 (d,1H), 6.10 (s,1H), 6.10-6.00 (t,1H), 5.05 (s,2H), 3.70-3.60 (m,2H), 2.90-2.80 (t,2H), 1.85 (s,3H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced



PREPARATION 18

(3S,4S)-6-(1-Benzyl-1H-tetrazol-5-yl)-3,4-dihydro-3,4-epoxy-2,2,3-trimethyl-2H-benzo[b]pyran



A solution of the compound of Preparation 19 (1.9g) and [(S,S)-1,2-bis(3,5-di-*tert*-butylsalicylideamino]cyclohexane manganese III chloride (see J. Amer. Chem. Soc., 1991, *113*, 7063) (0.23g) in dichloromethane (7ml) was added to a stirred solution of commercial bleach (21ml of a 3M solution) at 0°C. The mixture was allowed to warm to room temperature and stirred for 16 hours then extracted with dichloromethane (2 x 20ml). The dichloromethane extracts were concentrated *in vacuo* and the residue was purified by chromatography on silica eluting with dichloromethane containing methanol (1%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a foam, 1.03g.

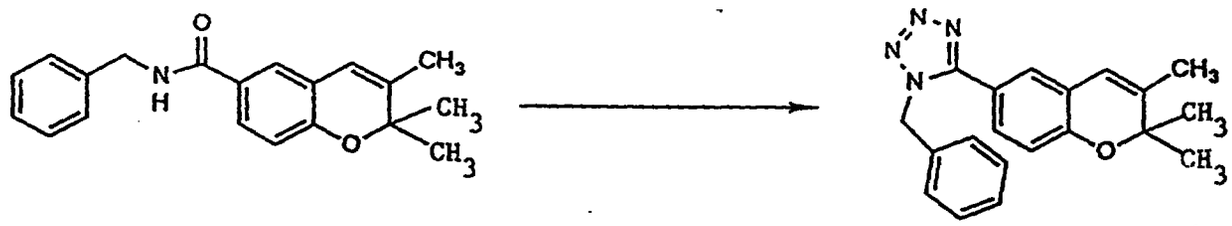
^{1}H-NMR ($CDCl_3$): δ = 7.55 (d,1H), 7.45-7.40 (dd,1H), 7.40-7.30 (m,3H), 7.20-7.15 (m,2H), 6.90-6.85 (d,1H), 5.65 (s,2H), 3.65 (s,1H), 1.60 (s,3H), 1.55 (s,3H), 1.30 (s,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 19

6-(1-Benzyl-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



Phosphorus pentachloride (1.1g) was added to a solution of the compound of Preparation 20 (1.6g) in chloroform (25ml) and the mixture heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (0.9g) was added and the mixture was allowed to stand at room temperature for 16 hours then diluted with chloroform (25ml) and washed with water (30ml). The chloroform solution was dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as an oil, 1.9g.

^{1}H-NMR ($CDCl_3$): δ = 7.40-7.30 (m,3H), 7.25-7.20 (dd,1H), 7.20-7.15 (m,3H), 6.85-6.80 (d,1H), 6.05 (s,1H), 5.60 (s,2H), 1.85 (s,3H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced



PREPARATION 20

6-(N-Benzyl)carbamoyl-2,2,3-trimethyl-2H-benzo[b]pyran



1,1'-Carbonyldiimidazole (1.17g) was added to a solution of the compound of Preparation 4 (1.5g) in dichloromethane (30ml) and the mixture was stirred at room temperature for 30 minutes. Benzylamine (1.47g) was added and the mixture was allowed to stand at room temperature for 16 hours then diluted with dichloromethane to a total volume of 70ml. The solution was washed sequentially with 10% aqueous sodium hydroxide (50ml), 2N hydrochloric acid (2 x 50 ml) and water (50ml), then concentrated *in vacuo* to give a solid which was purified by chromatography on silica eluting with dichloromethane containing methanol (1%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a foam, 1.64g.

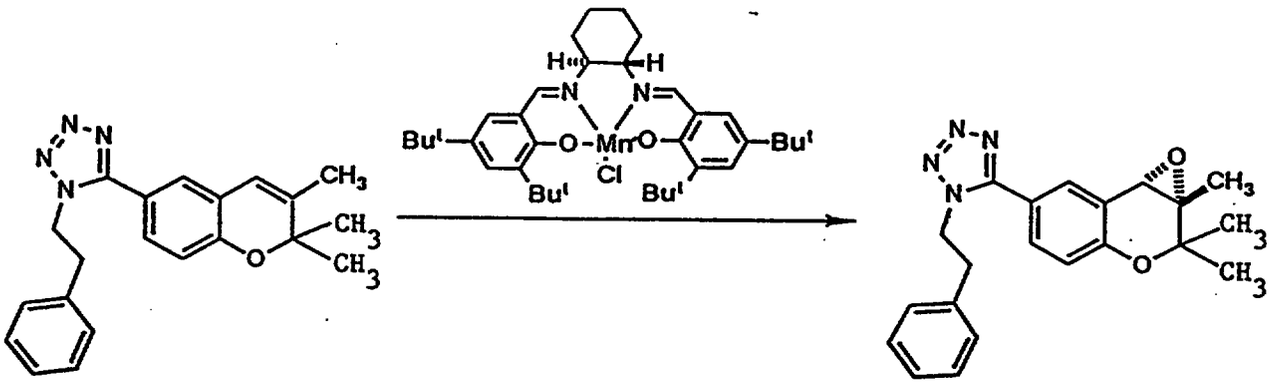
^{1}H-NMR ($CDCl_3$): δ = 7.50-7.45 (dd,1H), 7.40 (s,1H), 7.35-7.25 (m,5H), 6.80-6.75 (d,1H), 6.35-6.25 (brt,1H), 6.10 (s,1H), 4.65-4.60 (d,2H), 1.85 (s,3H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced



PREPARATION 21

(3S,4S)-3,4-Dihydro-3,4-epoxy-6-(1-[2-phenylethyl]-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



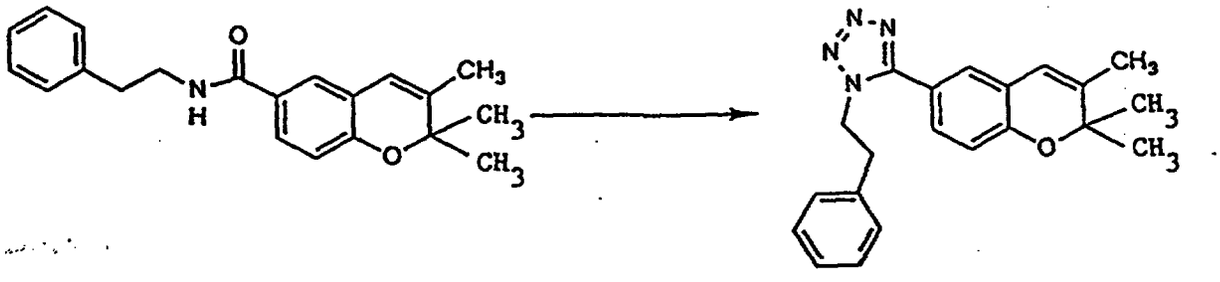
A solution of the compound of Preparation 22 (2g) and [(S,S)-1,2-bis(3,5-di-*tert*-butylsalicylideamino]cyclohexane manganese III chloride (see J. Amer. Chem. Soc., 1991, *113*, 7063) (0.23g) in dichloromethane (7ml) was added to a stirred solution of commercial bleach (21ml of a 3M solution) at 0°C. The mixture was allowed to warm to room temperature and stirred for 16 hours then diluted with dichloromethane (20ml) and filtered through a cellulose-based filter aid. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography on silica eluting with dichloromethane containing methanol (1%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a foam, 1.14g.

^{1}H-NMR ($CDCl_3$): δ = 7.30-7.15 (m,4H), 7.10-7.05 (dd,1H), 6.95-6.80 (m,2H), 6.90-6.80 (d,1H), 4.60-4.50 (t,2H), 3.60 (s,1H), 3.30-3.20 (t,2H), 1.60 (s,3H), 1.55 (s,3H), 1.30 (s,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 22

6-(1-(2-Phenylethyl)-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



Phosphorus pentachloride (1.2g) was added to a solution of the compound of Preparation 23 (1.8g) in chloroform (25ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature, trimethylsilyl azide (0.97g) was added and the mixture was allowed to stand at room temperature for 16 hours. Water (20ml) was added and the mixture was stirred vigorously for 20 minutes. The layers were separated and the chloroform solution was dried ($MgSO_4$) then concentrated *in vacuo* to give the title compound as an oil which solidified on standing, 2.07g.

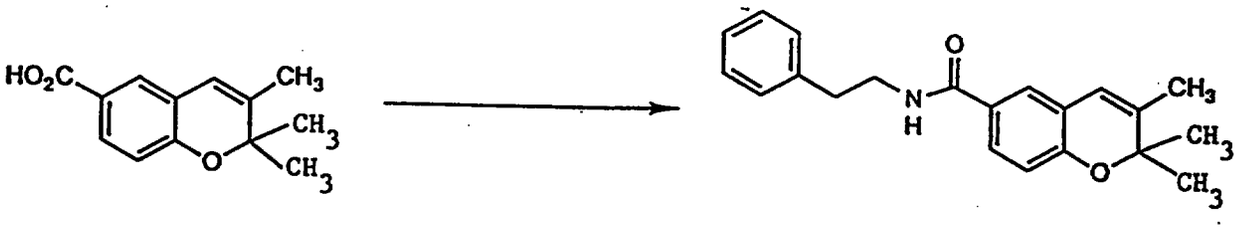
^{1}H-NMR ($CDCl_3$): δ = 7.30-7.20 (m,3H), 7.00-6.95 (m,3H), 6.80-6.75 (m,2H), 6.05 (s,1H), 4.65-4.55 (t,2H), 3.30-3.20 (t,2H), 1.85 (s,3H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced



PREPARATION 23

6-(N-[2-Phenylethyl])carbamoyl-2,2,3-trimethyl-2H-benzo[b]pyran



1,1'-Carbonyldiimidazole (1.17g) was added to a solution of the compound of Preparation 4 (1.5g) in dichloromethane (30ml) and the mixture was stirred at room temperature for 30 minutes. 2-Phenylethylamine (1.67g) was added and the mixture was allowed to stand at room temperature for 16 hours then diluted with dichloromethane to a total volume of 70ml. The solution was washed sequentially with 10% aqueous sodium hydroxide (50ml), 2N hydrochloric acid (2 x 50 ml) and water (50ml), then concentrated *in vacuo* to give a solid which was purified by chromatography on silica eluting with dichloromethane containing methanol (1%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as an oil, 1.87g.

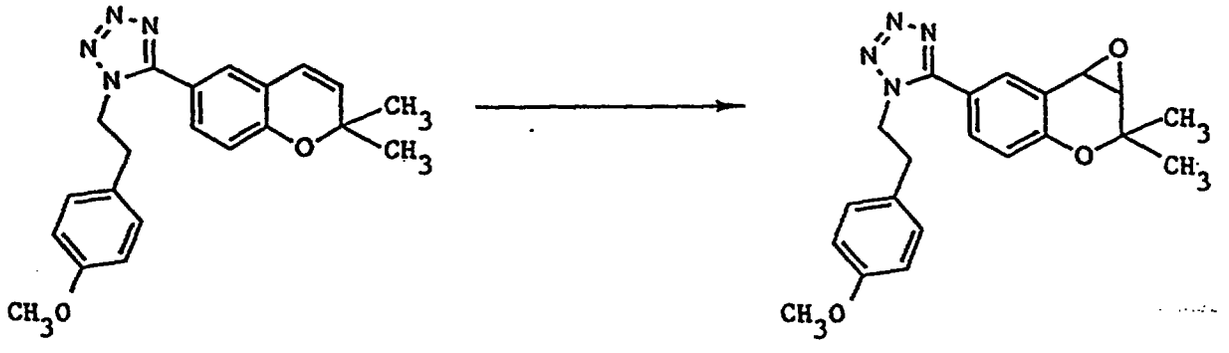
^{1}H-NMR ($CDCl_3$): δ = 7.40-7.20 (m,7H), 6.75-6.70 (d,1H), 6.10 (s,1H), 6.05-5.95 (brt,1H), 3.75-3.65 (q,2H), 2.95-2.90 (q,2H), 1.85 (s,3H), 1.40 (s,6H) ppm.

This Sheet Has Been Replaced



PREPARATION 24

(3R,4R/3S,4S)-3,4-Dihydro-2,2-dimethyl-3,4-epoxy-6-[1-[2-(4-methoxyphenyl)ethyl]-1H-tetrazol-5-yl]-2H-benzo[b]pyran



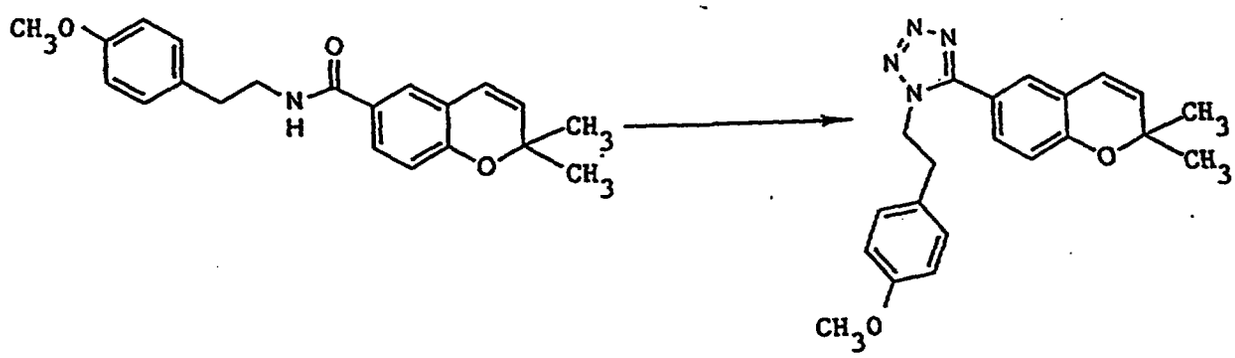
A solution of OXONE™ (12.5g) in water (50ml) was added, over 1 hour, to a stirred mixture of the compound of Preparation 25 (3.69g), sodium hydrogen carbonate (7.9g), water (50ml) and acetone (150ml). When the addition was complete the mixture was stirred at room temperature for a further 1 hour. The acetone was evaporated *in vacuo* and the resulting aqueous mixture was extracted with dichloromethane (3 x 100ml). The dichloromethane solution was dried (Na_2SO_4) then concentrated *in vacuo* to give the title compound as a foam, 3.6g. ^{1}H-NMR ($CDCl_3$): δ = 7.15-7.10 (m,2H), 6.90-6.70 (m,5H), 4.60-4.50 (m,2H), 3.80 (d,1H), 3.75 (s,3H), 3.50 (d,1H), 3.25 (t,2H), 1.60 (s,3H), 1.30 (s,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 25

2,2-Dimethyl-6-(1-[2-(4-methoxyphenyl)ethyl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



Phosphorus pentachloride (3.4g) was added to a solution of the compound of Preparation 26 (5.5g) in chloroform (100ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (1.9g) was added and the mixture was allowed to stand at room temperature for 5 hours. 10% Aqueous ceric ammonium nitrate (100ml) was added followed by dichloromethane (200ml) and water (50ml). The mixture was stirred vigorously for 20 minutes then filtered through a cellulose-based filter aid. The layers were separated and the organic solution was concentrated *in vacuo* to give an oil which was purified by chromatography on silica eluting with dichloromethane containing methanol (0.1%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as an oil, 3.75g.

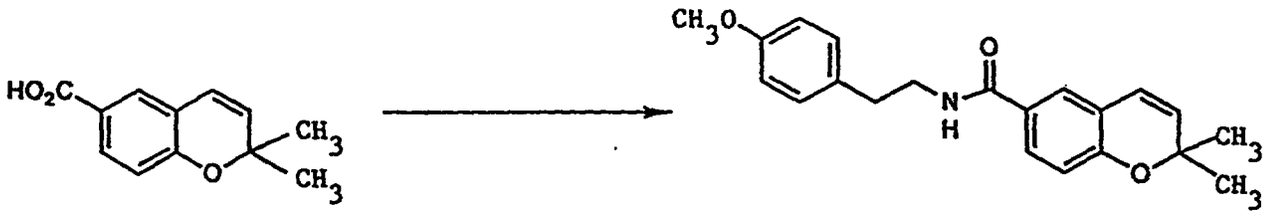
^{1}H-NMR ($CDCl_3$): δ = 7.05-7.00 (dd,1H), 6.90-6.70 (m,6H), 6.25-6.20 (d,1H), 5.70-5.65 (d,1H), 4.60-4.50 (t,2H), 3.75 (s,3H), 3.25-3.15 (t,2H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced



PREPARATION 26

2,2-Dimethyl-6-(N-[2-(4-methoxyphenyl)ethyl])carbamoyl-2H-benzo[b]pyran



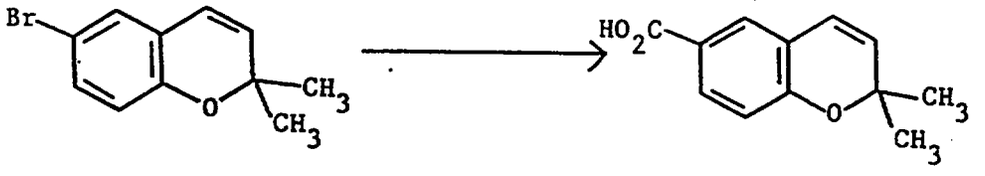
1,1'-Carbonyldiimidazole (2.62g) was added to a solution of the compound of Preparation 27 (3g) in dichloromethane (40ml) and the mixture was heated under reflux for 30 minutes. On cooling to room temperature 2-(4-methoxyphenyl)ethylamine (2.4g) was added and the mixture was allowed to stand at room temperature for 16 hours. Further 2-(4-methoxyphenyl)ethylamine (2g) was added and the mixture was allowed to stand at room temperature for 12 days then diluted with dichloromethane to a total volume of 100ml. The solution was washed sequentially with 10% aqueous sodium hydroxide (50ml), 2N hydrochloric acid (2 x 50 ml) and water (50ml), then dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a solid, 5.5g, m.p. 105-107°C.

^{1}H-NMR ($CDCl_3$): δ = 7.45-7.35 (m,2H), 7.15-7.10 (d,2H), 6.90-6.85 (d,2H), 6.75-6.70 (d,1H), 6.35-6.30 (d,1H), 6.05-5.95 (brt,1H), 5.65-5.60 (d,1H), 3.80 (s,3H), 3.70-3.60 (q,2H), 2.90-2.80 (t,2H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 27

2,2-Dimethyl-2H-benzo[b]pyran-6-carboxylic acid



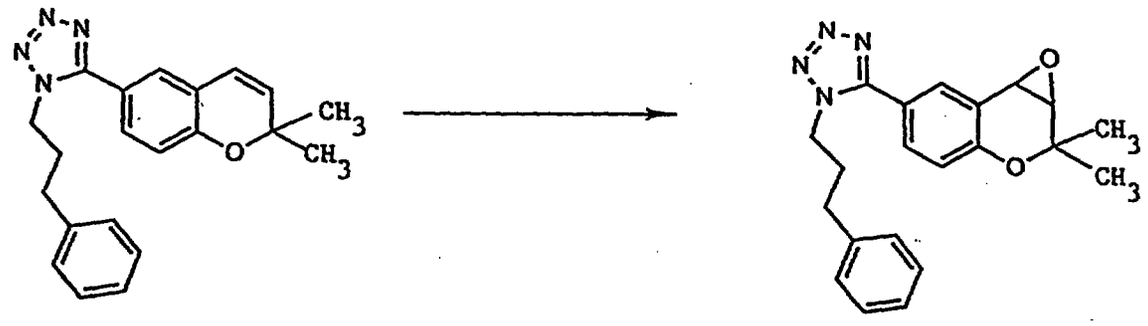
To a solution of 6-bromo-2,2-dimethyl-2H-benzo[b]pyran (see J. Med. Chem., 33, 3028 [1990]) (5.0g) in dry tetrahydrofuran (100ml) at -70°C under nitrogen was added, dropwise, a 1.6M solution of n-butyllithium in hexane (17ml). The reaction mixture was stirred at -70°C for 15 minutes then treated with an excess of finely ground solid CO_2. The reaction was further stirred for one hour, the solvent evaporated in vacuo and the residue taken up in ethyl acetate and washed with dilute aqueous hydrochloric acid. The organic layer was concentrated in vacuo to a solid which was triturated with hexane to provide a white solid, 1.6g.

^{1}H-NMR ($CDCl_3$): δ = 7.90 (d,1H), 7.76 (s,1H), 6.80 (d,1H), 6.34 (d,1H), 5.67 (d,1H), 1.49 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 28

(3R,4R/3S,4S)-3,4-Dihydro-2,2-dimethyl-3,4-epoxy-6-(1-[3-phenylprop-1-yl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



A solution of OXONE™ (4.62g) in water (20ml) was added, over 2 hours, to a stirred mixture of the compound of Preparation 29 (2.6g), sodium hydrogen carbonate (3.5g), water (20ml) and acetone (60ml). When the addition was complete the mixture was stirred at room temperature for a further 1 hour. The acetone was evaporated *in vacuo* and the resulting aqueous mixture was extracted with dichloromethane (2 x 100ml). The dichloromethane solution was dried (Na_2SO_4) then concentrated *in vacuo* to give the title compound as a foam, 2.6g.

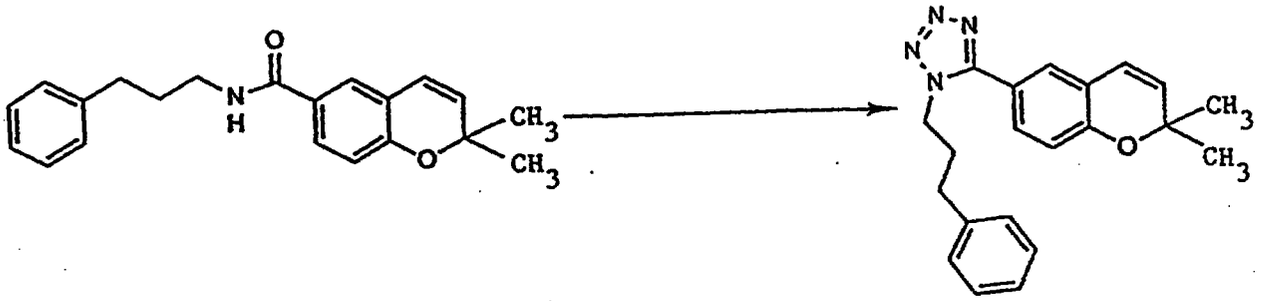
^{1}H-NMR ($CDCl_3$): δ = 7.65 (d,1H), 7.40-7.35 (dd,1H), 7.30-7.20 (m,3H), 7.15-7.10 (m,2H), 6.90-6.85 (d,1H), 4.25-4.15 (t,2H), 3.90 (d,1H), 3.55 (d,1H), 2.70-2.60 (t,2H), 2.35-2.20 (m,2H), 1.65 (s,3H), 1.30 (s,3H) ppm.

This Sheet Has Been Replaced

This Sheet Has Been Replaced

PREPARATION 29

2,2-Dimethyl-6-(1-[3-phenylprop-1-yl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



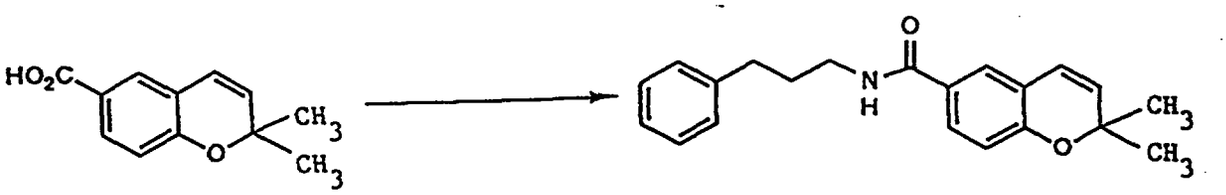
Phosphorus pentachloride (3.3g) was added to a solution of the compound of Preparation 30 (5.1g) in chloroform (100ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (1.8g) was added and the mixture was allowed to stand at room temperature for 16 hours. 10% Aqueous ceric ammonium nitrate (100ml) was added followed by dichloromethane (200ml) and water (50ml). The mixture was stirred vigorously for 20 minutes then filtered through a cellulose-based filter aid. The layers were separated and the organic solution was concentrated *in vacuo* to give an oil which was purified by chromatography on silica eluting with dichloromethane containing methanol (0.25%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as an oil, 2.7g.

^{1}H-NMR ($CDCl_3$): δ = 7.30-7.20 (m,5H), 7.15-7.10 (m,2H), 6.85-6.80 (d,1H), 6.35-6.25 (d,1H), 5.75-5.70 (d,1H), 4.45-4.35 (t,2H), 2.70-2.65 (m,2H), 2.35-2.25 (t,2H), 1.50 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 30

2,2-Dimethyl-6-(N-[3-phenylprop-1-yl])carbamoyl-2H-benzo[b]pyran

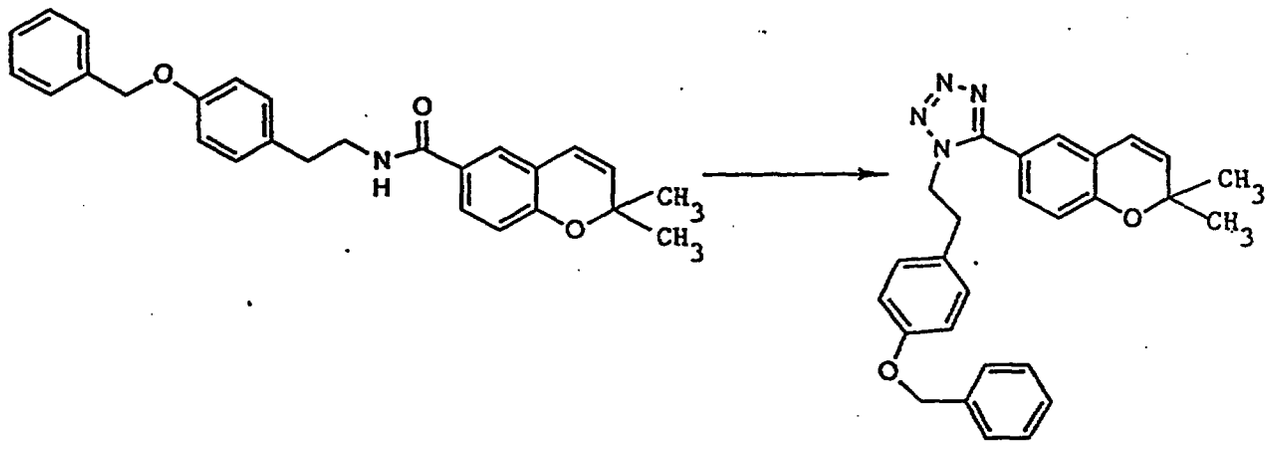


1,1'-Carbonyldiimidazole (2.6g) was added to a solution of the compound of Preparation 27 (3g) in dichloromethane (40ml) and the mixture was heated under reflux for 30 minutes. On cooling to room temperature 1-amino-3-phenylpropane (4g) was added and the mixture was allowed to stand at room temperature for 12 days. The mixture was diluted with dichloromethane to a total volume of 100ml then washed sequentially with 10% aqueous sodium hydroxide (50ml), 2N hydrochloric acid (2 x 50 ml) and water (50ml), then dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as an oil, 5.17g.
^{1}H-NMR ($CDCl_3$): δ = 7.40-7.15 (m,7H), 6.75-6.70 (d,1H), 6.35-6.30 (d,1H), 6.00-5.90 (brs,1H), 5.65-5.60 (d,1H), 3.50-3.40 (m,2H), 2.75-2.70 (t,2H), 2.00-1.90 (m,2H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 31

6-(1-[2-(4-Benzyloxyphenyl)ethyl]-1H-tetrazol-5-yl)-2,2-dimethyl-2H-benzo[b]pyran



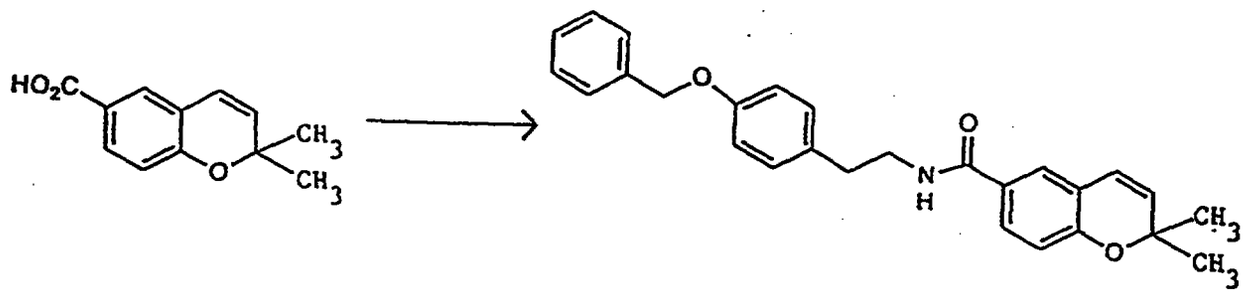
Phosphorus pentachloride (2.2g) was added to a solution of the compound of Preparation 32 (4.4g) in chloroform (100ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature tetramethylguanidinium azide (10.6ml of a 1M solution in dichloromethane) was added and the mixture was allowed to stand at room temperature. After 3 and 6 days, further portions of tetramethylguanidinium azide (8 and 20ml respectively of a 1M solution in dichloromethane) were added. Following the final addition the mixture was stirred for 24 hours then washed with water (3 x 100ml) and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with dichloromethane containing methanol (0.5%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as an oil, 3.2g.

^{1}H-NMR ($CDCl_3$): δ = 7.45-7.25 (m,5H), 7.05-7.00 (dd,1H), 6.90-6.75 (m,6H), 6.25-6.20 (d,1H), 5.70-5.65 (d,1H), 5.00 (s,2H), 4.60-4.50 (t,2H), 3.25-3.15 (t,2H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 32

6-(N-[2-(4-Benzyloxyphenyl)ethyl]carbamoyl-2,2-dimethyl-2H-benzo[b]pyran



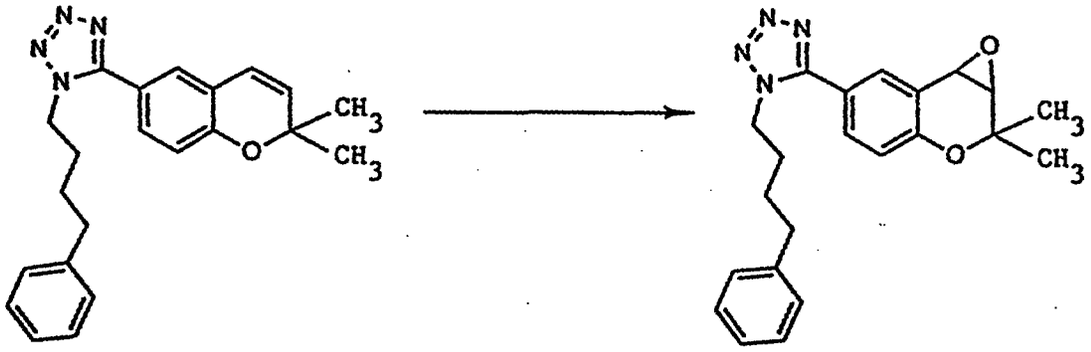
1,1'-Carbonyldiimidazole (2.6g) was added to a solution of the compound of Preparation 27 (3g) in dichloromethane (40ml) and the mixture was heated under reflux for 30 minutes. On cooling to room temperature 2-(4-benzyloxyphenyl)ethylamine (4g) and dichloromethane (50ml) were added and the mixture was allowed to stand at room temperature for 12 days. The mixture was diluted with dichloromethane to a total volume of 100ml then washed sequentially with 10% aqueous sodium hydroxide (50ml), 2N hydrochloric acid (2 x 50 ml) and water (50ml), then dried (Na_2SO_4) and concentrated *in vacuo* to give a solid which was purified by chromatography on silica eluting with dichloromethane containing methanol (1%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a solid, 4.7g, m.p. 133-135°C. Found: C,78.26; H,6.49; N,3.34; $C_{27}H_{27}NO_3$ requires: C,78.42; H,6.49; N,3.39%.

^{1}H-NMR ($CDCl_3$): δ = 7.45-7.30 (m,7H), 7.15-7.10 (d,2H), 6.95-6.90 (d,2H), 6.75-6.70 (d,1H), 6.35-6.30 (d,1H), 6.05-5.95 (brt,1H), 5.65-5.60 (d,1H), 5.05 (s,2H), 3.70-3.60 (q,2H), 2.90-2.80 (t,2H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 33

(3R,4R/3S,4S)-3,4-Dihydro-2,2-dimethyl-3,4-epoxy-6-(1-[4-phenylbut-1-yl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran

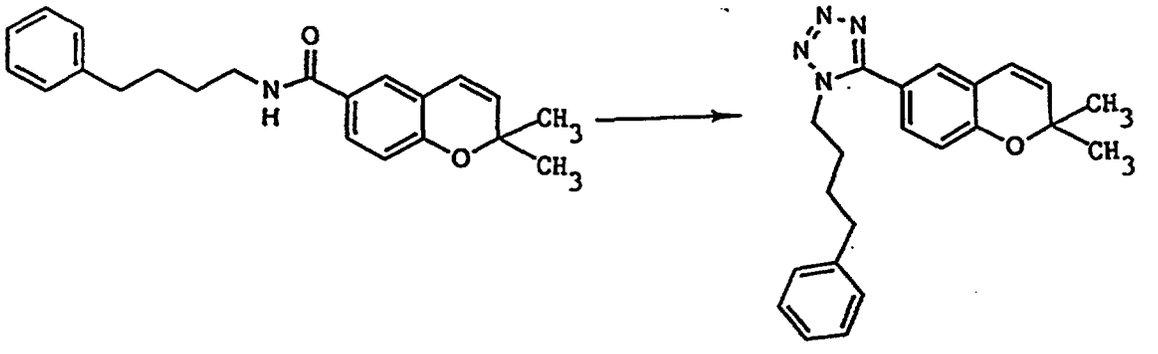


A solution of OXONE™ (7g) in water (30ml) was added, over 2 hours, to a stirred mixture of the compound of Preparation 34 (4g), sodium hydrogen carbonate (4g), water (30ml) and acetone (90ml). When the addition was complete the mixture was stirred at room temperature for a further 1 hour. The acetone was evaporated *in vacuo* and the resulting aqueous mixture was extracted with dichloromethane (2 x 100ml). The dichloromethane solution was dried (Na_2SO_4) then concentrated *in vacuo* to give the title compound as an oil, 4.1g. ^{1}H-NMR ($CDCl_3$): δ = 7.65 (d,1H), 7.45-7.40 (d,1H), 7.35-7.10 (m,5H), 7.00-6.95 (d,1H), 4.45-4.35 (t,2H), 3.95 (d,1H), 3.55 (d,1H), 2.70-2.55 (t,2H), 2.00-1.90 (m,2H), 1.70-1.55 (m,2H), 1.60 (s,3H), 1.30 (s,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 34

2,2-Dimethyl-6-(1-[4-phenylbut-1-yl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



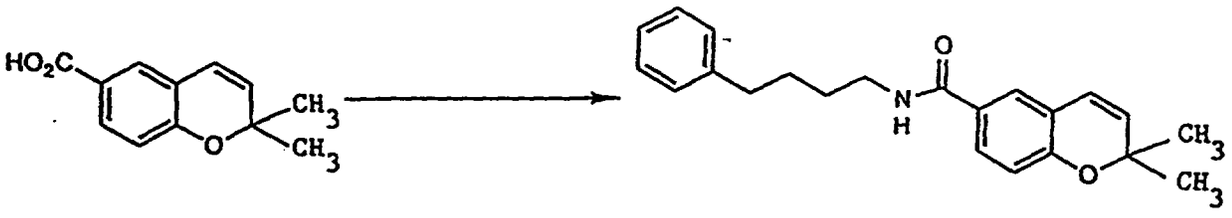
Phosphorus pentachloride (3.1g) was added to a solution of the compound of Preparation 35 (5.3g) in chloroform (100ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (1.7g) was added and the mixture allowed to stand at room temperature for 16 hours. The mixture was washed with water (100ml) and concentrated *in vacuo* to give an oil which was purified by chromatography on silica eluting with dichloromethane containing methanol (0.5%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as an oil, 4.07g.

^{1}H-NMR ($CDCl_3$): δ = 7.35-7.05 (m,7H), 6.90 (d,1H), 6.35-6.30 (d,1H), 5.75-5.70 (d,1H), 4.45-4.35 (t,2H), 2.65-2.55 (t,2H), 2.00-1.90 (m,2H), 1.70-1.60 (m,2H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 35

2,2-Dimethyl-6-(N-[4-phenylbut-1-yl])carbamoyl-2H-benzo[b]pyran



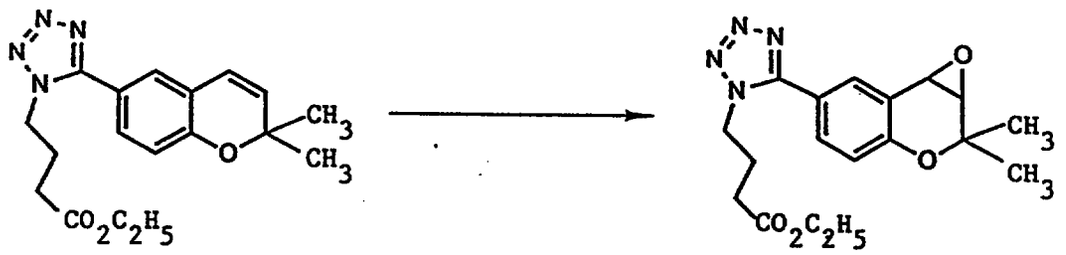
1,1'-Carbonyldiimidazole (2.62g) was added to a solution of the compound of Preparation 27 (3g) in dichloromethane (40ml) and the mixture was stirred at room temperature for 30 minutes. 1-Amino-4-phenylbutane (4.4g) was added and the mixture was allowed to stand at room temperature for 3 days. The mixture was washed sequentially with water (100ml), 2N hydrochloric acid (2 x 50 ml) and water (100ml), then dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as an oil which crystallised on standing, 5.35g, m.p. 65-70°C.

^{1}H-NMR ($CDCl_3$): δ = 7.50-7.45 (dd,1H), 7.40 (d,1H), 7.30-7.10 (m,5H), 6.80-6.75 (d,1H), 6.35-6.30 (d,1H), 6.10-6.00 (br^t,1H); 5.65-5.60 (d,1H), 3.50-3.40 (m,2H), 2.70-2.60 (m,2H), 1.75-1.60 (m,4H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 36

(3R,4R/3S,4S)-3,4-Dihydro-2,2-dimethyl-3,4-epoxy-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran

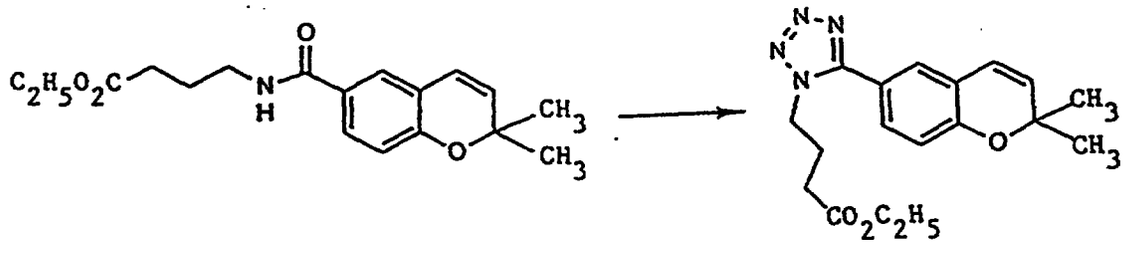


A solution of OXONE™ (2.2g) in water (10ml) was added, over 1.5 hours, to a stirred mixture of the compound of Preparation 37 (1.2g), sodium hydrogen carbonate (1.2g), water (8ml) and acetone (30ml). When the addition was complete the mixture was stirred at room temperature for a further 30 minutes. The acetone was evaporated *in vacuo* and the resulting aqueous mixture was extracted with dichloromethane (2 x 100ml). The dichloromethane solution was dried ($MgSO_4$) then concentrated *in vacuo* to give the title compound as an oil, 1.1g.

^{1}H-NMR ($CDCl_3$): δ = 7.80 (d,1H), 7.65-7.55 (dd,1H), 7.00-6.95 (d,1H), 4.55-4.50 (t,2H), 4.15-4.05 (q,2H), 4.00 (d,1H), 3.55 (d,1H), 2.45-2.40 (m,2H), 2.30-2.20 (m,2H), 1.65 (s,3H), 1.30 (s,3H), 1.30-1.20 (t,3H) ppm.

PREPARATION 37

2,2-Dimethyl-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



Phosphorus pentachloride (0.66g) was added to a solution of the compound of Preparation 38 (1g) in chloroform (20ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (0.54g) was added and the mixture was allowed to stand at room temperature for 4 days. The mixture was washed with water (100ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as an oil, 1.28g.

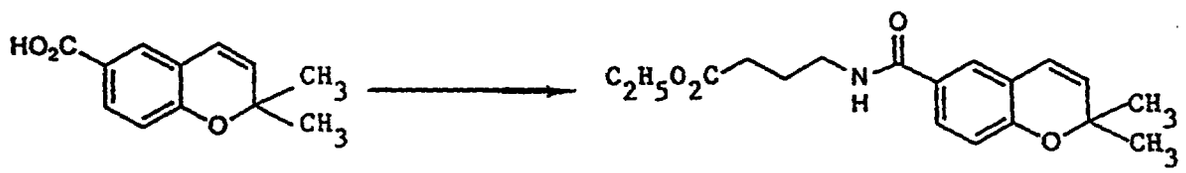
^{1}H-NMR ($CDCl_3$): δ = 7.45-7.40 (dd,1H), 7.40 (d,1H), 6.90 (d,1H), 6.40-6.35 (d,1H), 5.70 (d,1H), 4.55-4.45 (t,2H), 4.10-4.05 (q,2H), 2.45-2.35 (t,2H), 2.30-2.20 (m,2H), 1.45 (s,6H), 1.30-1.20 (t,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 38

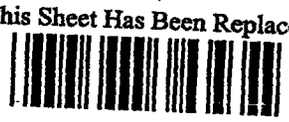
2,2-Dimethyl-6-(N-[3-ethoxycarbonylprop-1-yl])carbamoyl-2H-benzo[b]pyran



1,1'-Carbonyldiimidazole (4.4g) was added to a solution of the compound of Preparation 27 (5g) in dichloromethane (100ml) and the mixture was stirred at room temperature for 30 minutes. Ethyl 4-aminobutanoate hydrochloride (4.5g) was added and the mixture was allowed to stand at room temperature for 7 days. The mixture was washed with water (100ml) then concentrated *in vacuo* to give a gum which was purified by chromatography on silica eluting with dichloromethane containing methanol (1.25%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a solid, 4.3g, m.p. 88-89°C.

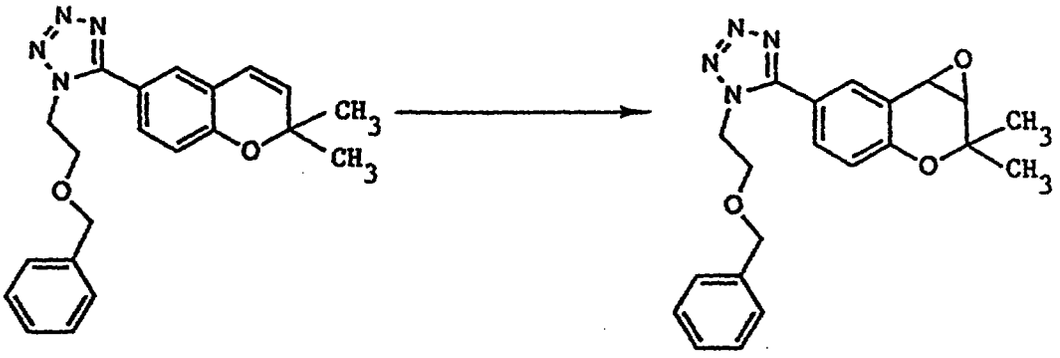
^{1}H-NMR ($CDCl_3$): δ = 7.60-7.50 (dd,1H), 7.45 (d,1H), 6.85-6.75 (d,1H), 6.45-6.40 (brt,1H), 6.40-6.35 (d,1H), 5.70-5.65 (d,1H), 4.20-4.10 (m,2H), 3.55-3.45 (q,2H), 2.50-2.45 (m,2H), 2.05-1.95 (m,2H), 1.50 (s,6H), 1.30-1.25 (t,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 39

(3R,4R/3S,4S)-6-(1-[2-Benzyloxyethyl]-1H-tetrazol-5-yl)-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2H-benzo[b]pyran



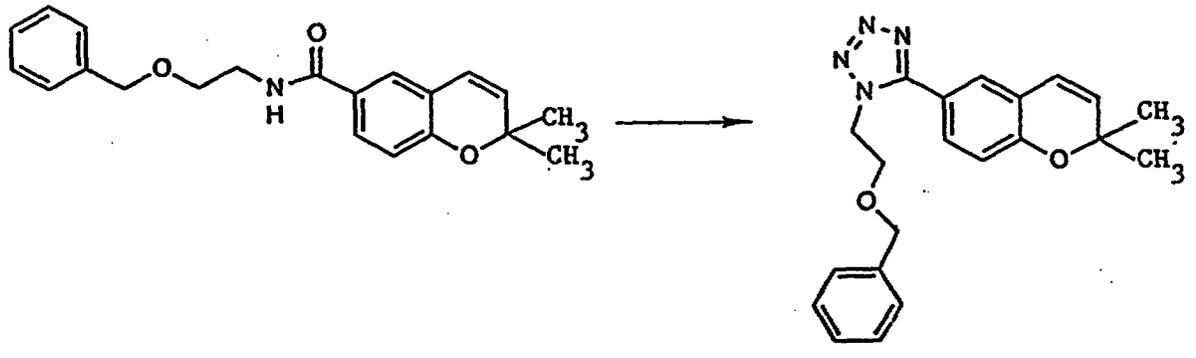
A solution of OXONE™ (6.8g) in water (20ml) was added, over 1 hour, to a stirred mixture of the compound of Preparation 40 (4g) sodium hydrogen carbonate (5.5g), water (60ml) and acetone (20ml). When the addition was complete the mixture was stirred at room temperature for a further 30 minutes. The acetone was evaporated *in vacuo* and the resulting aqueous mixture was extracted with dichloromethane (2 x 100ml). The dichloromethane solution was dried (Na_2SO_4) then concentrated *in vacuo* to give the title compound as a foam, 3.2g.
^{1}H-NMR ($CDCl_3$): δ = 7.85 (d,1H), 7.70-7.65 (dd,1H), 7.35-7.25 (m,3H), 7.20-7.15 (m,2H), 6.90 (d,1H), 4.60-4.55 (t,2H), 4.50 (s,2H), 4.05-4.00 (t,2H), 3.75 (d,1H), 3.50 (d,1H), 1.60 (s,3H), 1.30 (s,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 40

6-(1-[2-Benzyloxyethyl]-1H-tetrazol-5-yl)-2,2-dimethyl-2H-benzo[b]pyran



Phosphorus pentachloride (9.9g) was added to a solution of the compound of Preparation 41 (16g) in chloroform (300ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (5.5g) was added and the mixture was allowed to stand at room temperature for a total of 2 days during which time further trimethylsilyl azide was added after 16 (1.5g) and 43 (0.5g) hours. The mixture was washed with water (200ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as an oil, 20.6g.
^{1}H-NMR ($CDCl_3$): δ = 7.55-7.50 (dd,1H), 7.45 (d,1H), 7.35-7.25 (m,3H), 7.20-7.15 (m,2H), 6.90-6.85 (d,1H), 6.25-6.20 (d,1H), 5.70-5.65 (d,1H), 4.60-4.50 (t,2H), 4.45 (s,2H), 4.05-4.00 (t,2H), 1.45 (s,6H) ppm.

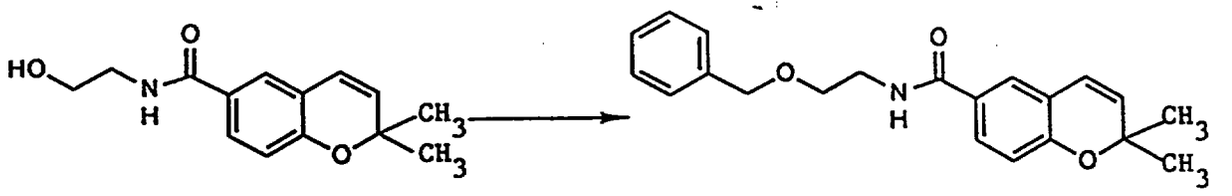
This Sheet Has Been Replaced



This Sheet Has Been Replaced

PREPARATION 41

6-(N-[2-Benzyloxyethyl])carbamoyl-2,2-dimethyl-2H-benzo[b]pyran



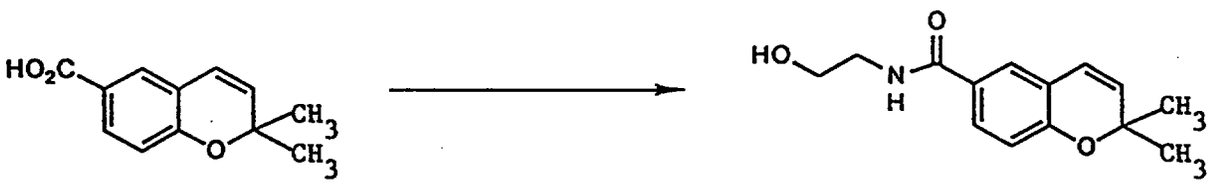
Sodium hydride (1.72g of an 80% suspension in mineral oil) was added, in portions, over 10 minutes to a cooled (0°C) solution of the compound of Preparation 42 (14.2g) in anhydrous tetrahydrofuran (200ml). The mixture was stirred at room temperature for 30 minutes then re-cooled to 0°C and a solution of benzyl bromide (9.94g) in anhydrous tetrahydrofuran (10ml) was added over 15 minutes. When the addition was complete the mixture was allowed to warm to room temperature and was stirred for 18 hours. Water (250ml) was added and the mixture was extracted with diethyl ether (2 x 300ml). The ethereal extracts were concentrated *in vacuo* and the residue was dissolved in dichloromethane (100ml). The water which separated was removed and the organic layer was concentrated *in vacuo* to give an oil which was purified by chromatography on silica eluting with dichloromethane containing methanol (0.5%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as an oil, 15.5g.

^{1}H-NMR ($CDCl_3$): δ = 7.50-7.45 (dd,1H), 7.45 (d,1H), 7.35-7.25 (m,5H), 6.80-6.75 (d,1H), 6.45-6.35 (brs,1H), 6.35-6.30 (d,1H), 5.70-5.65 (d,1H), 4.55 (s,2H), 3.65 (s,4H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 42

2,2-Dimethyl-6-(N-[2-hydroxyethyl])carbamoyl-2H-benzo[b]pyran



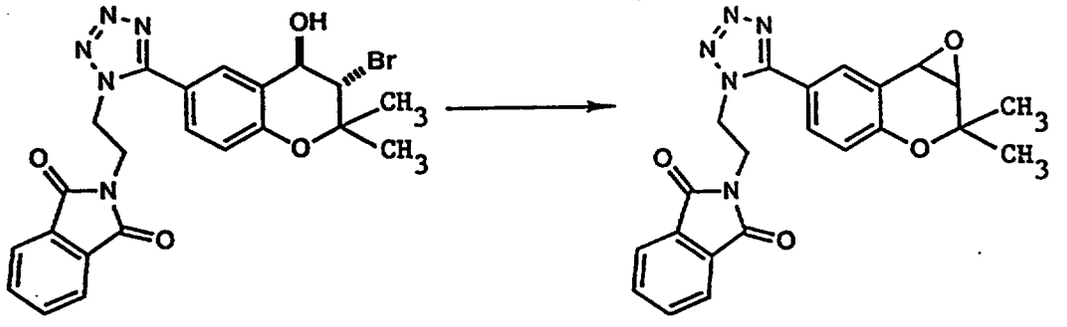
1,1'-Carbonyldiimidazole (10.5g) was added, in three portions, to a solution of the compound of Preparation 27 (12g) in dichloromethane (250ml) and the mixture was stirred at room temperature for 30 minutes. Ethanolamine (10g) was added and the mixture was stirred at room temperature for 4 days. The mixture was washed with water (250ml) and the washings back-extracted with dichloromethane (100ml). The dichloromethane extracts were combined and concentrated *in vacuo* and the residue was purified by chromatography on silica eluting with dichloromethane containing methanol (5%). The product-containing fractions were combined and concentrated *in vacuo* to give a foam which was azeotroped with dichloromethane and ethyl acetate to give the title compound as a colourless solid, 12.25g, m.p. 60-70°C.

^{1}H-NMR ($CDCl_3$): δ = 7.55-7.50 (dd,1H), 7.45 (d,1H), 6.80-6.75 (d,1H), 6.70-6.60 (brs,1H), 6.30 (d,1H), 5.65-5.60 (d,1H), 3.85-3.75 (m,2H), 3.65-3.55 (m,2H), 3.05-3.00 (t,1H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 43

(3R,4R/3S,4S)-3,4-Dihydro-2,2-dimethyl-3,4-epoxy-6-(1-[2-phthalimidoethyl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



(only one stereoisomer shown)

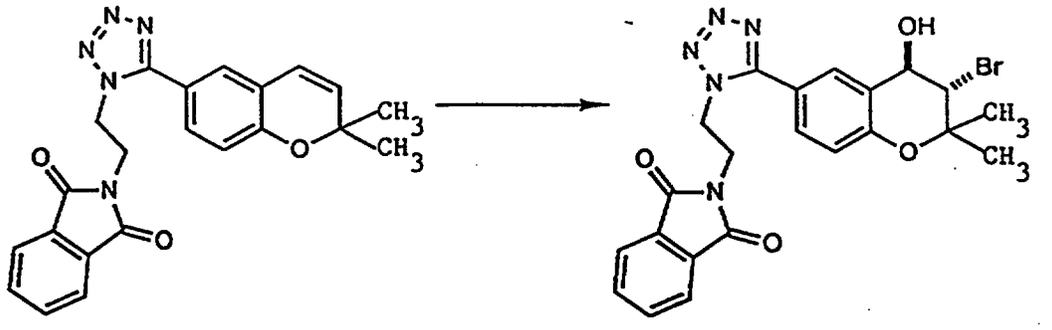
Sodium hydride (0.6g of an 80% suspension in mineral oil) was added to a solution of the compound of Preparation 44 (8.6g) in anhydrous dimethyl sulfoxide (40ml) and the mixture was stirred at room temperature for 30 minutes. The mixture was poured onto ice (100g) and extracted with ethyl acetate (3 x 100ml). The organic extracts were combined and washed with saturated sodium chloride solution (2 x 100ml), then dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound, 5.6g.

^{1}H-NMR ($CDCl_3$): δ = 7.80-7.65 (m,5H), 7.55-7.50 (dd,1H), 6.90-6.85 (d,1H), 4.85-4.75 (m,2H), 4.15-4.05 (m,2H), 3.90 (d,1H), 3.50 (d,1H), 1.60 (s,3H), 1.30 (s,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 44

(3R,4S/3S,4R)-3-Bromo-3,4-dihydro-2,2-dimethyl-4-hydroxy-6-(1-[2-phthalimidoethyl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



(only one stereoisomer shown)

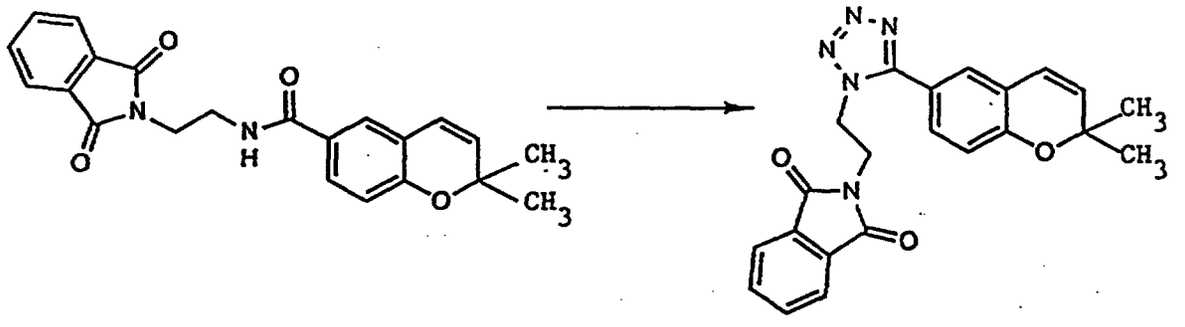
Water (0.5ml) was added to a solution of the compound of Preparation 45 (7.74g) in dimethyl sulfoxide (110ml) and the mixture was cooled to 0°C in an ice bath. *N*-Bromosuccinimide (7g) was added and the mixture was stirred at room temperature for 1 hour then poured onto ice (200g). The mixture was extracted with ethyl acetate (300ml) and the extract was washed with saturated sodium chloride solution (2 x 100ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a foam, 9.1g.

^{1}H-NMR ($CDCl_3$): δ = 7.90-7.65 (m,5H), 7.55-7.50 (dd,1H), 6.80 (d,1H), 4.95-4.90 (d,1H), 4.90-4.75 (m,2H), 4.20-4.05 (m,3H), 1.65 (s,3H), 1.45 (s,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 45

2,2-Dimethyl-6-(1-[2-phthalimidoethyl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



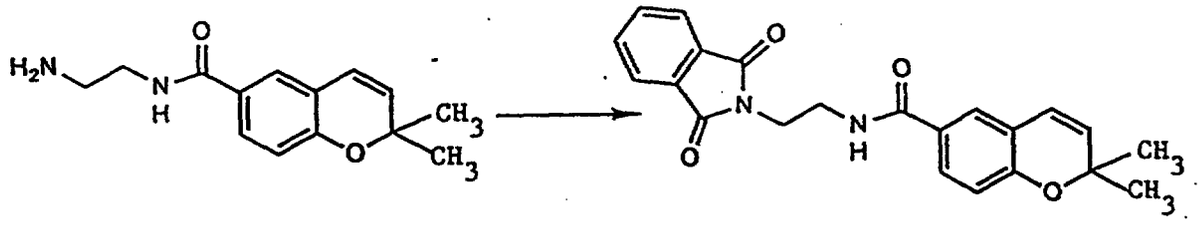
Phosphorus pentachloride (4.9g) was added to a solution of the compound of Preparation 46 (8.6g) in chloroform (200ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (4.3g) was added and the mixture was allowed to stand at room temperature for 18 hours. Water (100ml) was added and the mixture was stirred vigorously for 10 minutes. The layers were separated and the aqueous layer was extracted with dichloromethane (100ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a solid, 9.5g, m.p. 178-182°C.

^{1}H-NMR ($CDCl_3$): δ = 7.80-7.70 (m,4H), 7.35-7.30 (dd,1H), 7.25 (d,1H), 6.75-6.70 (d,1H), 6.30-6.25 (d,1H), 5.70-5.65 (d,1H), 4.85-4.75 (t,2H), 4.15-4.05 (t,2H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 46

2,2-Dimethyl-6-(N-[2-phthalimidoethyl])carbamoyl-2H-benzo[b]pyran



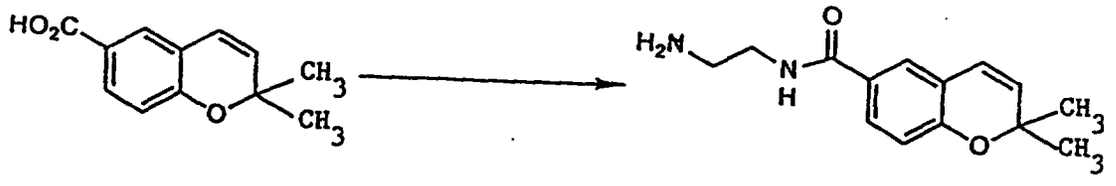
A mixture of the compound of Preparation 47 (0.57g) and phthalic anhydride (0.35g) was heated with stirring at 175-185°C for 15 minutes. On cooling to room temperature the mixture was purified by chromatography on silica eluting with dichloromethane containing methanol (8%) and concentrated aqueous ammonia (0.4%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a solid, 0.58g, m.p. 183-185°C.

^{1}H-NMR ($CDCl_3$): δ = 7.90-7.85 (m,2H), 7.75-7.70 (m,2H), 7.50-7.45 (dd,1H), 7.45 (d,1H), 6.80-6.75 (m,2H), 6.35-6.30 (d,1H), 5.65-5.60 (d,1H), 4.05-3.95 (m,2H), 3.75-3.70 (m,2H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 47

6-(N-[2-Aminoethyl])carbamoyl-2,2-dimethyl-2H-benzo[b]pyran



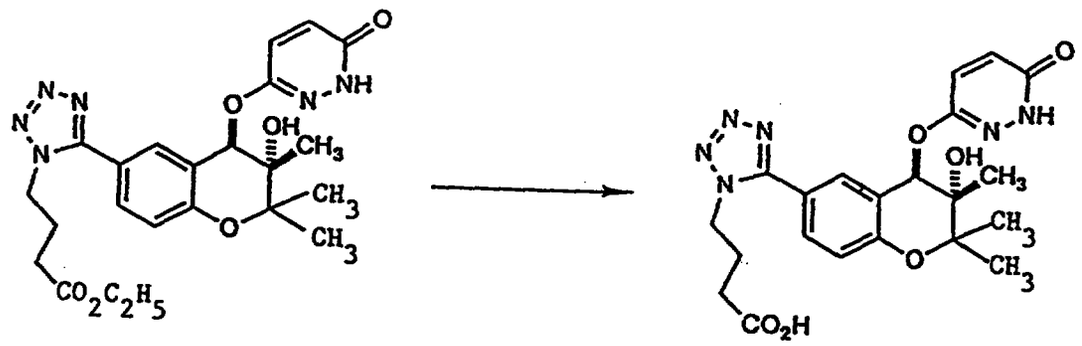
1,1'-Carbonyldiimidazole (4.4g) was added to a solution of the compound of Preparation 27 (5g) in dichloromethane (80ml) and the mixture was stirred for 30 minutes at room temperature. 1,2-Diaminoethane (4g) was added and the mixture was allowed to stand at room temperature for 16 hours. The mixture was concentrated *in vacuo* to give a solid which was purified by chromatography on silica eluting with dichloromethane containing methanol (2.5 up to 20%) and concentrated aqueous ammonia (0 up to 1%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as an oil, 4.9g.

^{1}H-NMR ($CDCl_3$): δ = 7.55-7.50 (dd,1H), 7.45 (s,1H), 6.80-6.70 (m,2H), 6.30 (d,1H), 5.65-5.60 (d,1H), 3.50-3.40 (m,2H), 2.95-2.90 (t,2H), 1.80-1.75 (brs,2H), 1.40 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 48

(3S,4R)-6-(1-[3-Carboxyprop-1-yl]-1H-tetrazol-5-yl)-3,4-dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran

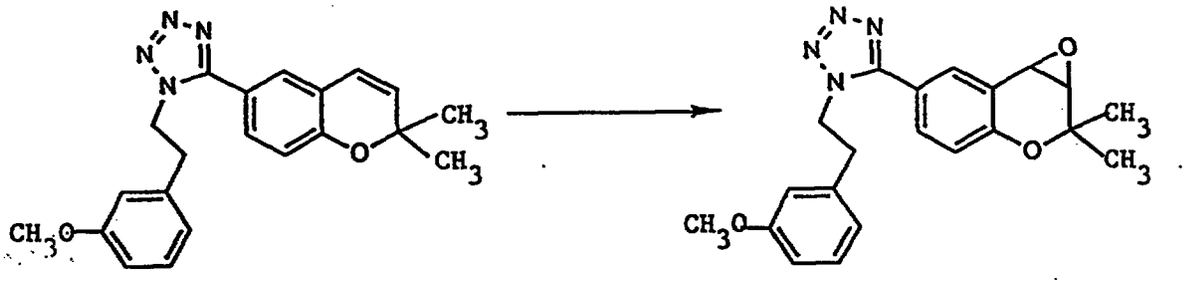


A mixture of the compound of Example 1 (0.078g), sodium hydroxide (1ml of a 0.35M aqueous solution) and ethanol (1ml) was allowed to stand at room temperature for 1 hour. The mixture was acidified to pH1 by the addition of 2N hydrochloric acid and the ethanol was removed *in vacuo* to leave a gum. The water was decanted off and the residual gum was triturated twice with water then dried *in vacuo* to give the title compound as a solid, 0.046g, m.p. 116-126°C. Found: C, 53.97; H, 5.45; N, 17.79; $C_{21}H_{24}N_6O_6.0.5H_2O$ requires: C, 54.19; H, 5.41; N, 18.06%.

^{1}H-NMR (d_6-DMSO): δ = 7.65-7.55 (m,2H), 7.30-7.20 (d,1H), 7.00-6.85 (m,2H), 5.95 (s,1H), 5.50-5.20 (brs,1H), 4.45-4.30 (m,2H), 2.30-2.20 (m,2H), 2.05-1.90 (m,2H), 1.40 (s,3H), 1.30 (s,3H), 1.20 (s,3H) ppm.

PREPARATION 49

(3R,4R/3S,4S)-3,4-Dihydro-2,2-dimethyl-3,4-epoxy-6-(1-[2-(3-methoxyphenyl)ethyl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



A solution of OXONE™ (5g) in water (20ml) was added, over 1 hour, to a stirred mixture of the compound of Preparation 50 (2.8g), sodium hydrogen carbonate (3.25g), water (20ml) and acetone (60ml). When the addition was complete the mixture was stirred at room temperature for a further 45 minutes. The acetone was evaporated *in vacuo* and the resulting aqueous mixture was extracted with dichloromethane (2 x 100ml). The dichloromethane solution was dried (Na_2SO_4) then concentrated *in vacuo* to give the title compound as a foam, 2.6g.

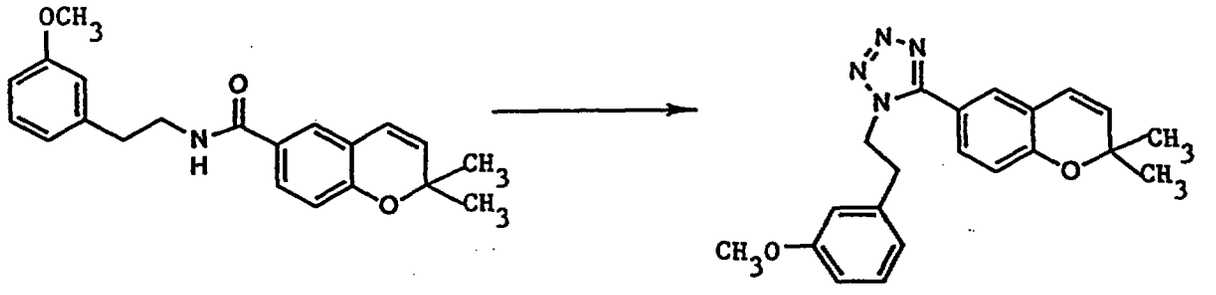
^{1}H-NMR ($CDCl_3$): δ = 7.15-7.05 (m,3H), 6.85-6.80 (d,1H) 6.80-6.75 (dd,1H), 6.55-6.50 (d,1H), 6.45 (s,1H), 4.65-4.55 (m,2H), 3.85 (d,1H), 3.70 (s,3H), 3.50 (d,1H), 3.30-3.20 (t,2H), 1.65 (s,3H), 1.30 (s,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 50

2,2-Dimethyl-6-(1-[2-(3-methoxyphenyl)ethyl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



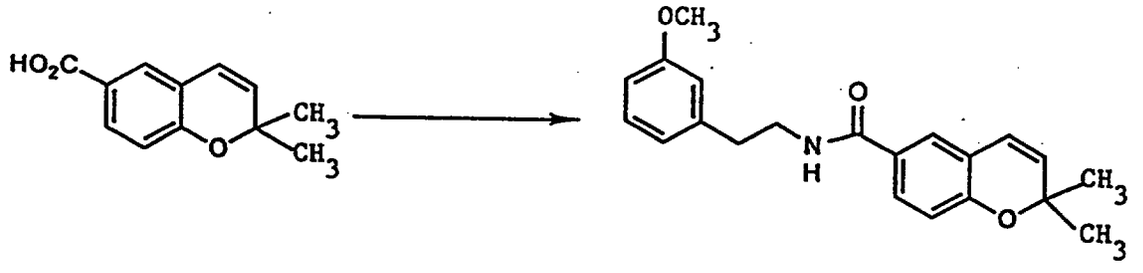
Phosphorus pentachloride (3.2g) was added to a solution of the compound of Preparation 51 (5.17g) in chloroform (100ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (1.8g) was added and the mixture was allowed to stand at room temperature for 5 hours. 10% Aqueous ceric ammonium nitrate (100ml) was added followed by dichloromethane (200ml) and water (50ml). The mixture was stirred vigorously for 20 minutes and then was filtered through a cellulose-based filter aid. The layers were separated and the organic solution was concentrated *in vacuo* to give an oil which was purified by chromatography on silica eluting with dichloromethane containing methanol (0.25%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as an oil, 2.9g.

^{1}H-NMR ($CDCl_3$): δ = 7.15-7.10 (t,1H), 7.05-7.00 (dd,1H), 6.85-6.75 (m,3H), 6.55-6.50 (d,1H), 6.45 (s,1H), 6.25-6.20 (d,1H), 5.70-5.65 (d,1H), 4.60-4.55 (t,2H), 3.70 (s,3H), 3.25-3.20 (t,2H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 51

2,2-Dimethyl-6-(N-[2-(3-methoxyphenyl)ethyl])carbamoyl-2H-benzo[b]pyran



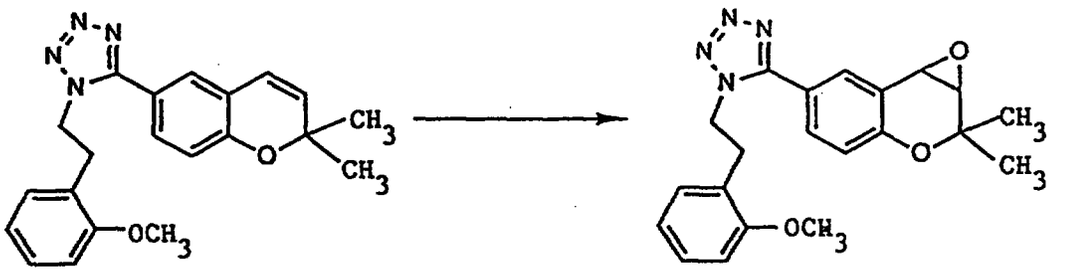
1,1'-Carbonyldiimidazole (2.62g) was added to a solution of the compound of Preparation 27 (3g) in dichloromethane (40ml) and the mixture was heated under reflux for 30 minutes. On cooling to room temperature 2-(3-methoxyphenyl)ethylamine (2.4g) was added and the mixture was allowed to stand at room temperature for 12 days. The mixture was diluted with dichloromethane to a total volume of 100ml, then washed sequentially with 10% aqueous sodium hydroxide (50ml), 2N hydrochloric acid (2 x 50 ml) and water (50ml), then dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as an oil which crystallised on standing, 5.26g, m.p. 105-110°C.

^{1}H-NMR ($CDCl_3$): δ = 7.45-7.35 (m,2H), 7.30-7.20 (m,1H), 6.85-6.70 (m,4H), 6.30 (d,1H), 6.05-6.00 (brt,1H), 5.65-5.60 (d,1H), 3.80 (s,3H), 3.75-3.65 (m,2H), 2.95-2.85 (t,2H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced

PREPARATION 52

(3R,4R/3S,4S)-3,4-Dihydro-2,2-dimethyl-3,4-epoxy-6-(1-[2-(2-methoxyphenyl)ethyl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



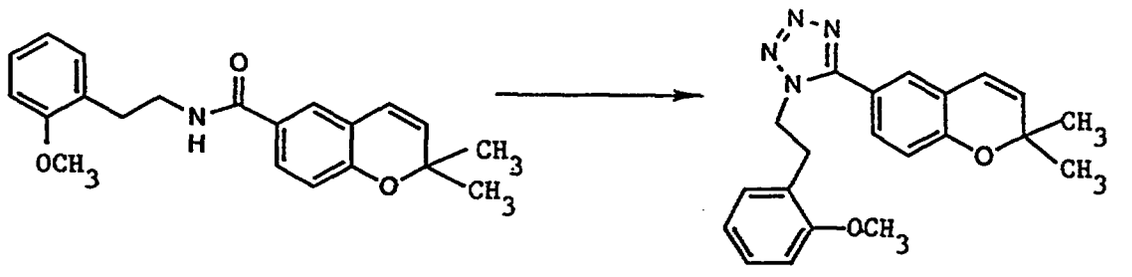
A solution of OXONE™ (4.5g) in water (20ml) was added, over 1 hour, to a stirred mixture of the compound of Preparation 53 (2.5g), sodium hydrogen carbonate (2.9g), water (20ml) and acetone (60ml). When the addition was complete the mixture was stirred at room temperature for a further 45 minutes. The acetone was evaporated *in vacuo* and the resulting aqueous mixture was extracted with dichloromethane (3 x 100ml). The dichloromethane solution was dried (Na_2SO_4) then concentrated *in vacuo* to give the title compound as a solid, 2.8g.

^{1}H-NMR ($CDCl_3$): δ = 7.30-7.15 (m,3H), 6.90-6.70 (m,4H), 4.70-4.60 (t,2H), 3.85 (d,1H), 3.65 (s,3H), 3.55 (d,1H), 3.30-3.15 (m,2H), 1.60 (s,3H), 1.30 (s,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 53

2,2-Dimethyl-6-(1-[2-(2-methoxyphenyl)ethyl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



Phosphorus pentachloride (3.1g) was added to a solution of the compound of Preparation 54 (5g) in chloroform (100ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (1.7g) was added and the mixture was allowed to stand at room temperature for 16 hours. 10% Aqueous ceric ammonium nitrate (100ml) was added followed by dichloromethane (250ml) and water (50ml). The mixture was stirred vigorously for 20 minutes then filtered through a cellulose-based filter aid. The layers were separated and the organic layer was concentrated *in vacuo* to give an oil which was purified by chromatography on silica eluting with dichloromethane containing methanol (0.25%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a solid, 2.65g, m.p. 101-105°C.

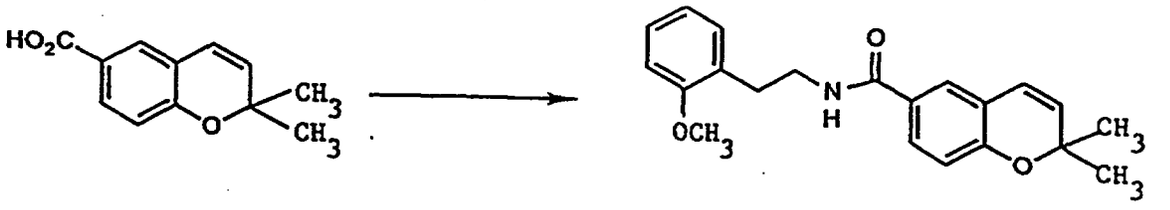
^{1}H-NMR ($CDCl_3$): δ = 7.20-7.10 (m,2H), 6.95 (d,1H), 6.90-6.75 (m,3H), 6.75-6.70 (d,1H), 6.30-6.25 (d,1H), 5.70 (d,1H), 4.70-4.60 (t,2H), 3.65 (s,3H), 3.25-3.20 (t,2H), 1.50 (s,6H) ppm.

This Sheet Has Been Replaced



PREPARATION 54

2,2-Dimethyl-6-(N-[2-(2-methoxyphenyl)ethyl]carbamoyl)-2H-benzo[b]pyran



1,1'-Carbonyldiimidazole (2.62g) was added to a solution of the compound of Preparation 27 (3g) in dichloromethane (40ml) and the mixture was heated under reflux for 30 minutes. On cooling to room temperature 1-amino-2-(2-methoxyphenyl)ethane (4g) was added and the mixture was allowed to stand at room temperature for 12 days. The mixture was diluted with dichloromethane to a total volume of 100ml then washed sequentially with 10% aqueous sodium hydroxide (50ml), 2N hydrochloric acid (2 x 50 ml) and water (50ml), then dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a solid, 5.15g, m.p. 125-130°C.

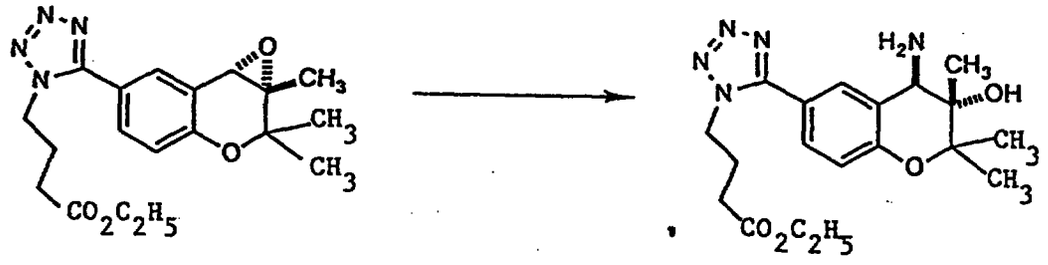
^{1}H-NMR ($CDCl_3$): δ = 7.45-7.35 (m,2H), 7.25-7.15 (m,2H), 6.95-6.85 (m,2H), 6.75 (d,1H), 6.40-6.35 (brt,1H), 6.30 (d,1H), 5.65 (d,1H), 3.85 (s,3H), 3.70-3.60 (t,2H), 2.95-2.80 (t,2H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced



PREPARATION 55

(3S,4R)-4-Amino-3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-2,2,3-trimethyl-2H-benzo[b]pyran



A mixture containing the compound of Preparation 1 (1g), concentrated aqueous ammonia (4ml) and ethanol (10ml) was heated at 60-65°C for 18 hours then concentrated *in vacuo* and the residue was purified by chromatography on silica eluting with dichloromethane containing methanol (5%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a foam, 0.56g. Found: C, 58.28; H, 7.03; N, 17.66; $C_{19}H_{27}N_5O_4$ requires: C, 58.57; H, 6.98; N, 17.97%.

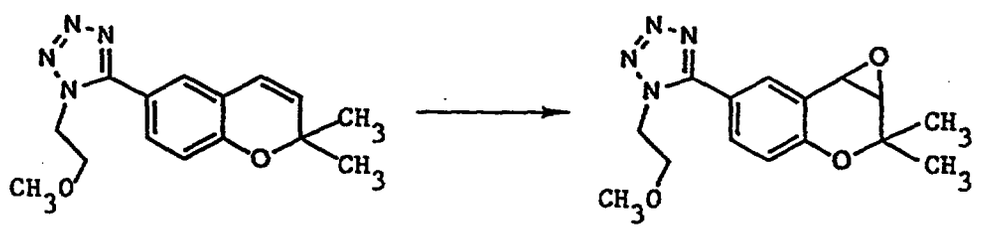
^{1}H-NMR ($CDCl_3$): δ = 7.85 (s,1H), 7.55-7.50 (dd,1H), 6.95-6.90 (d,1H), 4.55-4.40 (m,2H), 4.15-4.05 (q,2H), 3.95 (s,1H), 2.50-2.40 (m,2H), 2.30-2.20 (m,2H), 1.85-1.60 (brs,2H), 1.50 (s,3H), 1.35 (s,3H), 1.25-1.20 (t,3H), 1.05 (s,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 56

(3R,4R/3S,4S)-3,4-Dihydro-2,2-dimethyl-3,4-epoxy-6-(1-[2-methoxyethyl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



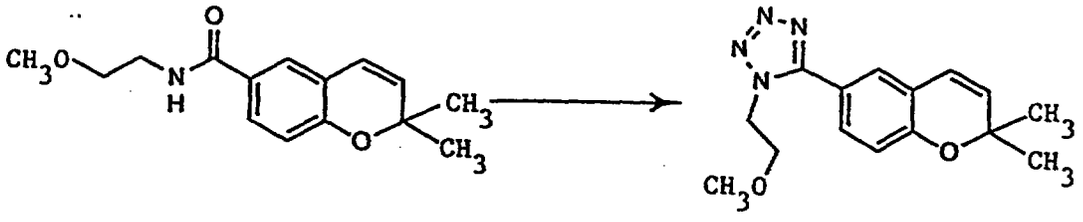
A solution of OXONE™ (3.5g) in water (15ml) was added, over 1 hour, to a stirred mixture of the compound of Preparation 57 (1.65g), sodium hydrogen carbonate (2g), water (15ml) and acetone (45ml). When the addition was complete the mixture was stirred at room temperature for a further 15 minutes then a second batch of OXONE™ (1.7g in 5ml water) was added. The acetone was evaporated *in vacuo* and the resulting aqueous mixture was extracted with dichloromethane (3 x 100ml). The combined dichloromethane extracts were dried (Na_2SO_4) then concentrated *in vacuo* to give the title compound as an oil, 1.7g.
^{1}H-NMR ($CDCl_3$): δ = 7.90 (d,1H), 7.75-7.70 (dd,1H), 6.95-6.90 (d,1H), 4.55-4.45 (m,2H), 4.00-3.90 (m,3H), 3.55 (d,1H), 3.30 (s,3H), 1.65 (s,3H), 1.30 (s,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 57

2,2-Dimethyl-6-(1-[2-methoxyethyl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



Phosphorus pentachloride (2.6g) was added to a solution of the compound of Preparation 58 (3.2g) in chloroform (75ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (1.4g) was added and the mixture was allowed to stand at room temperature for 16 hours. The mixture was washed with water (100ml) dried ($MgSO_4$) and concentrated *in vacuo* to give an oil which was purified by chromatography on silica eluting with dichloromethane containing methanol (1%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as an oil, 3.16g.

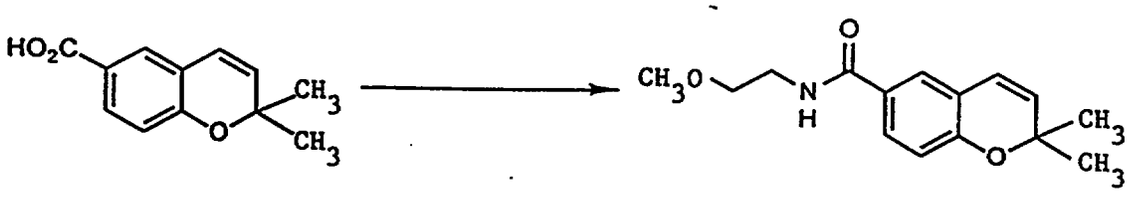
^{1}H-NMR ($CDCl_3$): δ = 7.55-7.50 (dd,1H), 7.45 (d,1H), 6.90 (d,1H), 6.40-6.35 (d,1H), 5.70 (d,1H), 4.55-4.50 (t,2H), 3.95-3.90 (t,2H), 3.30 (s,3H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced



PREPARATION 58

2,2-Dimethyl-6-(N-[2-methoxyethyl]carbamoyl)-2H-benzo[b]pyran



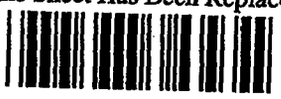
1,1'-Carbonyldiimidazole (2.62g) was added to a solution of the compound of Preparation 27 (3g) in dichloromethane (60ml) and the mixture was stirred for 30 minutes at room temperature. 1-Amino-2-methoxyethane (1.1g) was added and the mixture allowed to stand at room temperature for 48 hours. A further batch of 1-amino-2-methoxyethane (1g) was added and stirring was continued for 24 hours. The mixture was washed with 10% aqueous sodium hydroxide (50ml), 2N hydrochloric acid (2 x 50ml) and water (50ml), then concentrated *in vacuo* to give an oil which was purified by chromatography on silica eluting with dichloromethane containing methanol (1%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as an oil which crystallised on standing, 3.32g, m.p. 57-60°C.

^{1}H-NMR ($CDCl_3$): δ = 7.55-7.50 (dd,1H), 7.45 (d,1H), 6.80-6.75 (d,1H), 6.50-6.40 (brs,1H), 6.35-6.30 (d,1H), 5.65-5.60 (d,1H), 3.65-3.50 (m,4H), 3.40 (s,3H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced

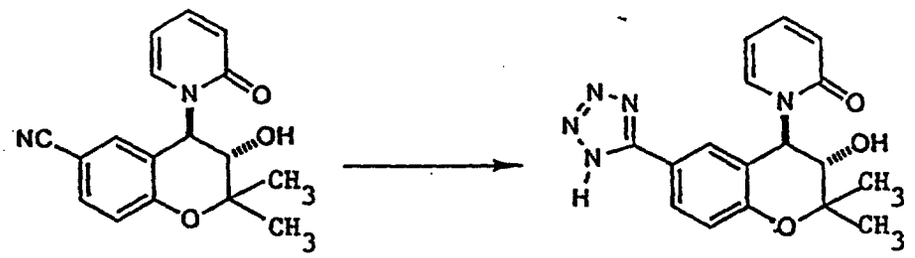


This Sheet Has Been Replaced



PREPARATION 59

(3R,4S/3S,4R)-3,4-Dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxo-1,2-dihydropyridin-1-yl)-6-(1H-tetrazol-5-yl)-2H-benzo[b]pyran



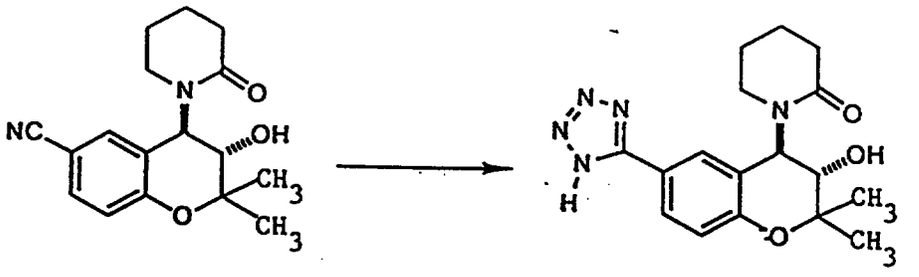
(only one stereoisomer shown)

A mixture containing (3R,4S/3S,4R)-6-cyano-3,4-dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxo-1,2-dihydropyridin-1-yl)-2H-benzo[b]pyran (see J. Med. Chem., 1990, *33*, 3028, and J.Med. Chem., 1990, *33*, 492) (1g), sodium azide (1g), triethylamine hydrochloride (1.2g) and 1-methyl-2-pyrrolidinone (10ml) was heated at 150°C for 2 hours. On cooling to room temperature the mixture was poured into water (100ml), basified with 10% aqueous sodium hydroxide and extracted with dichloromethane (2 x 50ml). The aqueous solution was filtered and then acidified with concentrated hydrochloric acid (CAUTION! HN_3 evolved). The resulting precipitate was filtered off and washed with water to give the title compound as a solid, 1g, m.p. >260°C. Found: C, 58.83; H, 5.10; N, 19.99; $C_{17}H_{17}N_5O_3.0.5H_2O$ requires: C, 58.61; H, 5.21; N, 20.10%.

^{1}H-NMR (d_6-DMSO): δ = 7.90-7.80 (m,1H), 7.80-7.70 (d,0.5H), 7.50-7.35 (m,2H), 7.30 (s,0.5H), 7.05-7.00 (d,0.67H), 7.00-6.95 (d,0.33H), 6.55-6.50 (d,0.5H), 6.35-6.30 (t,0.5H), 6.30-6.15 (m,1.5H), 5.85-5.70 (brs,1H), 4.95-4.90 (d,0.25H), 4.50-4.45 (d,0.25H), 4.00-3.90 (d,1H), .60-3.10 (brs), 1.45 (s,2H), 1.40 (s,1H), 1.25 (s,2H), 1.20 (s,1H) ppm.

PREPARATION 60

(3R,4S/3S,4R)-3,4-Dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-6-(1H-tetrazol-5-yl)-2H-benzo[b]pyran



(only one stereoisomer shown)

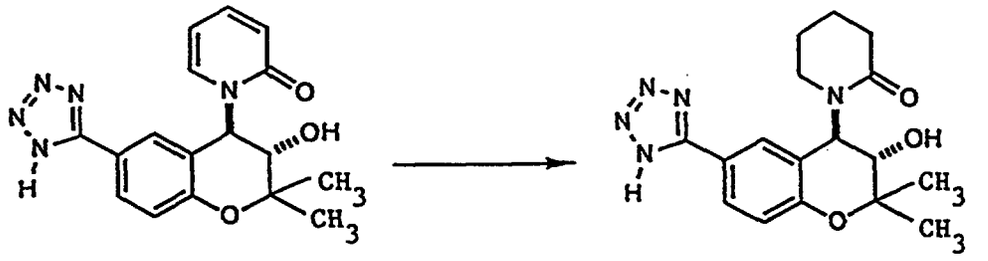
A mixture containing (3R,4S/3S,4R)-6-cyano-3,4-dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-2H-benzo[b]pyran (see J. Med. Chem., 1986, 29, 2194) (0.5g), sodium azide (0.5g), triethylamine hydrochloride (0.6g) and 1-methyl-2-pyrrolidinone (5ml) was heated at 150°C for 2 hours. On cooling to room temperature the mixture was partitioned between ethyl acetate (50ml) and 5% aqueous sodium hydroxide (30ml). The layers were separated and the aqueous layer was further extracted with ethyl acetate (2 x 20ml). The aqueous solution was filtered and acidified to pH1 with concentrated hydrochloric acid (CAUTION: HN_3 evolved). The resulting precipitate was triturated with hot ethanol containing a few drops of water, then filtered and dried *in vacuo* to give the title compound as a solid, 0.4g, m.p. >295°C.
^{1}H-NMR (d_6-DMSO): δ = 7.85-7.75 (d,1H), 7.55 (s,1H), 6.95-6.90 (d,1H), 5.80-5.70 (d,1H), 5.60-5.55 (d,1H), 3.75-3.65 (m,1H), 3.30-3.25 (brs,1H), 3.15-3.10 (brt,1H), 2.75-2.65 (m,1H), 2.50-2.40 (m,2H), 1.85-1.65 (m,3H), 1.60-1.50 (m,1H), 1.45 (s,3H), 1.15 (s,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 61

(3R,4S/3S,4R)-3,4-Dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-6-(1H-tetrazol-5-yl)-2H-benzo[b]pyran



(only one stereoisomer shown)

10% Aqueous sodium hydroxide (5ml) was added to a solution of the compound of Preparation 59 (5.8g) in water (200ml) and then 10% palladium-on-carbon (1g) was added. The mixture was hydrogenated at room temperature and 345kPa (50 psi) for 25 hours, then filtered through a cellulose-based filter aid. The filtrate was acidified to pH1 with concentrated hydrochloric acid to give the title compound as a solid which was filtered off and dried *in vacuo*, 5.3g.

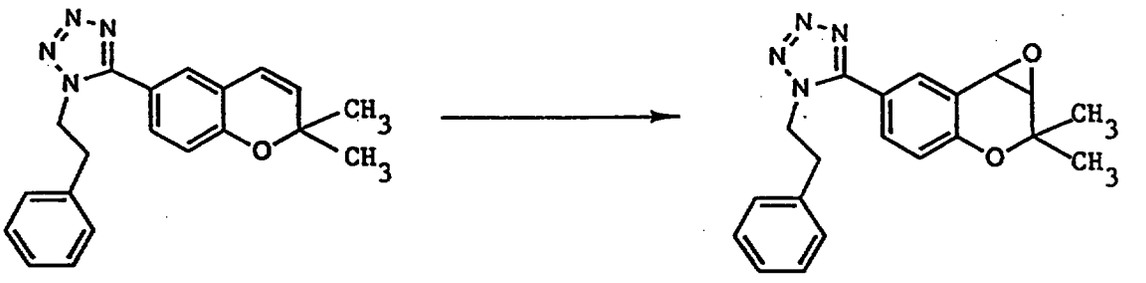
^{1}H-NMR (d_6-DMSO): δ = 7.85-7.80 (d,1H), 7.55 (s,1H), 6.95-6.90 (d,1H), 5.80-5.70 (d,1H), 5.65-5.50 (brs,1H), 3.75-3.65 (d,1H), 3.20-3.05 (m,1H), 2.75-2.65 (m,1H), 2.55-2.35 (m,3H), 1.85-1.65 (m,3H), 1.60-1.45 (m,1H), 1.45 (s,3H), 1.15 (s,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 62

(3R,4R/3S,4S)-3,4-Dihydro-2,2-dimethyl-3,4-epoxy-6-(1-[2-phenylethyl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



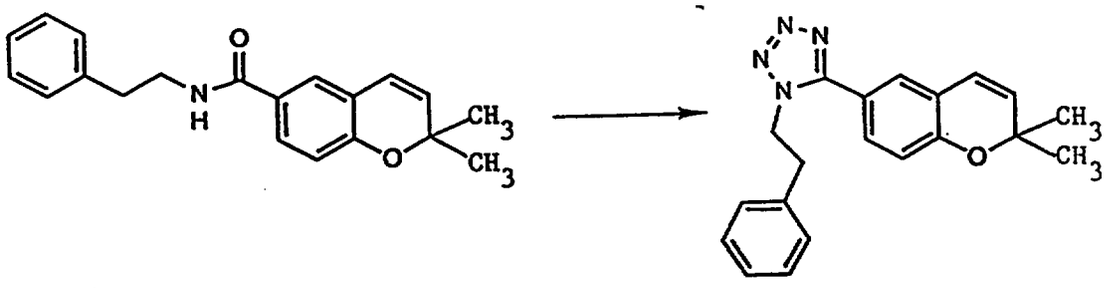
A solution of OXONE™ (8.75g) in water (35ml) was added, over 45 minutes, to a stirred mixture of the compound of Preparation 63 (4.5g), sodium hydrogen carbonate (5.7g), water (35ml) and acetone (100ml). When the addition was complete the mixture was stirred at room temperature for 16 hours. The acetone was evaporated *in vacuo* and the resulting aqueous mixture was extracted with ethyl acetate (2 x 100ml). The ethyl acetate solution was dried ($MgSO_4$), then concentrated *in vacuo* to give the title compound, 4.6g.
^{1}H-NMR ($CDCl_3$): δ = 7.35-7.20 (m,4H), 7.15-7.10 (m,1H), 7.00-6.95 (m,2H), 6.85-6.80 (d,1H), 4.65-4.55 (m,2H), 3.85 (d,1H), 3.55 (d,1H), 3.30-3.25 (t,2H), 1.60 (s,3H), 1.30 (s,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 63

2,2-Dimethyl-6-(1-[2-phenylethyl]-1H-tetrazol-5-yl)-2H-benzo[b]pyran



Phosphorus pentachloride (5g) was added to a solution of the compound of Preparation 64 (8.2g) in chloroform (100ml) and the mixture was heated under reflux for 25 minutes. On cooling to 0°C trimethylsilyl azide (3.2ml) was added and the mixture was allowed to stand at room temperature for 3 days. Further trimethylsilyl azide (0.8ml) was added and the mixture was stirred at room temperature for 5 hours. The mixture was washed with water (2 x 100ml) and the organic layer was dried ($MgSO_4$) then concentrated *in vacuo* in give an oil which was purified by chromatography on silica eluting with dichloromethane containing methanol (1%). The product-containing fractions were combined and concentrated *in vacuo* to give a gum which was further purified by chromatography on silica eluting with toluene containing ethyl acetate (5%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound, 6g.

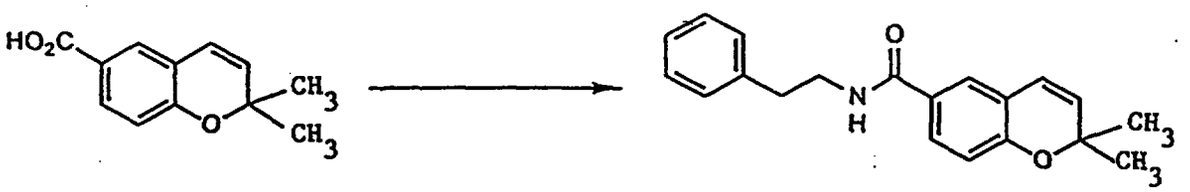
^{1}H-NMR ($CDCl_3$): δ = 7.30-7.15 (m,3H), 7.05-6.95 (m,3H), 6.85-6.75 (m,2H), 6.25-6.20 (d,1H), 5.70-5.65 (d,1H), 4.65-4.55 (t,2H), 3.30-3.20 (t,2H), 1.45 (s,6H) ppm.

This Sheet Has Been Replaced



PREPARATION 64

2,2-Dimethyl-6-(N-[2-phenylethyl]carbamoyl)-2H-benzo[b]pyran



1,1'-Carbonyldiimidazole (4.1g) was added to a solution of the compound of Preparation 27 (5g) in dichloromethane (40ml) and the mixture was stirred at room temperature for 30 minutes. 2-Phenylethylamine (4.2ml) was added and the mixture was stirred at room temperature for 16 hours. The mixture was diluted with dichloromethane to a total volume of 100ml then washed sequentially with 2N hydrochloric acid (2 x 50ml), 10% aqueous sodium hydroxide (50ml), water (50ml) and, finally, 2N hydrochloric acid (2 x 50ml), then dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound, 8g. ^{1}H-NMR ($CDCl_3$): δ = 7.45-7.15 (m,7H), 6.80-6.75 (d,1H), 6.35-6.30 (d,1H), 6.10-6.05 (brs,1H), 5.65-5.60 (d,1H), 3.70-3.65 (q,2H), 2.95-2.90 (t,2H), 1.45 (s,6H) ppm.

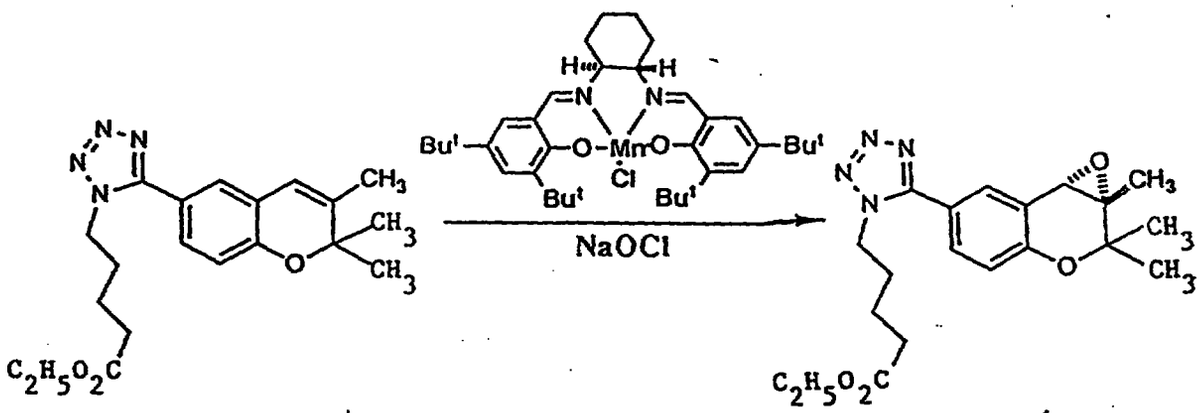
This Sheet Has Been Replaced



This Sheet Has Been Replaced

PREPARATION 65

(3S,4S)-3,4-Dihydro-3,4-epoxy-6-(1-[4-ethoxycarbonylbut-1-yl]-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



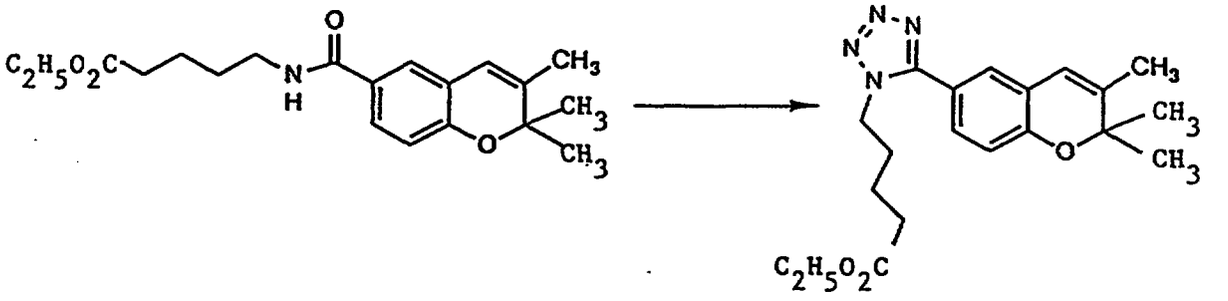
A solution of 4M commercial bleach (30ml) was diluted to a volume of 72ml with 0.05M aqueous sodium hydrogen phosphate solution and the pH of the mixture was adjusted to 11.3 with 5N aqueous sodium hydroxide solution. A portion of the resulting solution (51ml) was cooled to 0°C in an ice bath and a solution of the compound of Preparation 66 (5.6g) and [(S,S)-1,2-bis(3,5-di-*tert*-butylsalicylideamino]cyclohexane manganese III chloride (see J. Amer. Chem. Soc., 1991, *113*, 7063) (0.527g) in dichloromethane (25ml) was added. The resulting mixture was stirred at 0°C for 20 hours then the layers were separated and the dichloromethane layer was washed with saturated aqueous sodium chloride solution (20ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residual gum was purified by chromatography on silica eluting initially with hexane containing dichloromethane (5%) and then with hexane containing ethyl acetate (5% up to 20%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound, 3.72g.

^{1}H-NMR ($CDCl_3$): δ = 7.65 (d,1H), 7.50-7.45 (dd,1H), 6.95-6.90 (d,1H), 4.45-4.35 (t,2H), 4.10-4.00 (q,2H), 3.75 (s,1H), 2.30-2.25 (t,2H), 2.00-1.90 (m,2H), 1.65-1.55 (m,2H), 1.55 (s,3H), 1.50 (s,3H), 1.30 (s,3H), 1.25-1.15 (t,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 66

6-(1-[4-Ethoxycarbonylbut-1-yl]-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran



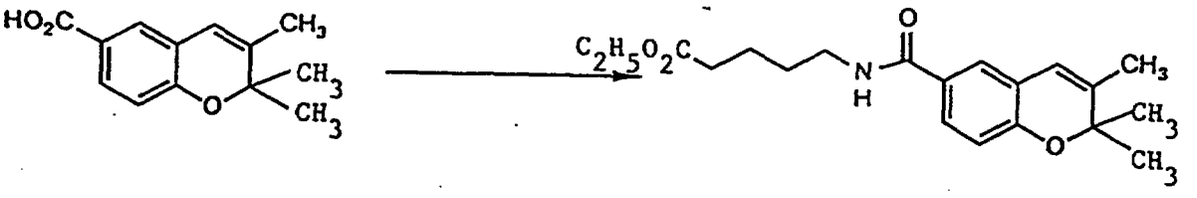
Phosphorus pentachloride (4.58g) was added to a solution of the compound of Preparation 67 (7.1g) in chloroform (90ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (3.32g) was added and the mixture was stirred at room temperature for 16 hours. Water (50ml) was added and the mixture was vigorously stirred. The layers were separated and the chloroform solution was washed with saturated aqueous sodium chloride solution (50ml) and 10% aqueous sodium carbonate solution (50ml), then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica eluting with dichloromethane containing methanol (5%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound, 5.7g.

^{1}H-NMR ($CDCl_3$): δ = 7.30-7.25 (dd,1H), 7.20 (d,1H), 6.90-6.85 (d,1H), 6.10 (s,1H), 4.45-4.35 (t,2H), 4.10 (q,2H), 2.30-2.25 (t,2H), 2.00-1.90 (m,2H), 1.85 (brs,3H), 1.70-1.55 (m,2H), 1.40 (s,6H), 1.25-1.15 (t,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 67

6-(N-[4-Ethoxycarbonylbut-1-yl]carbamoyl)-2,2,3-trimethyl-2H-benzo[b]pyran



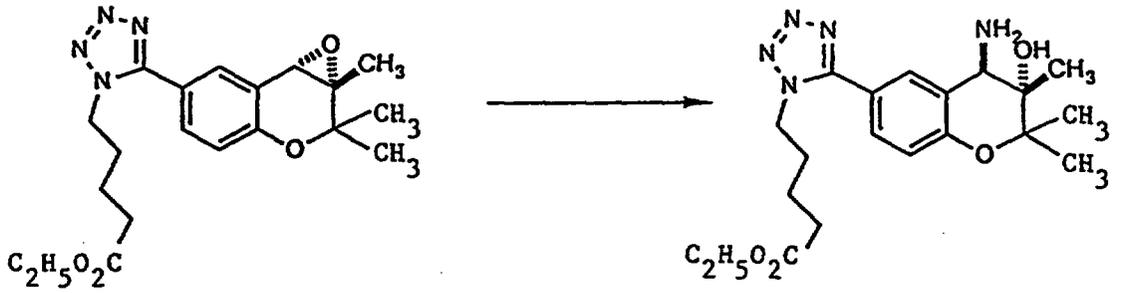
Oxalyl chloride (10ml) was added to a solution of the compound of Preparation 4 (7.5g) in dichloromethane (100ml). Anhydrous N,N-dimethylformamide (1 drop) was added and the mixture was heated under reflux for 30 minutes then allowed to cool to room temperature and concentrated *in vacuo*. The residue was azeotroped with dichloromethane (3 x 100ml) and the resulting residue was dissolved in dichloromethane (50ml) and added, dropwise, to a cooled (0°C) solution of ethyl 5-aminopentanoate hydrochloride (6.9g) and *N,N*-diisopropylethylamine (13.4g) in dichloromethane (150ml). The resulting mixture was stirred at room temperature for 16 hours then water (100ml) was added and the layers were separated. The dichloromethane layer was washed with saturated aqueous sodium chloride solution (100ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a gum which was purified by chromatography on silica eluting with dichloromethane containing methanol (2%) and concentrated aqueous ammonia (0.3%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound, 7.2g.

^{1}H-NMR ($CDCl_3$): δ = 7.50-7.45 (dd,1H), 7.35 (d,1H), 6.75-6.70 (d,1H), 6.55-6.50 (brt,1H), 6.05 (s,1H), 4.10-4.05 (q,2H), 3.45-3.35 (q,2H), 2.35-2.25 (t,2H), 1.80 (s,3H), 1.70-1.55 (m,4H), 1.40 (s,6H), 1.25-1.15 (t,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 68

(3S,4R)-4-Amino-3,4-dihydro-6-(1-[4-ethoxycarbonylbut-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-2,2,3-trimethyl-2H-benzo[b]pyran



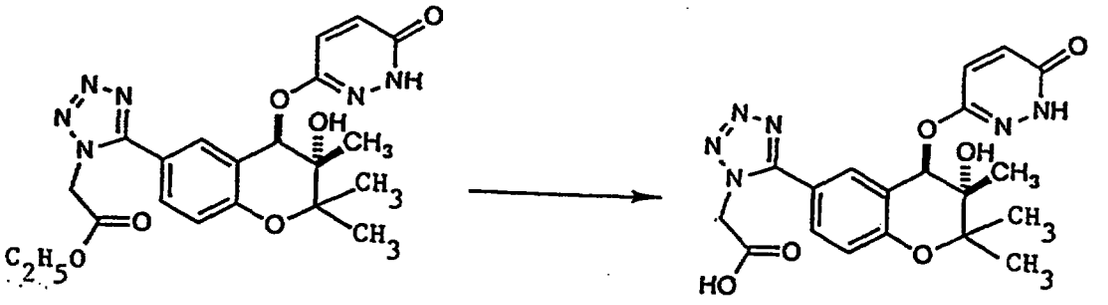
A mixture containing the compound of Preparation 65 (0.5g), concentrated aqueous ammonia (3ml) and ethanol (6ml) was heated at 60°C for 20 hours. Further concentrated aqueous ammonia (2ml) was added and heating was continued for 24 hours. The mixture was concentrated *in vacuo* and the residue was purified by chromatography on silica eluting with dichloromethane containing methanol (2%) and concentrated aqueous ammonia (0.3%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound, 0.36g.

^{1}H-NMR ($CDCl_3$): δ = 7.80 (s,1H), 7.65-7.55 (dd,1H),6.95-6.90 (d,1H), 4.40-4.30 (t,2H), 4.10-4.00 (q,2H), 4.00-3.95 (s,1H), 2.30-2.25 (t,2H), 2.10-1.90 (m,2H), 2.05-1.55 (brs,2H), 1.65-1.55 (m,2H), 1.50 (s,3H), 1.30 (s,3H), 1.25-1.20 (t,3H), 1.10 (s,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 69

(3S,4R)-6-(1-Carboxymethyl-1H-tetrazol-5-yl)-3,4-dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran



A mixture containing the compound of Example 4 (0.23g), 0.35N aqueous sodium hydroxide solution (3ml) and ethanol (3ml) was stirred at room temperature for 4 hours then concentrated *in vacuo*. The residue was extracted with ethyl acetate (50ml). The ethyl acetate extract was washed with water (50ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a foam, 0.14g, m.p. 210°C (dec.).

^{1}H-NMR ($CDCl_3$/d_6-DMSO): δ = 7.65-7.55 (dd,1H), 7.50 (s,1H), 7.10-7.05 (d,1H), 7.00-6.90 (m,2H), 5.95 (s,1H), 5.10-4.95 (ABq,2H), 2.00 (m,2H), 1.45 (s,3H), 1.40 (s,3H), 1.30 (s,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 70

5-(2-Methanesulphonyloxyethyl)-1,3-benzodioxolane



A solution of methanesulphonyl chloride (7.6g) in dichloromethane (25ml) was added, over 15 minutes, to a cooled (-5°C) solution of triethylamine (6.7g) and the compound of Preparation 71 (10g) in dichloromethane (75ml). The mixture was stirred at 0°C for 1 hour then poured into water (100ml). The layers were separated and the aqueous layer was extracted with dichloromethane (50ml). The combined dichloromethane layers were washed with water (100ml) then dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as an oil, 15.3g.

^{1}H-NMR ($CDCl_3$): δ = 6.80-6.65 (m,3H), 5.95 (s,2H), 4.40-4.30 (t,2H), 3.00-2.95 (t,2H), 2.90 (s,3H) ppm.

This Sheet Has Been Replaced

PREPARATION 71

5-(2-Hydroxyethyl)-1,3-benzodioxolane



5-Carboxymethyl-1,3-benzodioxolane (18g) was added, in portions over 30 minutes, to a stirred, ice-cooled (0°C) suspension of lithium aluminium hydride (4g) in diethyl ether (400ml). The mixture was stirred at room temperature for 2 hours then quenched by the cautious addition of saturated aqueous ammonium chloride solution. The mixture was filtered and the filtrate was washed with 10% aqueous sodium carbonate solution then dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as an oil, 15.01g.

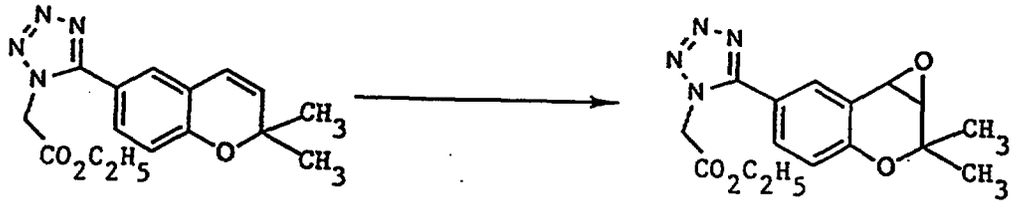
^{1}H-NMR ($CDCl_3$): δ = 6.69-6.83 (m,3H), 5.98 (s,2H), 3.82 (dt,2H), 2.81 (t,2H), 1.44 (t,1H) ppm.

This Sheet Has Been Replaced



PREPARATION 72

(3R,4R/3S,4S)-3,4-Dihydro-2,2-dimethyl-3,4-epoxy-6-(1-ethoxycarbonylmethyl-1H-tetrazol-5-yl)-2H-benzo[b]pyran



A solution of OXONE™ (3.1g) in water (12ml) was added, over 1.5 hours, to a stirred mixture of the compound of Preparation 73 (1.6g), sodium hydrogen carbonate (1.6g), water (12ml) and acetone (40ml). When the addition was complete the mixture was stirred at room temperature for 30 minutes. The acetone was evaporated *in vacuo* and the resulting aqueous mixture was extracted with dichloromethane (2 x 100ml). The combined dichloromethane extracts were dried ($MgSO_4$) then concentrated *in vacuo* to give the title compound as a foam, 1.4g. ^{1}H-NMR ($CDCl_3$): δ = 7.70 (d,1H), 7.50-7.45 (dd,1H), 6.95-6.90 (d,1H), 5.15 (s,2H), 4.30-4.20 (q,2H), 3.95 (d,1H), 3.55 (d,1H), 1.65 (s,3H), 1.30 (s,3H), 1.30-1.20 (t,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 73

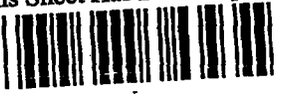
2,2-Dimethyl-6-(1-ethoxycarbonylmethyl-1H-tetrazol-5-yl)-2H-benzo[b]pyran



Phosphorus pentachloride (1.1g) was added to a solution of the compound of Preparation 74 (1.5g) in chloroform (30ml) and the mixture was heated under reflux for 15 minutes. On cooling to room temperature trimethylsilyl azide (0.9g) was added and the mixture was allowed to stand at room temperature for 4 days. The mixture was washed with water (100ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as an oil, 1.7g.

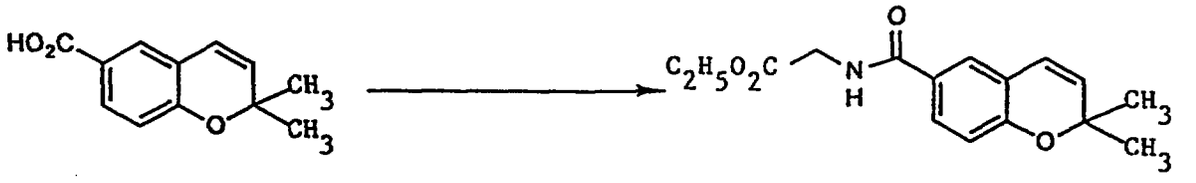
^{1}H-NMR ($CDCl_3$): δ = 7.35-7.30 (m,2H), 6.90-6.85 (d,1H), 6.35-6.30 (d,1H), 5.75-5.70 (d,1H), 5.15 (s,2H), 4.30-4.20 (q,2H), 1.45 (s,6H), 1.30-1.20 (t,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 74

2,2-Dimethyl-6-(N-ethoxycarbonylmethylcarbamoyl)-2H-benzo[b]pyran



1,1'-Carbonyldiimidazole (4.4g) was added to a solution of the compound of Preparation 27 (5g) in dichloromethane (100ml) and the mixture was stirred at room temperature for 30 minutes. Triethylamine (3g) was added followed by ethyl glycinate hydrochloride (3.8g) and the mixture was allowed to stand at room temperature for 2 days. The mixture was washed with water (100ml) and concentrated *in vacuo* to give a gum which was purified by chromatography on silica eluting with dichloromethane containing methanol (1.25%). The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as an oil which crystallised on standing, 7.5g.

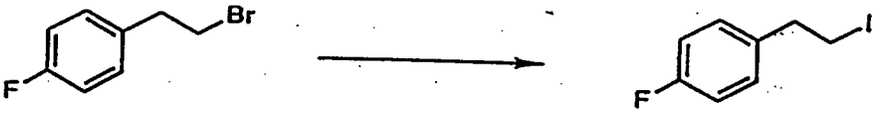
^{1}H-NMR ($CDCl_3$): δ = 7.60-7.55 (dd,1H), 7.50 (d,1H), 6.80-6.75 (d,1H), 6.60-6.50 (brt,1H), 6.35-6.30 (d,1H), 5.65-5.60 (d,1H), 4.30-4.15 (m,4H), 1.45 (s,6H), 1.30-1.25 (t,3H) ppm.

This Sheet Has Been Replaced



PREPARATION 75

2-(4-Fluorophenyl)ethyl iodide



A mixture containing 2-(4-fluorophenyl)ethyl bromide (see Preparation 76) (10g), sodium iodide (10g) and acetone (200ml) was stirred at room temperature for 20 hours then filtered. The filtrate was concentrated *in vacuo* to give the title compound as a colourless oil, 12g. ^{1}H-NMR ($CDCl_3$): δ = 7.20-7.10 (m,2H), 7.05-6.95 (m,2H), 3.35-3.30 (t,2H), 3.20-3.10 (t,2H) ppm.

This Sheet Has Been Replaced

PREPARATION 76

2-(4-Fluorophenyl)ethyl bromide



Phosphorus tribromide (14g) was added, over 2 minutes, to a solution of 2-(4-fluorophenyl)ethanol (14g) in carbon tetrachloride (80ml). The mixture was heated under reflux for 2 hours then cooled in an ice bath. 10% Aqueous sodium carbonate solution was added until all of the solid has dissolved. The mixture was transferred to a separating funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (50ml) and the organic solutions were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with 1:1 hexane/ dichloromethane. The product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a colourless oil, 10g.

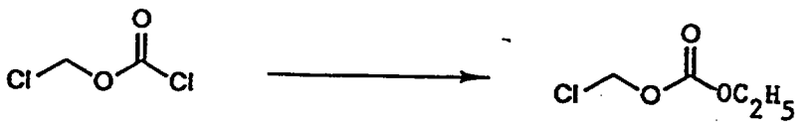
^{1}H-NMR ($CDCl_3$): δ = 7.30-7.20 (m,2H), 7.10-7.00 (m,2H), 3.65-3.55 (t,2H), 3.25-3.15 (t,2H) ppm.

This Sheet Has Been Replaced



PREPARATION 77

Chloromethyl ethyl carbonate



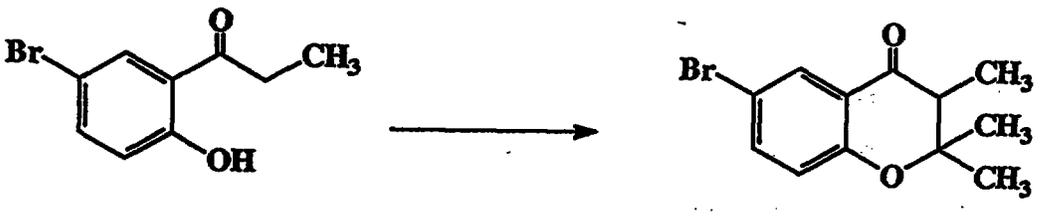
Ethanol (1.9ml) was added in one portion to a cooled (0°C) solution of chloromethyl chloroformate (4.2g) in dichloromethane (20ml). Pyridine (2.63ml) was then added (CAUTION! EXOTHERMIC) and the mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was diluted with dichloromethane (100ml), washed with ice-cold (0°C) 0.5M hydrochloric acid then dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as an oil, 0.17g.
^{1}H-NMR ($CDCl_3$): δ = 5.70 (s,2H), 4.30-4.20 (q,2H), 1.35-1.25 (t,3H) ppm.

This Sheet Has Been Replaced



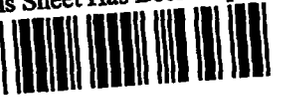
PREPARATION 78

6-Bromo-2,3-dihydro-2,2,3-trimethyl-4H-benzo[b]pyran-4-one



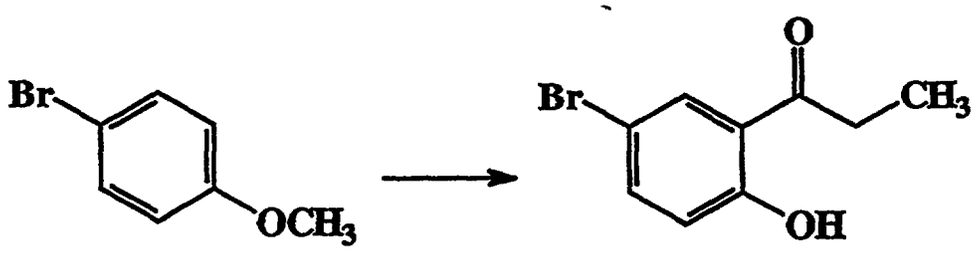
The compound of Preparation 79 (1.46kg) was dissolved in a mixture of acetone (7.30l) and xylene (6.57l) and piperidine (3.04kg) was added. The solution obtained was heated under reflux for 5 days, cooled, washed with water (2 x 3.0l), 2N aqueous hydrochloric acid solution (2 x 5.0l), 2N aqueous sodium hydroxide solution (1 x 3.0l) and water (2 x 3.0l). The organic layer was dried and concentrated under reduced pressure to provide the title compound as a brown oil (1.458kg).

This Sheet Has Been Replaced



PREPARATION 79

4-Bromo-2-propanoylphenol



Aluminium chloride (3.747kg) was added to dichloromethane (7.0l) at room temperature and propionyl chloride (1.297kg) was then added over a 10 minute period. The mixture was stirred for 45 minutes and then a solution of 4-bromoanisole (1.312kg) in dichloromethane (0.87l) was added over a 15 minute period. The mixture was heated under reflux for 6.5 hours and then kept overnight at room temperature. The ice-cooled reaction mixture was quenched by the slow addition of ice (15kg) over 1.5 hours. The mixture obtained was stirred for 15 minutes, the layers were separated and the aqueous layer extracted with dichloromethane (2 x 1.0l). The organic layers were combined and washed with water (2 x 2.0l), then two-thirds of the solvent removed by distillation at atmospheric pressure. Methanol (5.63l) was then added slowly and the distillation continued until a pot temperature of 64°C and a head temperature of 62°C was achieved. Water (0.4l) was added slowly and the mixture was cooled resulting in the precipitation of an off-white solid. Further water (0.4l) was then added slowly and the precipitated solid granulated at about 10°C for 2 hours. The solid was then filtered off, washed sparingly with a 6:1 methanol/water mixture and dried under reduced pressure at 50°C to provide the title compound (1.464kg).

This Sheet Has Been Replaced



Pharmacological Data

A selection of the compounds of the preceding Examples was tested for smooth muscle relaxant activity by the method involving measuring the in vitro relaxation of guinea pig tracheal ring preparations as described on pages 31 and 32 of the description. The results are shown in the Table below.

TABLE

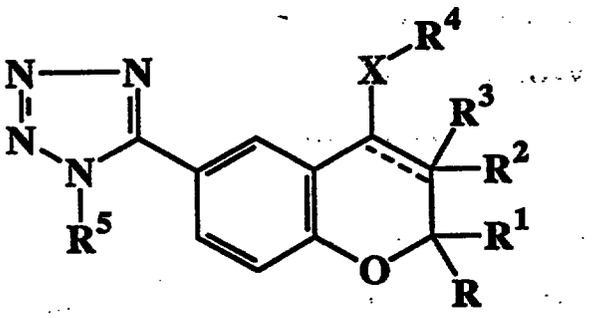
Compound of Example No.	IC_{50}(μM)
3	0.15
7	0.44
11	0.12
35 or 56	0.04
36	0.068

This Sheet Has Been Replaced

This Sheet Has Been Replaced

CLAIMS

1. A compound of the formula:-



(I)

or a pharmaceutically acceptable salt thereof,
wherein the dashed line represents an optional covalent bond;

X is O, NH, S or a direct link;

R and R^1 are either each independently selected from H, fluoro(C_1-C_4)alkyl and C_1-C_4 alkyl or taken together represent C_2-C_6 alkylene;

R^2 is H or C_1-C_4 alkyl;

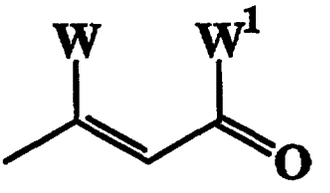
R^3 is hydroxy when the dashed line does not represent a covalent bond and R^3 is absent when the dashed line represents a covalent bond;

* C L M S *

This Sheet Has Been Replaced

R^4 is

(a) , when X is O, a group of the formula:-



wherein W and W^1 taken together represent C_1-C_4 alkylene, said alkylene being optionally benzo-fused when W and W^1 taken together represent C_2-C_4 alkylene, and optionally substituted, including in the benzo-fused portion, by C_1-C_6 alkyl, hydroxy, -OR^8, halo, -$N(R^8)_2$, -SR^8 or halo(C_1-C_4)alkyl,

(b) , when X is O, NH or S, hydroxyphenyl optionally substituted by C_1-C_6 alkyl, -OR^8, halo, -$N(R^8)_2$, -SR^8 or halo(C_1-C_4)alkyl,

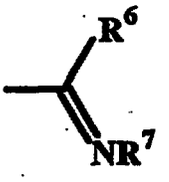
(c) a 4- to 7-membered heterocyclic ring containing either from 1 to 3 N hetero-atoms or one N hetero-atom and one O or one S hetero-atom, said ring being optionally benzo- or C_3-C_7 cycloalkyl-fused and optionally substituted, including in the benzo- or C_3-C_7 cycloalkyl-fused portion, by C_1-C_6 alkyl, hydroxy, hydroxy(C_1-C_4)alkyl, -OR^8, $R^8O(C_1$-$C_4)$alkyl, halo, halo(C_1-C_4)alkyl, -$S(O)_mR^8$, $R^8S(O)_m(C_1$-$C_4)$alkyl, oxo, N-cyanoimino, amino, amino(C_1-C_4)alkyl, -NHR^8,

* C L M S *

This Sheet Has Been Replaced

$R^8NH(C_1-C_4)$alkyl, $-N(R^8)_2$, $(R^8)_2N(C_1-C_4)$alkyl, cyano, cyano(C_1-C_4)alkyl, $-CO_2R^8$, $R^8O_2C-(C_1-C_4)$alkyl, $-CONH_2$, $H_2NCO(C_1-C_4)$alkyl, $-CONHR^8$, $R^8NHCO(C_1-C_4)$alkyl, $-CON(R^8)_2$ or $(R^8)_2NCO(C_1-C_4)$alkyl, or, as appropriate, a ring N- or S-oxide derivative of said heterocyclic ring, with the proviso that said heterocyclic ring is linked by a ring carbon atom when X is O, NH or S, or

(d) , when X is NH, a group of the formula:-



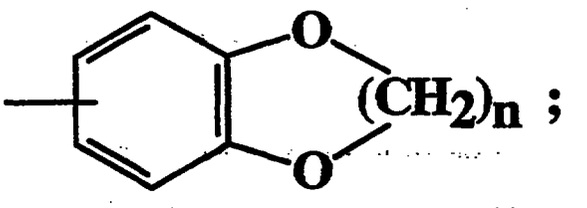
wherein R^6 is $-OR^8$, $-NHR^8$, $-SR^8$, -NH(aryl) or -NH(pyridinyl) and R^7 is cyano, nitro or C_2-C_6 alkanoyl;

R^5 is aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said C_1-C_{12} alkyl, C_2-C_{12} alkenyl and C_2-C_{12} alkynyl being optionally substituted by C_4-C_7 cycloalkyl, hydroxy, $-OR^8$, C_2-C_6 alkanoyloxy, halo, cyano, nitro, amino, $-NHR^8$,$-N(R^8)_2$, $-S(O)_mR^8$, $-NHSO_2R^8$, $-NHCOR^8$, $-COR^8$, $-CONH_2$, $-CONHR^8$, $-CON(R^8)_2$, $-OCO_2R^8$, $-CONH(C_1-C_6)alkylCO_2R^8$, $-CONR^8(C_1-C_6)alkylCO_2R^8$, $-CO_2R^9$, aryl, aryloxy, arylcarbonyl, arylcarbonyloxy, aryl(C_1-C_6)alkoxy,

* C L M S *

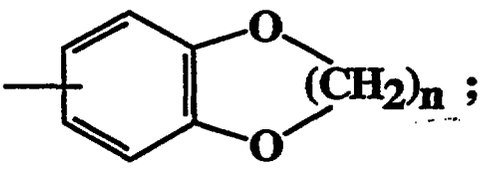
This Sheet Has Been Replaced

aryl(C_1-C_6)alkoxycarbonyl, phthalimido, or a group of the formula:-



R^8 is C_1-C_6 alkyl;

R^9 is indanyl, aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said C_1-C_{12} alkyl, C_2-C_{12} alkenyl and C_2-C_{12} alkynyl being optionally substituted by C_4-C_7 cycloalkyl, hydroxy, -OR^8, C_2-C_6 alkanoyloxy, halo, cyano, nitro, amino, -NHR^8, -$N(R^8)_2$, -$S(O)_mR^8$, -$NHSO_2R^8$, -$NHCOR^8$, -COR^8, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -OCO_2R^8, -$CONH(C_1$-$C_6)alkylCO_2R^8$, -$CONR^8(C_1$-$C_6)alkylCO_2R^8$, -$CO_2(C_1$-C_{12} alkyl), aryl, aryloxy, arylcarbonyl, arylcarbonyloxy, aryl-(C_1-C_6)alkoxy, aryl(C_1-C_6)alkoxycarbonyl, phthalimido, or a group of the formula:-



"aryl", used in the definitions of R^5, R^6 and R^9 and in this definition, means phenyl optionally substituted by C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, hydroxy(C_1-C_6)alkyl, -OR^8, $R^8O(C_1$-$C_6)alkyl, R^8O-

* C L M S *

(C_1-C_6)alkoxy, $R^8O(C_1$-$C_6)$alkoxy(C_1-$C_6)$alkyl, halo, halo(C_1-$C_6)$alkyl, cyano, cyano(C_1-$C_6)$alkyl, nitro, nitro(C_1-$C_6)$alkyl, amino, amino(C_1-$C_6)$alkyl, $-NHR^8$, $R^8NH(C_1$-$C_6)$alkyl, $-N(R^8)_2$, $(R^8)_2N(C_1$-$C_6)$alkyl, $-S(O)_mR^8$, $R^8S(O)_m(C_1$-$C_6)$alkyl, $-NHCOR^8$, $R^8CONH(C_1$-$C_6)$alkyl, $-COR^8$, $R^8CO(C_1$-$C_6)$alkyl, $-CONH_2$, $H_2NCO(C_1$-$C_6)$alkyl, $-CONHR^8$, $R^8NHCO(C_1$-$C_6)$alkyl, $-CON(R^8)_2$, $(R^8)_2NCO$-$(C_1$-$C_6)$alkyl, $-CONH(C_1$-$C_6)$alkylCO_2R^8, $R^8O_2C(C_1$-$C_6)$-alkyl$NHCO(C_1$-$C_6)$alkyl, $-CONR^8(C_1$-$C_6)$alkylCO_2R^8, $R^8O_2C(C_1$-$C_6)$alkyl$NR^8CO(C_1$-$C_6)$alkyl, $-CO_2R^{9A}$, $R^{9A}O_2C(C_1$-$C_6)$alkyl, aryl, aryl(C_1-$C_6)$alkyl, aryl(C_1-$C_6)$-alkoxy or aryl(C_1-$C_6)$alkoxy(C_1-$C_6)$alkyl;

R^{9A} is indanyl, phenyl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12}alkynyl, said C_1-C_{12} alkyl, C_2-C_{12} alkenyl and C_2-C_{12} alkynyl being optionally substituted as previously defined for those definitions for R^9 and said phenyl being optionally substituted by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, hydroxy, $-OR^6$, halo, halo(C_1-$C_6)$alkyl, nitro and cyano;

m is 0, 1 or 2; and

n is 1, 2 or 3.

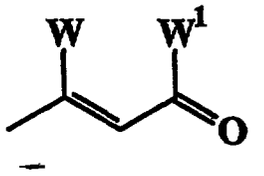
2. A compound as claimed in claim 1 wherein

R and R^1 are either each independently selected from H and C_1-C_4 alkyl or taken together represent C_2-C_6 alkylene;

R^4 is

(a) , when X is O, a group of the formula:-

This Sheet Has Been Replaced



CLMS

wherein W and W^1 taken together represent C_1-C_4 alkylene, said alkylene being optionally benzo-fused when W and W^1 taken together represent C_2-C_4 alkylene, and optionally substituted, including in the benzo-fused portion, by C_1-C_6 alkyl, hydroxy, $-OR^8$, halo, $-N(R^8)_2$, $-SR^8$ or halo(C_1-C_4)alkyl,

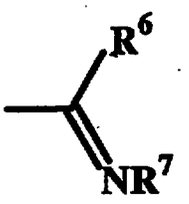
(b) , when X is O, NH or S, hydroxyphenyl optionally substituted by C_1-C_6 alkyl, $-OR^8$, halo, $-N(R^8)_2$, $-SR^8$ or halo(C_1-C_4)alkyl,

(c) a 4- to 7-membered heterocyclic ring containing either from 1 to 3 N hetero-atoms or one N hetero-atom and one O or one S hetero-atom, said ring being optionally benzo-fused and optionally substituted, including in the benzo-fused portion, by C_1-C_6 alkyl, hydroxy, hydroxy(C_1-C_4)alkyl, $-OR^8$, R^8O-(C_1-C_4)alkyl, halo, halo(C_1-C_4)alkyl, $-S(O)_mR^8$, $R^8S(O)_m$(C_1-C_4)alkyl, oxo, N-cyanoimino, amino, amino(C_1-C_4)alkyl, $-NHR^8$, R^8NH(C_1-C_4)alkyl, $-N(R^8)_2$, $(R^8)_2N$(C_1-C_4)alkyl, cyano, cyano-(C_1-C_4)alkyl, $-CO_2R^8$, R^8O_2C(C_1-C_4)alkyl, $-CONH_2$, H_2NCO(C_1-C_4)alkyl, $-CONHR^8$, R^8NHCO(C_1-C_4)alkyl, $-CON(R^8)_2$ or $(R^8)_2NCO$-(C_1-C_4)alkyl, or, as appropriate, a ring N- or S-oxide derivative of said heterocyclic ring, with the proviso that said heterocyclic ring is linked by a ring carbon atom when X is O, NH or S, or

This Sheet Has Been Replaced

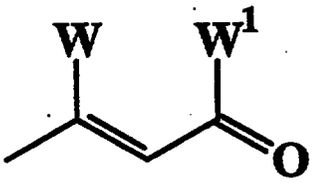
* C L M S *

(d) , when X is NH, a group of the formula:-



wherein R^6 is $-OR^8$, $-NHR^8$, $-SR^8$, -NH(aryl) or -NH(pyridinyl) and R^7 is cyano, nitro or C_2-C_6 alkanoyl; and the dashed line, X, R^2, R^3 and R^5 are as defined in claim 1.

3. A compound as claimed in claim 1 or 2 wherein the dashed line does not represent a covalent bond; X is O, NH or a direct link; R and R^1 are each independently selected from H and C_1-C_4 alkyl;
R^2 is H or methyl;
R^3 is hydroxy;
R^4 is a group of the formula:-

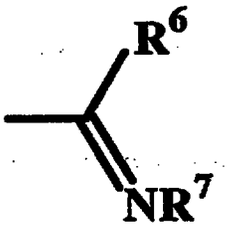


This Sheet Has Been Replaced

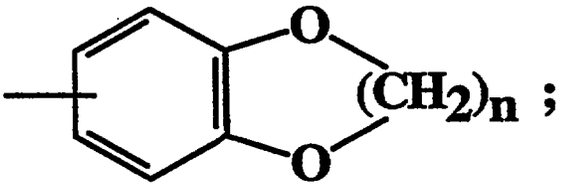




wherein W and W^1 taken together represent C_1-C_4 alkylene, a 6-membered heterocyclic ring containing 1 or 2 nitrogen heteroatoms and optionally substituted by C_1-C_6 alkyl, hydroxy, halo, C_1-C_4 alkylthio or oxo, or is a group of the formula:-



wherein R^6 is $-OR^8$, $-NHR^8$ or $-SR^8$ and R^7 is cyano; R^5 is aryl or C_1-C_{12} alkyl, said C_1-C_{12} alkyl being optionally substituted by hydroxy, $-OR^8$, C_2-C_6 alkanoyloxy, amino, $-CONHR^8$, $-CONH(C_1$-$C_6)alkylCO_2R^8$, $-CO_2R^8$, aryl, aryloxy, arylcarbonyloxy, aryl(C_1-C_6)alkoxy, phthalimido, or a group of the formula:-



This Sheet Has Been Replaced

R^8 is methyl or ethyl;

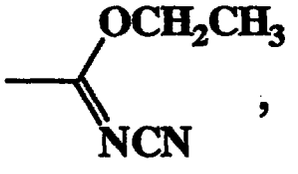
R^9 is indanyl, aryl, C_1-C_{12} alkyl or C_2-C_{12} alkenyl, said C_1-C_{12} alkyl being optionally substituted by halo, C_2-C_6 alkanoyloxy, $-OCO_2R^8$ or aryl;

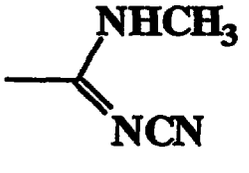
"aryl" means phenyl optionally substituted by C_1-C_6 alkyl, hydroxy, $-OR^8$, halo or aryl(C_1-C_6)alkoxy;

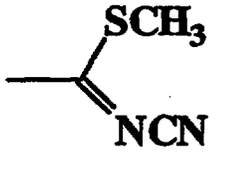
m is O; and
n is 1.

4. A compound as claimed in claim 3 wherein R and R^1 are each C_1-C_4 alkyl;

R^4 is 1-oxocyclopent-2-en-3-yl, 2-oxo-1,2-dihydropyridin-1-yl, 2-oxo-1H-1,2-dihydropyridin-4-yl, 2-oxopiperidin-1-yl, 3-hydroxypyridazin-6-yl, 2-methyl-3-oxopyridazin-6-yl, 4-chloropyrimidin-2-yl, 2-chloropyrimidin-4-yl, 2-methylthiopyrimidin-4-yl or is a group of the formula:-



,


or


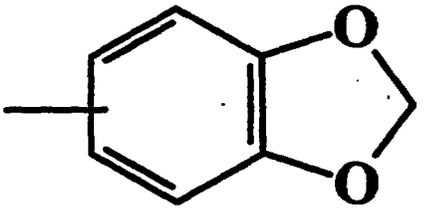
;

This Sheet Has Been Replaced





R^5 is phenyl or C_1-C_4 alkyl, said C_1-C_4 alkyl being optionally substituted by hydroxy, methoxy, acetoxy, amino, methylaminocarbonyl, N-(ethoxycarbonyl-methyl)carbamoyl, $-CO_2R^9$, phenyl, methylphenyl, methoxyphenyl, hydroxyphenyl, halophenyl, benzyl-oxyphenyl, phenoxy, benzoyloxy, benzyloxy, phthalimido, or a group of the formula:-

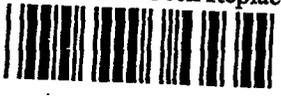


;

and R^9 and R^{9A} are each independently indanyl, phenyl, C_1-C_4 alkyl or vinyl, said C_1-C_4 alkyl being optionally substituted by fluoro, pivaloyloxy, ethoxycarbonyloxy or phenyl.

5. A compound as claimed in claim 4 wherein

This Sheet Has Been Replaced

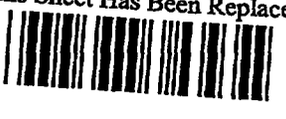




R^5 is phenyl, methyl, ethyl, n-propyl, 2-hydroxyethyl, 2-methoxyethyl, 2-acetoxyethyl, 2-aminoethyl, 2-(methylaminocarbonyl)ethyl, N-(ethoxycarbonylmethyl)carbamoylmethyl, ethoxycarbonylmethyl, 3-methoxycarbonylprop-1-yl, 3-ethoxycarbonylprop-1-yl, 4-ethoxycarbonylbut-1-yl, 3-vinyloxycarbonylprop-1-yl, 3-(2,2,2-trifluoroethoxycarbonyl)prop-1-yl, 3-(ethoxycarbonyloxymethoxycarbonyl)prop-1-yl, 3-(pivaloyloxymethoxycarbonyl)prop-1-yl, 3-phenoxycarbonylprop-1-yl, 3-benzyloxycarbonylprop-1-yl, 3-(5-indanyloxycarbonyl)prop-1-yl, benzyl, 2-phenylethyl, 3-phenylprop-1-yl, 4-phenylbut-1-yl, 2-(2-methylphenyl)ethyl, 2-(3-methylphenyl)ethyl, 2-(4-methylphenyl)ethyl, 2-(2-methoxyphenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(4-hydroxyphenyl)ethyl, 2-(4-fluorophenyl)ethyl, 2-(4-benzyloxyphenyl)ethyl, 2-phenoxyethyl, 2-benzoyloxyethyl, 2-benzyloxyethyl, 2-phthalimidoethyl or 2-(1,3-benzodioxolan-5-yl)-ethyl;

and R^9 and R^{9A} are each independently 5-indanyl, phenyl, methyl, ethyl, vinyl, 2,2,2-trifluoroethyl, pivaloyloxymethyl, ethoxycarbonyloxymethyl or benzyl.

This Sheet Has Been Replaced





6. A compound as claimed in claim 5 wherein

R and R^1 are each methyl; R^2 is methyl; and R^5 is methyl, ethyl, n-propyl, 3-ethoxycarbonyl-prop-1-yl, 4-ethoxycarbonylbut-1-yl or 2-phenylethyl.

7. A compound as claimed in claim 1 or 2 that is selected from the group:-

4-(2-chloropyrimidin-4-yl)amino-3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-2,2,3-trimethyl-2H-benzo[b]pyran;

3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran;

3,4-dihydro-6-(1-[4-ethoxycarbonylbut-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran;

3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-4-(2-methyl-3-oxopyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran;

This Sheet Has Been Replaced

* C L M S *

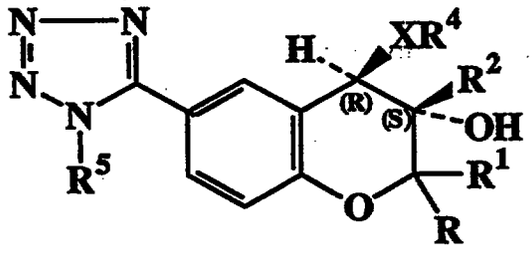
3,4-dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-6-(1-[2-phenylethyl]-1H-tetrazol-5-yl)-2H-benzo-[b]pyran;

3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-4-(2-oxo-1H-1,2-dihydropyridin-4-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran;

3,4-dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-6-(1-[2-phenylethyl]-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran:

or a pharmaceutically acceptable salt of any of these compounds, or, preferably, the 3S,4R- form of any of the aforementioned compounds.

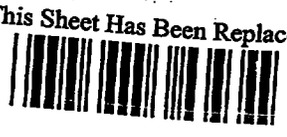
8. A compound as claimed in claim 1 or 2 of the formula:-



(IA)

wherein X is O or NH; R and R^1 are each C_1-C_4 alkyl; R^2 is H or C_1-C_4 alkyl; and R^4 and R^5 are as defined in claim 1 or 2.

This Sheet Has Been Replaced





9. A pharmaceutical composition comprising a compound of the formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any of claims 1 to 8, together with a pharmaceutically acceptable diluent or carrier.

10. A compound of the formula (I) or a pharmaceutically acceptable salt or composition thereof, as claimed in any of claims 1 to 8 and 9 respectively, for use as a medicament.

11. The use of a compound of the formula (I) or of a pharmaceutically acceptable salt or composition thereof, as claimed in any of claims 1 to 8 and 9 respectively, for the manufacture of a medicament for treating angina or a disease associated with the altered tone and/or motility of smooth muscle.

12. Use as claimed in claim 11 where the disease is chronic obstructive airways disease, asthma, urinary incontinence, irritable bowel syndrome, diverticular disease, oesophageal achalasia or hypertension.

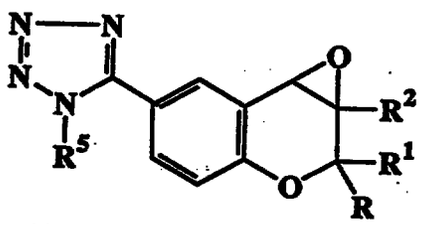
13. A method of treatment of a human to treat angina or a disease associated with the altered tone and/or motility of smooth muscle which comprises administering to said human an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt or composition thereof, as claimed in any one of claims 1 to 8 and 9 respectively.

This Sheet Has Been Replaced

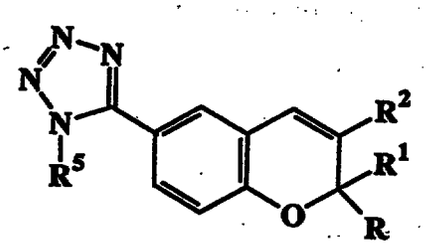
* C L M S *

14. A method as claimed in claim 13 where the disease is chronic obstructive airways disease, asthma, urinary incontinence, irritable bowel syndrome, diverticular disease, oesophageal achalasia or hypertension.

15. A compound of the formula:-

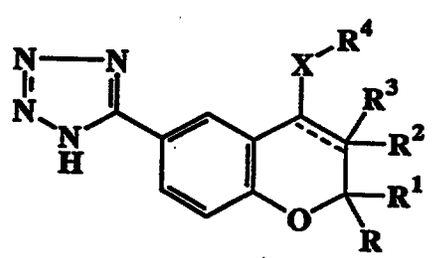


(II) ,



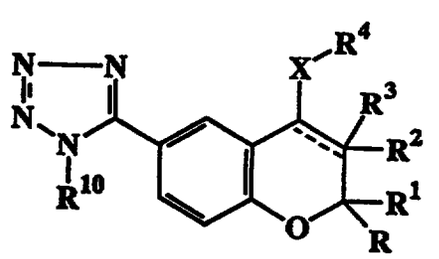
(V) ,

This Sheet Has Been Replaced



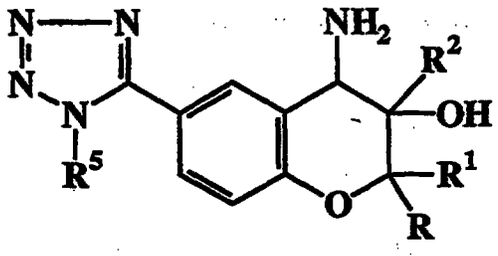
(VI)

or a base salt thereof,



(VIII)

or an activated derivative thereof, or

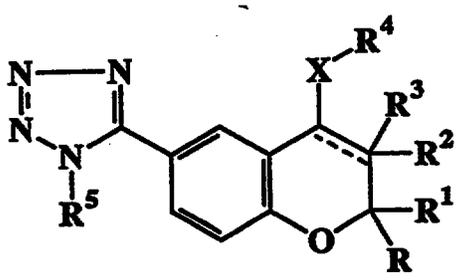


(IX)

wherein R^{10} is aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said alkyl, alkenyl and alkynyl being substituted by -CO_2H or by aryl substituted by -CO_2H or $HO_2C(C_1$-$C_6)$ alkyl, and said aryl being substituted by -CO_2H or $HO_2C(C_1$-$C_6)$ alkyl, and the dashed line, X, R, R^1, R^2, R^3, R^4, R^5 and "aryl" are as defined in claim 1 or 2.

This Sheet Has Been Replaced

16. A process for the preparation of a compound of the formula:-



(I)

or a pharmaceutically acceptable salt thereof,
wherein the dashed line represents an optional covalent bond;

X is O, NH, S or a direct link;

R and R^1 are either each independently selected from H, fluoro(C_1-C_4)alkyl and C_1-C_4 alkyl or taken together represent C_2-C_6 alkylene;

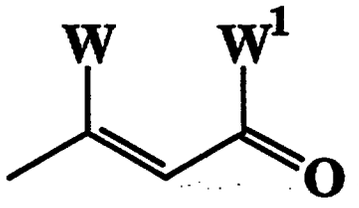
R^2 is H or C_1-C_4 alkyl;

R^3 is hydroxy when the dashed line does not represent a covalent bond and R^3 is absent when the dashed line represents a covalent bond;

This Sheet Has Been Replaced

R^4 is

(a) , when X is O, a group of the formula:-



wherein W and W^1 taken together represent C_1-C_4 alkylene, said alkylene being optionally benzo-fused when W and W^1 taken together represent C_2-C_4 alkylene, and optionally substituted, including in the benzo-fused portion, by C_1-C_6 alkyl, hydroxy, -OR^6, halo, -$N(R^6)_2$, -SR^6 or halo(C_1-C_4)alkyl,

(b) , when X is O, NH or S, hydroxyphenyl optionally substituted by C_1-C_6 alkyl, -OR^6, halo, -$N(R^6)_2$, -SR^6 or halo(C_1-C_4)alkyl,

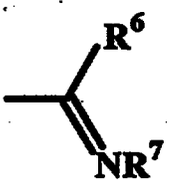
(c) a 4- to 7-membered heterocyclic ring containing either from 1 to 3 N hetero-atoms or one N hetero-atom and one O or one S hetero-atom, said ring being optionally benzo- or C_3-C_7 cycloalkyl-fused and optionally substituted, including in the benzo- or C_3-C_7 cycloalkyl-fused portion, by C_1-C_6 alkyl, hydroxy, hydroxy(C_1-C_4)alkyl, -OR^6, $R^6O(C_1$-$C_4)$alkyl, halo, halo(C_1-C_4)alkyl, -$S(O)_mR^6$, $R^6S(O)_m(C_1$-$C_4)$alkyl, oxo, N-cyanoimino, amino, amino(C_1-C_4)alkyl, -NHR^6,

This Sheet Has Been Replaced

* C L M S *

$R^8NH(C_1-C_4)$alkyl, $-N(R^8)_2$, $(R^8)_2N(C_1-C_4)$alkyl, cyano, cyano(C_1-C_4)alkyl, $-CO_2R^8$, $R^8O_2C(C_1-C_4)$alkyl, $-CONH_2$, $H_2NCO(C_1-C_4)$alkyl, $-CONHR^8$, $R^8NHCO(C_1-C_4)$alkyl, $-CON(R^8)_2$ or $(R^8)_2NCO-(C_1-C_4)$alkyl, or, as appropriate, a ring N- or S-oxide derivative of said heterocyclic ring, with the proviso that said heterocyclic ring is linked by a ring carbon atom when X is O, NH or S, or

(d) , when X is NH, a group of the formula:-



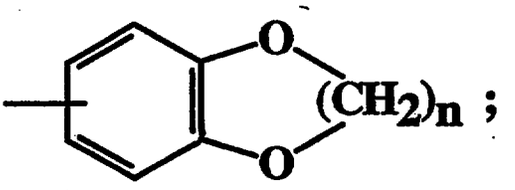
wherein R^6 is $-OR^8$, $-NHR^8$, $-SR^8$, -NH(aryl) or -NH(pyridinyl) and R^7 is cyano, nitro or C_2-C_6 alkanoyl;

R^5 is aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said C_1-C_{12} alkyl, C_2-C_{12} alkenyl and C_2-C_{12} alkynyl being optionally substituted by C_4-C_7 cycloalkyl, hydroxy, $-OR^8$, C_2-C_6 alkanoyloxy, halo, cyano, nitro, amino, $-NHR^8$,$-N(R^8)_2$, $-S(O)_mR^8$, $-NHSO_2R^8$, $-NHCOR^8$, $-COR^8$, $-CONH_2$, $-CONHR^8$, $-CON(R^8)_2$, $-OCO_2R^8$, $-CONH(C_1-C_6)alkylCO_2R^8$, $-CONR^8(C_1-C_6)alkylCO_2R^8$, $-CO_2R^9$, aryl, aryloxy, arylcarbonyl, arylcarbonyloxy, aryl(C_1-C_6)alkoxy,

This Sheet Has Been Replaced

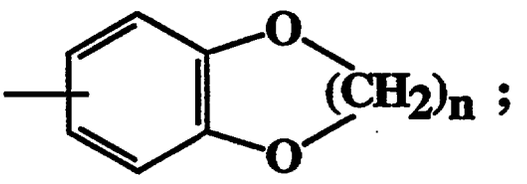
* C L M S. *

aryl(C_1-C_6)alkoxycarbonyl, phthalimido, or a group of the formula:-



R^8 is C_1-C_6 alkyl;

R^9 is indanyl, aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said C_1-C_{12} alkyl, C_2-C_{12} alkenyl and C_2-C_{12} alkynyl being optionally substituted by C_4-C_7 cycloalkyl, hydroxy, -OR^8, C_2-C_6 alkanoyloxy, halo, cyano, nitro, amino, -NHR^8, -$N(R^8)_2$, -$S(O)_mR^8$, -$NHSO_2R^8$, -$NHCOR^8$, -COR^8, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -OCO_2R^8, -$CONH(C_1$-$C_6)alkylCO_2R^8$, -$CONR^8(C_1$-$C_6)alkylCO_2R^8$, -$CO_2(C_1$-C_{12} alkyl), aryl, aryloxy, arylcarbonyl, arylcarbonyloxy, aryl-(C_1-C_6)alkoxy, aryl(C_1-C_6)alkoxycarbonyl, phthalimido, or a group of the formula:-



This Sheet Has Been Replaced

* C L M S *

"aryl", used in the definitions of R^5, R^6 and R^9 and in this definition, means phenyl optionally substituted by C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, hydroxy(C_1-C_6)alkyl, -OR^8, $R^8O(C_1$-$C_6)$alkyl, R^8O-(C_1-C_6)alkoxy, $R^8O(C_1$-$C_6)$alkoxy(C_1-C_6)alkyl, halo, halo(C_1-C_6)alkyl, cyano, cyano(C_1-C_6)alkyl, nitro, nitro(C_1-C_6)alkyl, amino, amino(C_1-C_6)alkyl, -NHR^8, $R^8NH(C_1$-$C_6)$alkyl, -$N(R^8)_2$, $(R^8)_2N(C_1$-$C_6)$alkyl, -$S(O)_mR^8$, $R^8S(O)_m(C_1$-$C_6)$alkyl, -$NHCOR^8$, $R^8CONH(C_1$-$C_6)$alkyl, -COR^8, $R^8CO(C_1$-$C_6)$alkyl, -$CONH_2$, $H_2NCO(C_1$-$C_6)$alkyl, -$CONHR^8$, $R^8NHCO(C_1$-$C_6)$alkyl, -$CON(R^8)_2$, $(R^8)_2NCO$-(C_1-C_6)alkyl, -$CONH(C_1$-$C_6)$alkylCO_2R^8, $R^8O_2C(C_1$-$C_6)$-alkyl$NHCO(C_1$-$C_6)$alkyl, -$CONR^8(C_1$-$C_6)$alkylCO_2R^8, $R^8O_2C(C_1$-$C_6)$alkyl$NR^8CO(C_1$-$C_6)$alkyl, -CO_2R^{9A}, $R^{9A}O_2C(C_1$-$C_6)$alkyl, aryl, aryl(C_1-C_6)alkyl, aryl(C_1-C_6)-alkoxy or aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl;

R^{9A} is indanyl, phenyl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12}alkynyl, said C_1-C_{12} alkyl, C_2-C_{12} alkenyl and C_2-C_{12} alkynyl being optionally substituted as previously defined for those definitions for R^9 in this claim and said phenyl being optionally substituted by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, hydroxy, -OR^8, halo, halo(C_1-C_6)alkyl, nitro and cyano;

m is 0, 1 or 2; and

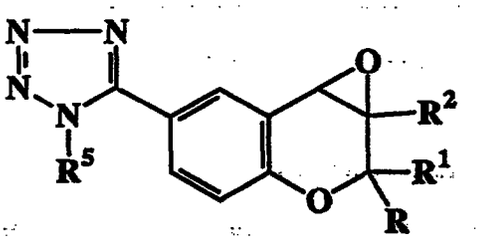
n is 1, 2 or 3, which comprises,

(i) for a compound of the formula (I) wherein the dashed line does not represent a covalent bond, X is O, NH or S, R^4 has the definition (a), (b) or (c) as previously defined for R^4 for a compound of the formula (I) in

This Sheet Has Been Replaced

* C L M S *

this claim and R, R^1, R^2, R^3 and R^5 are as previously defined for a compound of the formula (I) in this claim, reacting a compound of the formula:-



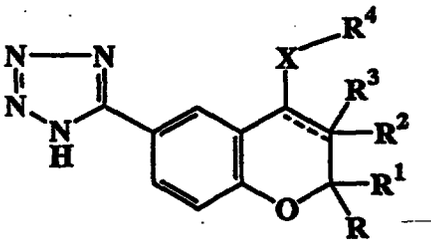
(II)

wherein R, R^1, R^2 and R^5 are as previously defined for a compound of the formula (I) in this claim, with a compound of the formula:-

R^4-XH

or, as appropriate, a tautomer thereof, or, where X is O or S, with a base salt thereof, wherein X and R^4 are as defined for this part (i);

(ii) , for a compound of the formula (I) wherein the dashed line, X, R, R^1, R^2, R^3, R^4 and R^5 are as previously defined for a compound of the formula (I) in this claim, reacting a compound of the formula:-



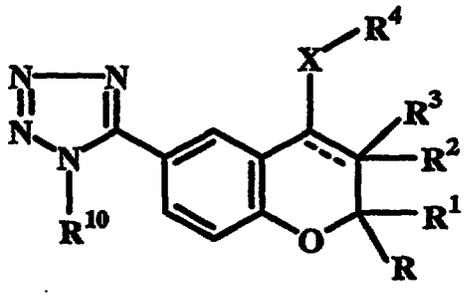
(VI)

or a base salt thereof, wherein the dashed line, X, R, R^1, R^2, R^3 and R^4 are as previously defined for a compound of the formula (I) in this claim, with a compound of the formula:-

R^5Z

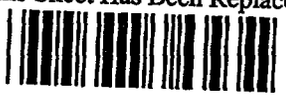
wherein R^5 is as previously defined for a compound of the formula (I) in this claim and Z is a leaving group such as halo, methanesulphonyloxy, p-toluenesulphonyoxy or trifluoromethanesulphonyl oxy;

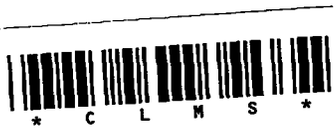
(iii) , for a compound of the formula (I) wherein R^5 is aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said alkyl, alkenyl and alkynyl being substituted by $-CO_2R^9$ or by aryl substituted by $-CO_2R^9$ or R^9O_2C-(C_1-C_6)alkyl, and said aryl being substituted by $-CO_2R^9$ or $R^9O_2C(C_1$-$C_6)$alkyl, and the dashed line, X, R, R^1, R^2, R^3, R^4, R^9 and "aryl" are as previously defined for a compound of the formula (I) in this claim, esterification of a compound of the formula:-



(VIII)

This Sheet Has Been Replaced





wherein the dashed line, X, R, R^1, R^2, R^3 and R^4 are as previously defined for a compound of the formula (I) in this claim and R^{10} is aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said alkyl, alkenyl and alkynyl being substituted by $-CO_2H$ or by aryl substituted by $-CO_2H$ or $HO_2C(C_1$-$C_6)$alkyl, and said aryl being substituted by $-CO_2H$ or $HO_2C(C_1$-$C_6)$alkyl, or an activated derivative of such a carboxylic acid, such as the corresponding acid bromide, acid chloride, imidazolide or activated ester derivative, with a compound of the formula R^9OH wherein R^9 is as previously defined for a compound of the formula (I) in this claim;

(iv) , for a compound of the formula (I) wherein the dashed line, X, R, R^1, R^2, R^3, R^4 and R^5 are as previously defined for a compound of the formula (I) in part (iii) and R^9 is C_1-C_{12} alkyl optionally substituted as previously defined for the definition of R^9 as C_1-C_{12} alkyl for a compound of the formula (I) in this claim, esterification of a compound of the formula (VIII), or a base salt thereof, wherein the dashed line, X, R, R^1, R^2, R^3 and R^4 are as previously defined for a compound of the formula (I) in this claim and R^{10} is aryl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, said alkyl, alkenyl and alkynyl being substituted by $-CO_2H$ or by aryl substituted by -COOH or HO_2C-$(C_1$-$C_6)$alkyl, and said aryl being substituted by -COOH or $HO_2C(C_1$-$C_6)$alkyl, with a compound of the formula:-

This Sheet Has Been Replaced

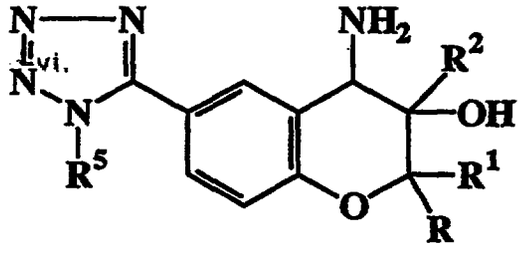
* C L M S *

R^9Z^1

wherein Z^1 is a leaving group such as halo, and R^9 is as previously defined for this part (iv);

(v) , for a compound of the formula (I) wherein R^4 is 2-methyl-3-oxopyridazin-6-yl and the dashed line, X, R, R^1, R^2, R^3 and R^5 are as previously defined for a compound of the formula (I) for this claim, methylation of a compound of the formula (I) wherein R^4 is 3-hydroxypyridazin-6-yl and the dashed line, X, R, R^1, R^2, R^3 and R^5 are as previously defined for a compound of the formula (I) for this claim;

(vi) for a compound of the formula (I) wherein the dashed line does not represent a covalent bond, X is NH, R^4 is a C-linked 4- to 7-membered heterocyclic ring containing from 1 to 3 nitrogen hetero-atoms which is optionally substituted as previously defined in definition (c) for R^4 for a compound of the formula (I) in this claim and R, R^1, R^2, R^3 and R^5 are as previously defined for a compound of the formula (I) in this claim, reacting a compound of the formula:-



(IX)

* C L M S *

This Sheet Has Been Replaced

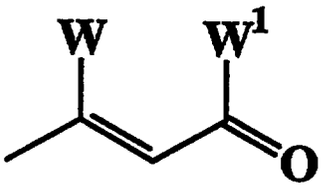
wherein R, R^1, R^2 and R^5 are as previously defined for a compound of the formula (I) in this claim, with a 4- to 7-membered ring heterocyclic compound containing from 1 to 3 nitrogen hetero-atoms which is substituted on a ring carbon atom by a leaving group such as halo or a group of the formula C_1-C_4 alkylS(O)$_p$- where p is 0, 1 or 2, and optionally further substituted as previously defined for R^4 for this part (vi):

any of the reactions of parts (i) to (vi) being optionally followed by conversion of the compound of the formula (I) to a pharmaceutically acceptable salt thereof.

17. A process as claimed in claim 16 wherein

R and R^1 are either each independently selected from H and C_1-C_4 alkyl or taken together represent C_2-C_6 alkylene;
R^4 is

(a) , when X is O, a group of the formula:-



* C L M S *

This Sheet Has Been Replaced

wherein W and W^1 taken together represent C_1-C_4 alkylene, said alkylene being optionally benzo-fused when W and W^1 taken together represent C_2-C_4 alkylene, and optionally substituted, including in the benzo-fused portion, by C_1-C_6 alkyl, hydroxy, -OR^6, halo, -$N(R^6)_2$, -SR^6 or halo(C_1-C_4)alkyl,

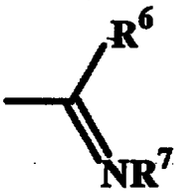
(b) , when X is O, NH or S, hydroxyphenyl optionally substituted by C_1-C_6 alkyl, -OR^6, halo, -$N(R^6)_2$, -SR^6 or halo(C_1-C_4)alkyl,

(c) a 4- to 7-membered heterocyclic ring containing either from 1 to 3 N hetero-atoms or one N hetero-atom and one O or one S hetero-atom, said ring being optionally benzo-fused and optionally substituted, including in the benzo-fused portion, by C_1-C_6 alkyl, hydroxy, hydroxy(C_1-C_4)alkyl, -OR^6, R^6O-(C_1-C_4)alkyl, halo, halo(C_1-C_4)alkyl, -$S(O)_mR^6$, $R^6S(O)_m$(C_1-C_4)alkyl, oxo, N-cyanoimino, amino, amino(C_1-C_4)alkyl, -NHR^6, R^6NH(C_1-C_4)alkyl, -$N(R^6)_2$, $(R^6)_2N$(C_1-C_4)alkyl, cyano, cyano-(C_1-C_4)alkyl, -CO_2R^6, R^6O_2C(C_1-C_4)alkyl, -$CONH_2$, H_2NCO(C_1-C_4)alkyl, -$CONHR^6$, R^6NHCO(C_1-C_4)alkyl, -$CON(R^6)_2$ or $(R^6)_2NCO$-(C_1-C_4)alkyl, or, as appropriate, a ring N- or S-oxide derivative of said heterocyclic ring, with the proviso that said heterocyclic ring is linked by a ring carbon atom when X is O, NH or S, or

* C L M S *

This Sheet Has Been Replaced

(d) , when X is NH, a group of the formula:-



wherein R^6 is $-OR^8$, $-NHR^8$, $-SR^8$, -NH(aryl) or -NH(pyridinyl) and R^7 is cyano, nitro or C_2-C_6 alkanoyl; and the dashed line, X, R^2, R^3 and R^5 are as defined in claim 16.

18. A process as claimed in claim 16(i) or 17 which is carried out by reacting a compound of the formula (II) with a compound of the formula:-

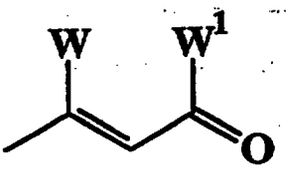
$$R^4XH,$$

or a tautomer thereof, and in the presence of a base such as pyridine or triethylamine.

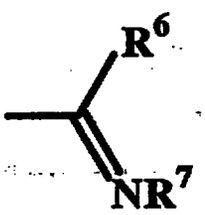
19. A process as claimed in claim 16 or 17 wherein the dashed line does not represent a covalent bond; X is O, NH or a direct link; R and R^1 are each independently selected from H and C_1-C_4 alkyl;
R^2 is H or methyl;
R^3 is hydroxy;
R^4 is a group of the formula:-

* C L M S *

This Sheet Has Been Replaced

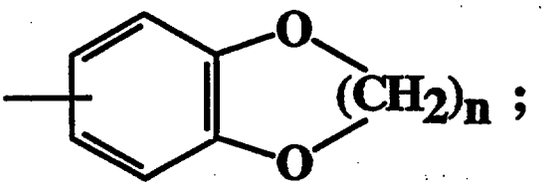


wherein W and W^1 taken together represent C_1-C_4 alkylene, a 6-membered heterocyclic ring containing 1 or 2 nitrogen heteroatoms and optionally substituted by C_1-C_6 alkyl, hydroxy, halo, C_1-C_4 alkylthio or oxo, or is a group of the formula:-



wherein R^6 is $-OR^8$, $-NHR^9$ or $-SR^8$ and R^7 is cyano; R^5 is aryl or C_1-C_{12} alkyl, said C_1-C_{12} alkyl being optionally substituted by hydroxy, $-OR^8$, C_2-C_6 alkanoyloxy, amino, $-CONHR^8$, $-CONH(C_1$-$C_6)alkylCO_2R^8$, $-CO_2R^9$, aryl, aryloxy, arylcarbonyloxy, aryl(C_1-C_6)alkoxy, phthalimido, or a group of the formula:-

This Sheet Has Been Replaced



R^8 is methyl or ethyl;

R^9 is indanyl, aryl, C_1-C_{12} alkyl or C_2-C_{12} alkenyl, said C_1-C_{12} alkyl being optionally substituted by halo, C_2-C_6 alkanoyloxy, $-OCO_2R^8$ or aryl;

"aryl" means phenyl optionally substituted by C_1-C_6 alkyl, hydroxy, $-OR^6$, halo or aryl(C_1-C_6)alkoxy;

m is 0; and
n is 1.

20. A process as claimed in claim 19 wherein R and R^1 are each C_1-C_4 alkyl;

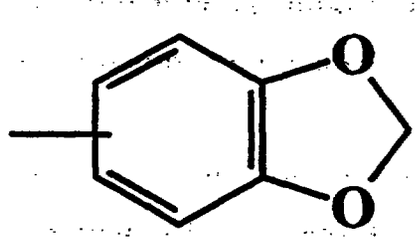
R^4 is 1-oxocyclopent-2-en-3-yl, 2-oxo-1,2-dihydropyridin-1-yl, 2-oxo-1H-1,2-dihydropyridin-4-yl, 2-oxopiperidin-1-yl, 3-hydroxypyridazin-6-yl, 2-methyl-3-oxopyridazin-6-yl, 4-chloropyrimidin-2-yl, 2-chloropyrimidin-4-yl, 2-methylthiopyrimidin-4-yl or is a group of the formula:-

* C L M S *

This Sheet Has Been Replaced



R^5 is phenyl or C_1-C_4 alkyl, said C_1-C_4 alkyl being optionally substituted by hydroxy, methoxy, acetoxy, amino, methylaminocarbonyl, N-(ethoxycarbonyl-methyl)carbamoyl, $-CO_2R^9$, phenyl, methylphenyl, methoxyphenyl, hydroxyphenyl, halophenyl, benzyl-oxyphenyl, phenoxy, benzoyloxy, benzyloxy, phthalimido, or a group of the formula:-



and R^9 and R^{9A} are each independently indanyl, phenyl, C_1-C_4 alkyl or vinyl, said C_1-C_4 alkyl being optionally substituted by fluoro, pivaloyloxy, ethoxycarbonyloxy or phenyl.

This Sheet Has Been Replaced

21. A process as claimed in claim 20 wherein

R^5 is phenyl, methyl, ethyl, n-propyl, 2-hydroxyethyl, 2-methoxyethyl, 2-acetoxyethyl, 2-aminoethyl, 2-(methylaminocarbonyl)ethyl, N-(ethoxycarbonylmethyl)carbamoylmethyl, ethoxycarbonylmethyl, 3-methoxycarbonylprop-1-yl, 3-ethoxycarbonylprop-1-yl, 4-ethoxycarbonylbut-1-yl, 3-vinyloxycarbonylprop-1-yl, 3-(2,2,2-trifluoroethoxycarbonyl)prop-1-yl, 3-(ethoxycarbonyloxymethoxycarbonyl)prop-1-yl, 3-(pivaloyloxymethoxycarbonyl)prop-1-yl, 3-phenoxycarbonylprop-1-yl, 3-benzyloxycarbonylprop-1-yl, 3-(5-indanyloxy-carbonyl)prop-1-yl, benzyl, 2-phenylethyl, 3-phenylprop-1-yl, 4-phenylbut-1-yl, 2-(2-methylphenyl)ethyl, 2-(3-methylphenyl)ethyl, 2-(4-methylphenyl)ethyl, 2-(2-methoxyphenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(4-hydroxyphenyl)ethyl, 2-(4-fluorophenyl)ethyl, 2-(4-benzyloxyphenyl)ethyl, 2-phenoxyethyl, 2-benzoyloxyethyl, 2-benzyloxyethyl, 2-phthalimidoethyl or 2-(1,3-benzodioxolan-5-yl)ethyl;

CLMS

This Sheet Has Been Replaced

and R^9 and R^{9A} are each independently 5-indanyl, phenyl, methyl, ethyl, vinyl, 2,2,2-trifluoroethyl, pivaloyloxymethyl, ethoxycarbonyloxymethyl or benzyl.

22. A process as claimed in claim 21 wherein R and R^1 are each methyl; R^2 is methyl; and R^5 is methyl, ethyl, n-propyl, 3-ethoxycarbonyl-prop-1-yl, 4-ethoxycarbonylbut-1-yl or 2-phenylethyl.

23. A process as claimed in claim 16 or 17 which is used to prepare a compound of the formula (I) that is selected from the group:-

4-(2-chloropyrimidin-4-yl)amino-3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-2,2,3-trimethyl-2H-benzo[b]pyran;

3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran;

3,4-dihydro-6-(1-[4-ethoxycarbonylbut-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran;

CLMS

This Sheet Has Been Replaced

3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-4-(2-methyl-3-oxopyridazin-6-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran;

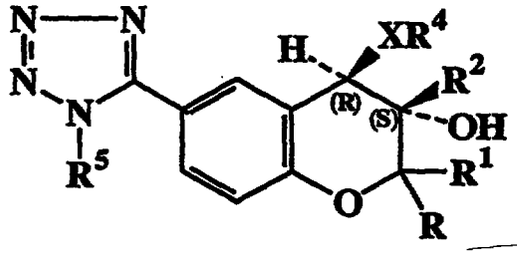
3,4-dihydro-2,2-dimethyl-3-hydroxy-4-(2-oxopiperidin-1-yl)-6-(1-[2-phenylethyl]-1H-tetrazol-5-yl)-2H-benzo-[b]pyran;

3,4-dihydro-6-(1-[3-ethoxycarbonylprop-1-yl]-1H-tetrazol-5-yl)-3-hydroxy-4-(2-oxo-1H-1,2-dihydropyridin-4-yl)oxy-2,2,3-trimethyl-2H-benzo[b]pyran;

3,4-dihydro-3-hydroxy-4-(3-hydroxypyridazin-6-yl)oxy-6-(1-[2-phenylethyl]-1H-tetrazol-5-yl)-2,2,3-trimethyl-2H-benzo[b]pyran:

or a pharmaceutically acceptable salt of any of these compounds, or, preferably, the 3S,4R- form of any of the aforementioned compounds.

24. A process as claimed in claim 16 or 17 which is used to prepare a compound of the formula:-



(IA)

* C L M S *

This Sheet Has Been Replaced

wherein X is O or NH; R and R^1 are each C_1-C_4 alkyl; R^2 is H or C_1-C_4 alkyl; and R^4 and R^5 are as defined in claim 16 or 17.

25. A process for the preparation of a pharmaceutical composition which comprises combining a compound of the formula (I), or a pharmaceutically acceptable salt thereof, which has been prepared by a process as claimed in any of claims 16 to 24, together with a pharmaceutically acceptable diluent or carrier.



This Sheet Has Been Replaced

