

PATENT SPECIFICATION

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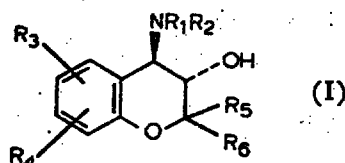
(54) CHROMAN DERIVATIVES

(71) We, BEECHAM GROUP LIMITED, a British company, of Beecham House, Great West Road, Brentford, Middlesex, England, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to chroman derivatives, to a process for their preparation and to pharmaceutical compositions containing them.

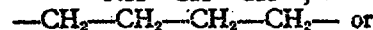
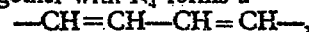
More specifically, this invention relates to derivatives of *trans*-3-hydroxy-4-amino-chroman which possess blood pressure lowering activity, to their preparation by the reaction of amines on chroman epoxide derivatives and to pharmaceutical compositions containing the compounds of the invention which may be used in the treatment of hypertension in mammals including humans.

The compounds according to this invention are of the formula (I):



and acid addition salts thereof wherein R₁ is a hydrogen atom or a C₁₋₆ hydrocarbon group optionally substituted by a hydroxyl or a C₁₋₆ alkoxy group; R₂ is a hydrogen atom or C₁₋₆ alkyl group, or NR₁R₂ is a 3-8 membered heterocyclic group optionally substituted by one or two methyl groups; R₃ is a hydrogen or halogen atom or a C₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ alkoxy, C₂₋₆ alkenoxy, C₁₋₆ alkylthio, hydroxyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, nitro, trifluoromethyl, C₂₋₇ acylamino, C₁₋₆ alkoxysulphonylamino, carb-

oxyl or nitrile group; R₄ is a hydrogen or halogen atom or a methyl or methoxy group or R₄ together with R₅ forms a



$-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CO}-$ system; R₅ and R₆ are each a hydrogen atom or a C₁₋₆ alkyl or phenyl group.

Suitably R₁ is a hydrogen atom or a methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl, allyl, phenyl, benzyl, tolyl, cyclopropylmethyl, or cyclohexyl group.

Particularly suitable groups R₁ include C₁₋₆ alkyl groups.

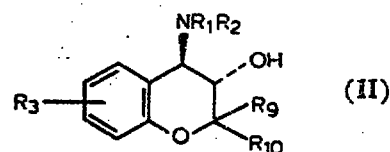
Suitably R₂ is a hydrogen atom or a methyl, ethyl or propyl group.

Suitable heterocyclic groups NR₁R₂ include the pyrrolidyl, piperidyl, morpholino, methyl-pyrrolidyl, N-methylpiperazine, hexamethyleneamino, N-phenylpiperazine and hexamethylenetetramine groups.

Especially suitable groups R₃ and R₄ include the methyl and ethyl groups.

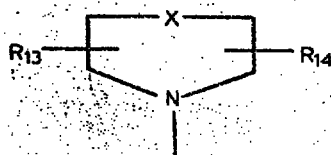
Preferred groups R₅ and R₆ include the methyl group.

Particularly suitable compounds of the formula (I) wherein R₁ is a hydrogen atom include those of the formula (II):



and their salts wherein R₃ is as defined in relation to formula (I), R₉ is a methyl or ethyl group, R₁₀ is a methyl or ethyl group and either (a), NR₁R₂ is a group NR₁₁R₁₂ wherein R₁₁ is an alkyl group of 1-4 carbon atoms

and R_{12} is a hydrogen atom or a methyl or ethyl group or (b) NR_1R_2 is a group of the sub-formula:



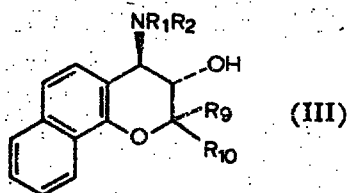
- 5 wherein X is a bond joining the two carbon atoms or is a CH_2 , $CH_2 \cdot CH_2$, $CH_2 \cdot CH_2 \cdot CH_2$, $CH:CH$, O, S or NCH_3 group, R_{13} is a hydrogen atom or a methyl group and R_{14} is a hydrogen atom or a methyl group.

10 Most suitably X is a bond or a CH_2 or NH C_{1-4} alkyl group.

Most suitably X is a bond or a CH_2 or CH_2CH_2 group.

- 15 Particularly suitable groups R_3 for inclusion in compounds of the formula (I) or (II) include the allyl, allyloxy, nitro, trifluoromethyl, nitrile, $NH \cdot CO \cdot R_{16}$ and $NHSO_2R_{16}$ groups where R_{16} is an alkyl group of 1-4 carbon atoms and n is 1, 2 or 3.

20 A further particularly suitable group of compound of the formula (I) is that of the formula (III):

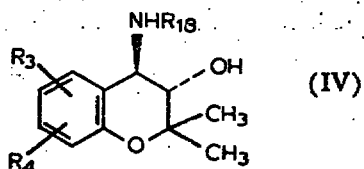


- 25 and salts thereof wherein NR_1R_2 , R_9 and R_{10} are defined as in relation to formula (II).

Particularly suitable groups NR_1R_2 in compounds of formulae (I), (II) or (III) include $NHC(CH_3)_3$, $NH \cdot CH(CH_3)_2$, pyrrolidyl and piperidyl groups.

30 Particularly suitable groups R_3 , R_4 , R_5 and R_{10} for inclusion in compounds of formulae (I), (II) or (III) include the methyl group.

One suitable sub-group of the compounds of formula (I) are those of formula (IV):

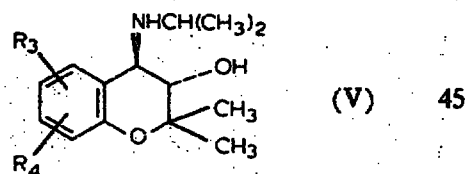


and salts thereof wherein R_{18} is a C_{1-4} alkyl, phenyl or benzyl group and R_3 and R_4 are as defined in relation to formula (I).

40 Most suitably R_{18} is an iso-propyl, iso-butyl or t-butyl group.

A further sub-group of the compounds of

formula (I) we believe worthy of mention are those of formula (V):



and salts thereof wherein R_3 and R_4 are as defined in relation to formula (I).

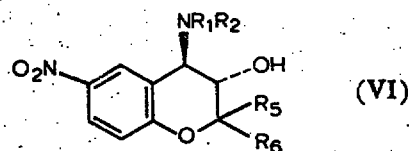
Suitable groups R_3 for inclusion in the compounds of formulae (II), (IV) or (V) include the hydrogen, fluorine and chlorine atoms and the methyl, ethyl, propyl, allyl, trifluoromethyl, methoxyl, methylthio, hydroxyl, nitro, allyloxy, amino, acetamido and methoxy-sulphonylamino.

Suitable groups R_4 for inclusion in the compounds of formulae (I), (IV) or (V) include the hydrogen, fluorine and chlorine atoms and the methyl and methoxyl groups.

Particularly suitable groups R_3 for inclusion in the compounds of the formulae (II), (IV) or (V) include the hydrogen, fluorine and chlorine atoms and the methyl, trifluoromethyl, allyl, nitro, amino, acetamido, allyloxy and methoxysulphonylamino groups.

Particularly suitable groups R_4 for inclusion in the compounds of the formulae (I), (IV) or (V) include the hydrogen and chlorine atoms, the hydrogen atom being preferred.

Compounds having vasodilatory activity may be found within formula (VI):



and salts thereof wherein R_1 , R_2 , R_5 and R_6 are as defined in relation to formula (I).

Most suitably, NR_1R_2 is a cyclic group of sub-formula (b) as defined in relation to formula (II).

Most suitably, R_5 is a methyl or ethyl group and R_6 is a methyl or ethyl group.

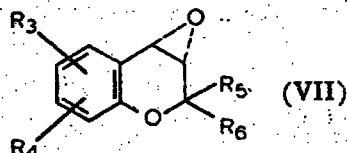
Preferably R_5 and R_6 are both methyl groups.

Acid addition salts of the amino compounds of formulae (I)-(VI) may be made with acids in conventional manner. Suitable salt-forming acids include hydrochloric, hydrobromic, sulphuric, phosphoric, methanesulphonic, p-toluene sulphonic, acetic, propionic, succinic, citric, tartaric, mandelic, lactic, gluconic or other pharmaceutically acceptable organic or inorganic acid.

The compounds of the invention exist in optionally active forms. Those skilled in the chemical arts will realise that racemic mixtures

of amino compounds can often be separated into pure optical isomers using such techniques as fractional crystallisation using optically active acids.

- 5 The compounds of formula (I) may be prepared by the reaction of an amine of the formula NHR_1R_2 with an epoxide of the formula (VII):—



- 10 wherein R_3 , R_4 , R_5 and R_6 are as defined in relation to formula (I).

The reaction of the amine and epoxide may be carried out at any non-extreme low, medium or high temperature (for example -10°C to 200°C) but in general ambient or slightly elevated temperatures are most suitable (for example, 12°C to 100°C). The reaction is normally carried out in the presence of a solvent such as an alkanolic or ketonic solvent (for example, methanol, ethanol, propanol, acetone or methylethylketone).

It has been found that the reaction frequently proceeds smoothly and efficiently if the reaction is carried out in warmed or refluxing ethanol.

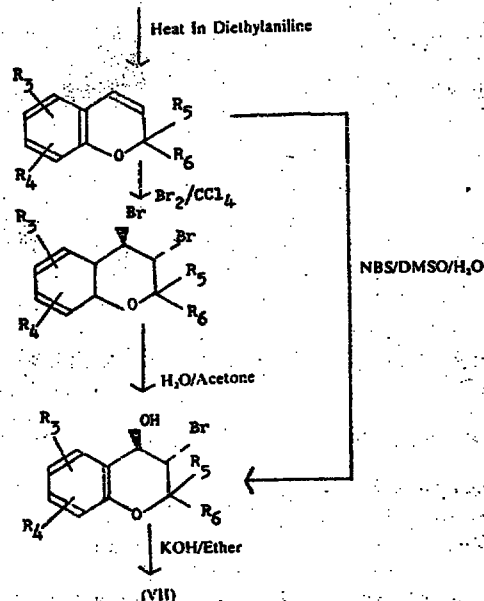
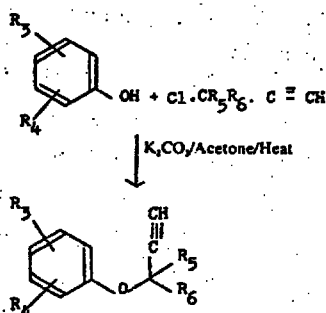
25 The above reaction has been found to give a *trans* product substantially free from the *cis*-isomer.

Compounds of formula (I) wherein R_3 is an amino group or substituted amino group may also be prepared by reduction (and optionally thereafter acylation or sulphonation) of the corresponding compound in which R_3 is a nitro group. Similarly, hydroxyl groups may be alkylated by conventional methods under conventional conditions if desired.

Frequently, pure compounds of this invention prepared by the preceding method may form crystals which contain water of crystallisation, for example, from 1 to 4 molecules of water per compound of formula (I).

The useful intermediates of the formula (VII) may be prepared by the method of Livingstone, R.; (J.Chem.Soc., 76 (1962)).

45 This method is summarised by reaction sequence A.



If necessary, the groups R_3 and/or R_4 may be protected during the above reaction sequence or may be transformed after the above reactions. For example, a compound of the formula (VII) in which R_3 is a hydroxyl group may be converted to the corresponding compound in which R_3 is an allyloxyl group by reaction with allyl bromide or a compound of the formula (VII) wherein R_3 is an amine group may be converted into the corresponding compound wherein R_3 is an acetamido group by reaction with acetyl chloride.

A further aspect of this invention provides pharmaceutical compositions suitable for the treatment of hypertension. Such compositions may be suitable for parenteral or oral administration, but in general, compositions adapted for oral administration are preferred because of convenience of administration. Frequently, it is advantageous to administer compounds of the formula (VI) together with an adrenergic β -blocking agent. The compositions of this invention comprise a compound of the formula (I) together with a pharmaceutically acceptable carrier.

The compositions are preferably in the form of unit dosage forms adapted for oral administration such as tablets or capsules. Such unit dosage forms will usually contain from 0.5 to 250 mg., for example, 2 to 100 mg. of a compound of the formula (I), and will usually be administered from 1 to 6 times a day so that the daily dose for a 70 kg. human is from 2 to 250 mg., for example 10 to 100 mg.

The compositions of this invention may be formulated in conventional manner, for example, in a manner similar to that used for known antihypertensive agents such as α -methyldopa, propranolol and guanethidine. In conventional manner, the compositions of this

invention may contain further active agents such as additional antihypertensive agents and diuretics.

The following Examples are illustrative of the invention.

EXAMPLE 1.

Trans - 4 - isopropylamino - 3,4 - dihydro - 2,2 - dimethyl - 2H - benzo [b]pyran - 3 - ol & Analogues.

3,4 - Epoxy - (3,4 - dihydro - 2,2 - dimethyl - 2H - benzo [b]pyran (10.00 g.) prepared as described by R. Livingstone, *J. Chem. Soc.*, 76, (1962), was treated with isopropylamine (12 ml: an excess) in refluxing ethanol (50 ml.) for 16 hours. The solution was then evaporated to dryness *in vacuo* to give an off-white solid (13.00g.). This residue was dissolved in diethyl ether and treated with ethereal hydrogen chloride to give a crystalline hydrochloride (12.06g). Re-crystallisation from ethanol/diethyl ether yielded *trans*-4-isopropyl - amino - 3,4 - dihydro - 2,2 - dimethyl - 2H - benzo [b]pyran - 3 - ol hydrochloride as colourless crystals, m.p. 172—174°.

Similarly prepared were *trans*-4-dimethyl-amino - 3,4 - dihydro - 2,2 - dimethyl - 2H - benzo [b]pyran-3-ol hydrochloride as colourless crystals m.p. 175—176°, *trans*-4-*t*-butyl-amino - 3,4 - dihydro - 2,2 - dimethyl - 2H - benzo [b]pyran-3-ol hydrochloride as colourless crystals mp. 239—241°, *trans*-4-morpholino - 3,4 - dihydro - 2,2 - dimethyl - 2H - benzo [b]pyran-3-ol hydrochloride m.p. 181—187°.

EXAMPLE 2.

Trans - 4 - amino - 3,4 - dihydro - 2,2 - dimethyl - 2H - benzo [b]pyran - 3 - ol hydrochloride.

3,4 - Epoxy - 3,4 - dihydro - 2,2 - dimethyl - 2H - benzo [b]pyran (3.00 g.) and sodium azide (1.23g.; and excess) were refluxed in dioxane (25 ml.) and water (5 ml.) mixture for 24 hours. Dilution with water and extraction via diethyl ether gave *trans*-4-azido-3,4-dihydro-2,2-dimethyl - 2H - benzo [b]pyran - 3 - ol (3.06g.) as needles from 60—80° petroleum ether m.p. 70—71°. To a solution of the hydroxy azide (2.90 g.) in acetone (50 ml.) containing concentrated hydrochloric acid (10 ml.) was added with stirring and in portions, zinc dust (10 g.). Stirring was continued until gas evolution ceased. The zinc was filtered and washed with acetone. The combined washings and filtrate were diluted with water and extracted with diethyl ether. Basification of the aqueous layer and isolation via diethyl ether gave *trans*-4-amino-3,4-dihydro-2,2-dimethyl-2H-benzo [b]pyran-3-ol (2.70 g.), re-crystallised from ethanol m.p. 138°.

Treatment with anhydrous hydrochloric acid as in Example 1 yielded *trans*-4-amino-3,4-

dihydro - 2,2 - dimethyl - 2H - benzo [b]pyran-3-ol hydrochloride, m.p. 223—225°.

EXAMPLE 3.

Trans - 4 - isopropylamino - 3,4 - dihydro - 2,2 - dimethyl - 2H - naphtho [1,2 - b]pyran-3-ol & Analogues.

2,2 - Dimethyl - 2H 1 naphtho - [1,2 - b]pyran (18.92 g., prepared *via* reaction between sodium 1-naphthoxide and 3-chloro-3-methylbutyne in refluxing toluene) was treated with bromine (14.42 g.) in carbon tetrachloride (300 ml.) at ambient temperature. Removal of solvent *in vacuo* gave *trans*-3,4-dibromo - 3,4 - dihydro - 2,2 - dimethyl - 2H-naphtho [1,2-b]pyran as a viscous oil (38.00 g.). This oil was dissolved in 400 ml. of a 2:1 mixture of acetone-water and refluxed for 17 hours. Isolation through diethyl-ether yielded *trans* - 3 - bromo - 3,4 - dihydro - 2,2 - dimethyl - 2H - naphtho [1,2-b]pyran - 4 - ol as a viscous oil (25.00 g.). This crude bromohydrin was dissolved in diethyl-ether (200 ml.), potassium hydroxide flakes (25.00 g.) were added and the mixture was stirred for 3 days at ambient temperature. Filtration and removal of solvent *in vacuo* gave crude epoxide, which was crystallised from 40—60° petroleum ether to yield 3,4 - epoxy - 3,4 - dihydro - 2,2 - dimethyl - 2H - naphtho [1,2 - b]pyran (9.29 g.) as pale-yellow crystals, m.p. 120—121°.

Treatment of this epoxide (2.72g.) with isopropylamine (1.77g., an excess) in refluxing ethanol (30 ml.) for 24 hours, followed by removal of solvent, gave a brown gum (3.37g.). This residue was dissolved in acetone and treated with D-(+)-tartaric acid (1.77g.). The acetone was evaporated to yield the crude salt (5.14g.), which was recrystallised from acetone/ether to give *trans* - 4 - isopropylamino - 3,4 - dihydro - 2,2 - dimethyl - 2H - naphtho [1,2 - b]pyran-3-ol D-(+)-hydrogen tartrate as a hydrate (2.75 g.) m.p. 107—114°.

Similarly prepared was *trans*-4-pyrrolidino-3,4 - dihydro - 2,2 - dimethyl - 2H - naphtho [1,2 - b]pyran - 3 - ol D - (+) - hydrogen tartrate as a hydrate m.p. greater than 340°.

EXAMPLE 4.

Trans - 4 - isopropylamino - 3,4 - dihydro - 2H - naphtho [1,2 - b]pyran - 3 - ol.

2H-Naphtho [1,2-b]pyran (4.00 g., prepared *via* cyclisation of 1-naphthyl propargyl ether in diethylaniline at 210°) was converted, via the same route as that described in Example 3, to 3,4 - epoxy - 3,4 - dihydro - 2H-naphtho [1,2-b]pyran (1.44 g.) m.p. 96—99°.

This epoxide (1.40g.) was treated with isopropylamine (1.00g., an excess) in refluxing ethanol (100 ml.) for 24 hours. Work-up as described in Example 4 yielded *trans*-4-isopropylamino - 3,4 - dihydro - 2H - naphtho [1,2 - b]pyran - 3 - ol D - (+) - hydrogen tartrate hydrate (0.30 g.) m.p. 108—110°.

EXAMPLE 5.

Trans - 4 - isopropylamino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b] - pyran - 3 - ol & Analogues.

- 5 2,2 - Dimethyl - 6 - nitro - 2H - benzo[b] - pyran (5.18 g., prepared *via* cyclisation of 3- (p-nitrophenoxy)-3-methyl-butyne in diethyl-aniline at 220°) was treated with bromine (4.03 g.) in carbon tetrachloride (110 ml.) at ambient temperature. Removal of solvent *in vacuo* gave trans-3,4-dibromo-3,4-dihydro-2,2 - dimethyl - 6 - nitro - 2H - benzo[b] - pyran as brown crystals (9.01 g.) m.p. 130—134°. This dibromide (8.85 g.) was refluxed in a mixture of acetone (80 ml.) and water (35 ml.) for 20 hours and isolation *via* ether extraction gave the crude bromohydrin, which was recrystallised from 60—80° petroleum-ether to yield trans-3-bromo-3,4-dihydro-2,2-dimethyl - 6 - nitro - 2H - benzo[b] pyran-4-ol as fawn microcrystals (2.00 g.) m.p. 114—116°. [Alternatively, 2,2-dimethyl-6-nitro-2H-benzo[b]pyran (8.20 g.) dissolved in dimethyl sulphoxide (80 ml.) containing water (1.4 ml.) and cooled in ice-water was treated with freshly recrystallised N-bromosuccinimide (14.24 g.) added in one portion. Dilution with water and isolation *via* ethyl acetate gave the bromohydrin (11.3 g.). This bromohydrin (1.92 g.) was stirred with potassium hydroxide pellets (1.92 g.) in diethyl-ether (50 ml.) for 4 days. Filtration and removal of solvent yielded 3,4-epoxy-3,4-dihydro-2,2-dimethyl-6-nitro-2H-benzo[b]pyran as a cream solid (1.33 g.) m.p. 91—93°. Treatment of this epoxide (1.14 g.) with isopropylamine (0.59 g., an excess) in refluxing ethanol (50 ml.) for 18 hours, followed by work-up as described in Example 1, gave trans-4-isopropylamino-3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b] pyran-3-ol hydrochloride (1.37 g.) m.p. 253—257°.

- Similarly prepared were trans-4-methyl-amino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b] pyran - 3 - ol hydrochloride m.p. 296—299°, trans-4-dimethyl-amino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b] pyran - 3 - ol hydrochloride m.p. 260—261°, trans - 4 - diethyl-amino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b] pyran - 3 - ol hydrochloride m.p. 198—204°, trans-4-ethanol-amino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b] pyran - 3 - ol hydrochloride m.p. 264—267°, trans - 4 - cyclopropylmethylamino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b] pyran - 3 - ol hydrochloride m.p. 256—259°, trans-4-tert-Butylamino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b] pyran - 3 - ol hydrochloride m.p. 280°, trans - 4 - pyrrolidino-3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b] pyran - 3 - ol hydrochloride m.p. 238—243°, trans - 4 - morpholino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b] -

pyran - 3 - ol hydrochloride m.p. 243—248°, trans - 4 - piperidino - 3,4 - dihydro - 2,2-dimethyl - 6 - nitro - 2H - benzo[b] - benzo[b]pyran - 3 - ol hydrochloride m.p. 240—245°, trans - 4 - [4 - methylpiperidino]-3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b]pyran - 3 - ol hydrochloride m.p. 226—230°, trans - 4 - hexamethylenimino-3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b]pyran - 3 - ol hydrochloride m.p. 215—220°, trans - 4 - heptamethylenimino-3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b]pyran - 3 - ol hydrochloride m.p. 214—220°, trans - 4 - N - phenylpiperazino-3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b]pyran - 3 - ol dihydrochloride m.p. 147—188°, trans - 4 - [2,5 - dimethyl - pyrrolidino] - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b]pyran - 3 - ol hydrochloride m.p. 158—206°.

EXAMPLE 6.

Trans - 4 - isopropylamino - 3,4 - dihydro - 2,2 - dimethyl - 6 - amino - 2H - benzo[b] - pyran - 3 - ol - sulphate.

Trans - 4 - Isopropylamino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2H - benzo[b] - pyran-3-ol (3.54 g.) was added to a solution of stannous chloride (7.90 g.) in ethanol (36 ml.) and concentrated hydrochloric acid (60 ml.) and stirred for 3 hours at ambient temperature. After dilution, work-up *via* diethyl ether gave a gum (3.25 g.). Purification of this gum (2.00 g.) by application to silica gel plates and development with ethyl acetate/60—80° petroleum ether mixture gave an amorphous solid (1.01 g.) which was dissolved in dilute sulphuric acid and evaporated to dryness to yield trans-4-isopropylamino-3,4-dihydro - 2,2 - dimethyl - 6 - amino - 2H - benzo[b]pyran-3-ol sulphate as a light brown solid m.p. 180—190°.

EXAMPLE 7.

Trans - 4 - Isopropylamino - 3,4 - dihydro - 2,2 - dimethyl - 6 - acetamido - 2H - benzo[b]pyran - 3 - ol hydrochloride.

2,2 - Dimethyl - 6 - acetamido - 2H - benzo[b]pyran [(1.26 g.), prepared as described in British Patent No. 1,121,307] dissolved in dimethyl sulphoxide (20 ml.) containing water (0.2 ml.) and cooled in an ice-bath was treated with N-bromosuccinimide (2.20 g., an excess). Work-up as described in Example 6, gave a gum (1.46 g.) which was purified by application to silica gel plates and developed with ethyl acetate-60—80° petroleum ether mixtures gave pale yellow crystals (0.96 g.) from ethylacetate acetate/60—80° petroleum ether of trans - 3 - bromo - 3,4 - dihydro - 2,2-dimethyl - 6 - acetamido - 2H - benzo[b]pyran-4-ol mp. 170°. This bromohydrin (0.92 g.) was stirred with potassium hydroxide pellets (1.50 g.) in diethyl ether (120 ml.) for 4.5 days. Filtration and removal of solvent gave

3,4 - epoxy - 3,4 - dihydro - 2,2 - dimethyl - 6-
acetamido-2H-benzo[b]pyran (0.55 g.) re-
crystallised from ethyl acetate 60—80° petro-
leum ether as colourless needles m.p. 173—
175°. Treatment of this epoxide (0.50 g.) with
isopropylamine (1.5 g., an excess) and work-
up as in Example 1, gave *trans*-4-isopropyl-
amino - 3,4 - dihydro - 2,2 - dimethyl - 6-
acetamido - 2H - benzo[b]pyran - 3 - ol
hydrochloride (0.38 g) m.p. 259—260° from
diethyl ether ethanol.

EXAMPLE 8.

Trans - 4 - Isopropylamino - 3,4 - dihydro-
2,2 - diethyl - 2H - benzo[b]pyran - 3 - ol
hydrochloride.
2,2-Diethyl-2H-benzo[b]pyran (3.86 g.)
was treated with N-bromosuccinimide (7.40
g.) under the conditions described in Example
5 yielding *trans*-3-bromo-3,4-dihydro-2,2-
diethyl-2H-benzo[b]pyran-4-ol (5.70 g.), as
a pale yellow solid m.p. 75—77° after tritura-
tion with 60—80° petroleum ether. Reaction
of this bromohydrin (5.60 g.) with potassium
hydroxide pellets (6.38 g.) in diethyl ether
(300 ml.) for 4.5 days following Example 7
gave 3,4 - epoxy - 3,4 - dihydro - 2,2 - diethyl-
2H-benzo[b]pyran as a colourless liquid (4.28
g.) displaying signals centred at δ 3.66 and

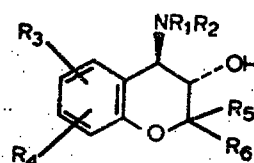
3.78 (doublets, of coupling constant $J=4\text{Hz}$)
in its p.m.r. spectrum (CDCl_3 , with TMS as
internal standard) corresponding to protons
located at C—3 and C—4. Treatment of this
epoxide (1.40 g.) with isopropylamine (3.50
g., an excess) and work-up as in Example 1,
gave *trans* - 4 - isopropylamino - 3,4 - dihydro-
2,2 - diethyl - 2H - benzo[b]pyran - 3 - ol
hydrochloride (1.67 g.) m.p. 200—202°.

A similar preparation gave *trans*-4-pyrroli-
dino - 3,4 - dihydro - 2,2 - diethyl - 2H-
benzo [b]pyran - 3 - ol hydrochloride m.p.
133—138°.

EXAMPLE 9.

Pharmacology.

Compounds of formula (I):



and certain standard compounds were tested
in DOCA treated hypertensive rats. The results
obtained 6 hours after oral administration at a
dose of 100 mg/kg of compound are shown in
Table 1.

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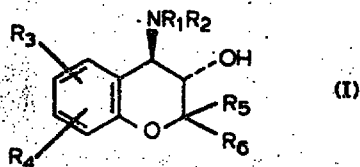
13

TABLE I

R_1	R_2	R_3	R_4	R_5	R_6	Salt	Approximate % Change in Systolic Blood Pressure
$CH(CH_3)_2$	H	$CH-CH-CH-CH$	H	CH_3	CH_3	Tartrate	-13
$CH(CH_3)_2$	H	6- NO_2	H	CH_3	CH_3	HCl	-20
-	$(CH_2)_5-$	6- NO_2	H	CH_3	CH_3	HCl	-56
C_2H_5	C_2H_5	6- NO_2	H	CH_3	CH_3	HCl	-22
$(CH_3)_4$	-	6- NO_2	H	CH_3	CH_3	HCl	-66
$CH(CH_3)_2$	H	H	H	C_2H_5	C_2H_5	HCl	-16
dl practalol							-3
dl pindolol							-10
α -methyldopa							-24

WHAT WE CLAIM IS:—

1. Compounds of the formula (I):

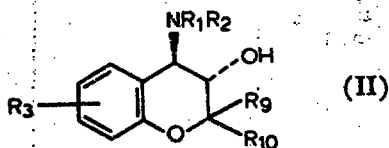


and acid addition salts thereof wherein R_1 is a hydrogen atom or a C_{1-6} hydrocarbon group, optionally substituted by a hydroxyl or C_{1-6} alkoxy group; R_2 is a hydrogen atom or a C_{1-6} alkyl group; or NR_1R_2 is a 3-8 membered heterocyclic group, optionally substituted by one or two methyl groups; R_5 is a hydrogen or halogen atom or a C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{2-6} alkenoxy, C_{1-6} alkylthio, hydroxyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, nitro, trifluoromethyl, C_{2-7} acylamino, C_{1-6} alkoxysulphonylamino, carboxyl or nitrile group; R_6 is a hydrogen or halogen atom or a methyl or methoxy group; or R_3 together with R_4 forms a $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{NH}-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CO}-$ system; R_5 and R_6 are each a hydrogen atom or a C_{1-6} alkyl or phenyl group.

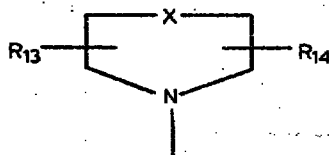
2. Compounds according to Claim 1 wherein R_1 is C_{1-6} alkyl group and R_2 is a hydrogen atom or a C_{1-6} alkyl group or NR_1R_2 is a pyrrolidyl, piperidyl, morpholino, methylpyrrolidyl, N-methylpiperazine, hexamethylenecamino, N-phenylpiperazine or hexamethylenetetramine group.

3. Compounds according to Claims 1 or 2 wherein R_5 and R_6 are methyl groups.

4. Compound according to Claim 1 of the formula (II):

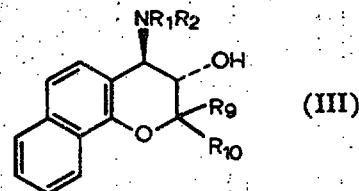


and their salts wherein R_3 is as defined in relation to formula (I) in Claim 1, R_9 is a methyl or ethyl group, R_{10} is a methyl or ethyl group and either (a), NR_1R_2 is a group $NR_{11}R_{12}$, wherein R_{11} is an alkyl group or 1-4 carbon atoms and R_{12} is a hydrogen atom or a methyl or ethyl group or (b) NR_1R_2 is a group of the sub-formula:



wherein X is a bond joining the two carbon atoms or is a CH_2 , $\text{CH}_2 \cdot \text{CH}_2$, $\text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2$, $\text{CH} \cdot \text{CH}$, O, S or NCH_3 group, R_{13} is a hydrogen atom or a methyl group and R_{14} is a hydrogen atom or a methyl group.

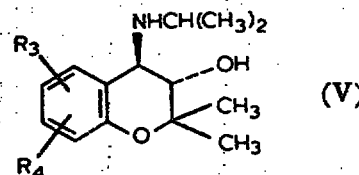
5. Compounds according to Claim 1 of the formula (III):



and salts thereof wherein NR_1R_2 , R_9 and R_{10} are defined as in relation to formula (II) in Claim 4.

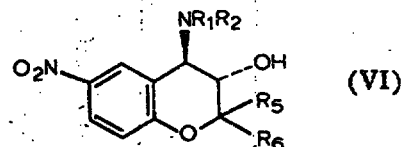
6. Compounds according to Claim 4 or 5 wherein R_9 and R_{10} are methyl groups.

7. Compounds according to Claim (I) of the formula (V):



wherein R_3 and R_4 are defined as in relation to formula (I) in Claim 1.

8. Compounds according to Claim 1 of the formula (VI):



wherein R_1 , R_2 , R_5 and R_6 are as defined in Claim 1.

9. Compounds according to Claim 8 wherein R_5 and R_6 are both methyl groups.

10. Compounds according to Claims 8 or 9 wherein NR_1R_2 is a group of the sub-formula (b) as defined in Claim 4.

11. *Trans* - 4 - isopropylamino - 3,4 - dihydro - 2,2 - dimethyl - 2H - benzo[b]pyran-3-ol and pharmaceutically acceptable salts thereof.

12. *Trans* - 4 - dimethylamino - 3,4 - dihydro - 2,2 - dimethyl - 2H - benzo[b]pyran-3-ol and pharmaceutically acceptable salts thereof.

13. *Trans* - 4 - t - butylamino - 3,4 - dihydro - 2,2 - dimethyl - 2H - benzo[b]pyran-3-ol and pharmaceutically acceptable salts thereof.



14. *Trans* - 4 - morpholino - 3,4 - dihydro-2,2 - dimethyl - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
15. *Trans* - 4 - amino - 3,4 - dihydro - 2,2 - dimethyl - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
16. *Trans* - 4 - isopropylamino - 3,4 - dihydro - 2,2 - dimethyl - 2*H* - naphtho[1,2-*b*]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
17. *Trans* - 4 - pyrrolidino - 3,4 - dihydro-2,2 - dimethyl - 2*H* - naphtho[1,2-*b*]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
18. *Trans* - 4 - isopropylamino - 3,4 - dihydro - 2*H* - naphtho[1,2 - *b*]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
19. *Trans* - 4 - isopropylamino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
20. *Trans* - methylamino - 3,4 - dihydro-2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
21. *Trans* - 4 - dimethylamino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
22. *Trans* - 4 - diethylamino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
23. *Trans* - 4 - ethanolamino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
24. *Trans* - 4 - cyclopropylmethylamino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
25. *Trans* - 4 - tert - butylamino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
26. *Trans* - 4 - pyrrolidino - 3,4 - dihydro-2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
27. *Trans* - 4 - morpholino - 3,4 - dihydro-2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
28. *Trans* - 4 - piperidino - 3,4 - dihydro-2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
29. *Trans* - 4 - [4 - methylpiperidino] - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
30. *Trans* - 4 - hexamethylenimino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
31. *Trans* - 4 - heptamethylenimino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
32. *Trans* - 4 - *N* - phenylpiperazino - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
33. *Trans* - 4 - [2,5 - dimethyl - pyrrolidino] - 3,4 - dihydro - 2,2 - dimethyl - 6 - nitro - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
34. *Trans* - 4 - isopropylamino - 3,4 - dihydro - 2,2 - dimethyl - 6 - amino - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
35. *Trans* - 4 - isopropylamino - 3,4 - dihydro - 2,2 - dimethyl - 6 - acetamido - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
36. *Trans* - 4 - isopropylamino - 3,4 - dihydro - 2,2 - diethyl - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
37. *Trans* - 4 - pyrrolidino - 3,4 - dihydro-2,2 - diethyl - 2*H* - benzo[b]pyran - 3 - ol and pharmaceutically acceptable salts thereof.
38. A process for the preparation of compounds according to Claim 1 which comprises the reaction of an amine of the formula NHR_1R_2 with an epoxide of the formula (VII):
- (VII)
- wherein R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are as defined in relation to formula (I).
39. A pharmaceutical composition which comprises a compound according to Claim 1 together with a pharmaceutically acceptable carrier.
40. A composition according to Claim 39 in unit dose form adapted for oral administration.
41. A composition according to claim 40 which comprises from 0.5 to 250 mg of a compound according to claim 1.
42. A composition according to claim 41 which comprises from 2 to 100 mg of a compound according to claim 1.
43. A compound according to Claim 1 when prepared substantially as described in any of Examples 1—8 herein.

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