

PATENT SPECIFICATION

(11) 1230 087

NO DRAWINGS

- (21) Application No. 37912/67 (22) Filed 17 Aug. 1967
 (23) Complete Specification filed 30 July 1968
 (45) Complete Specification published 28 April 1971
 (51) International Classification A 61 k 27/00; C 07 d 7/46
 (52) Index at acceptance

C2C 181—193—275 1E7B1 1E7C1 1E7D1 1E7E1 1E7F1
 1E7H2 1E7J 1E7N5 1E7P3 213 220 227 22Y 247
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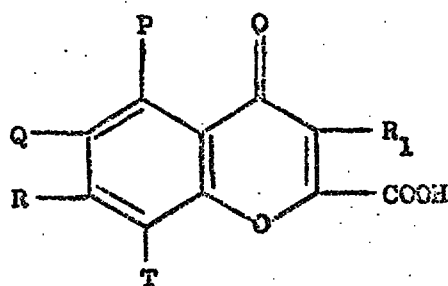
(72) Inventors HUGH CAIRNS and ROBERT MINSHULL

(54) SUBSTITUTED BENZODIPYRONES

(71) We, Fisons Pharmaceuticals Limited, a British Company, of 12 Derby Road, Loughborough, Leicestershire, 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 novel compounds, their preparation and use.

According to the invention there are provided, as new compounds, benzodipyrone of the formula:—



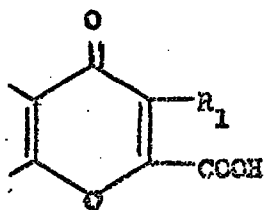
FORMULA I

and pharmaceutical acceptable derivatives thereof, in which an adjacent pair of P, Q, R and T, together form the chain

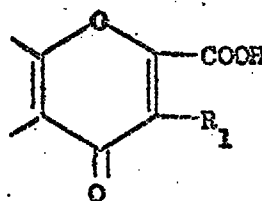


which may be bonded to the benzene ring in either sense; the other two of P, Q, R and T are the same or different and each is hydrogen or a substituent other than hydrogen; and each R₁ may be the same or different and is hydrogen, an alkyl group containing from 1—10 carbon atoms, an alkoxy group containing from 1—10 carbon atoms, an aryl group, a substituted alkyl or alkoxy group containing from 1—10 carbon atoms, or a substituted aryl group.

It will be appreciated that the chain $-\text{CO}-\text{CR}_1=\text{C}(\text{COOH})-\text{O}-$ may be bonded to the benzene ring in either sense to form the rings



or



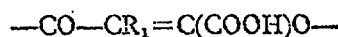
and reference to one chain or ring is intended herein and in the claims to denote bonding in both senses.

Compounds of the invention include those wherein those of P, Q, R and T which do not form the pyrone ring may be the same or different and may be, for example, hydrogen; alkyl groups containing from 1 to 10 carbon atoms (e.g. methyl, ethyl, butyl, pentyl, and hexyl groups); substituted alkyl groups (e.g. alkyl groups carrying halo; hydroxy; alkoxy, e.g. methoxy, ethoxy, propoxy or pentoxy; acetoxo; carboxy; amino; alkylamino, e.g. ethylamino, butylamino or pentylamino; dialkylamino e.g. dimethylamino, diethylamino, dibutylamino, dipentylamino; hydroxylamino; or hydrazino substituent groups) corresponding to the above alkyl groups; unsaturated alkyl groups (e.g. alkenyl groups such as allyl and propargyl groups) derived from the above alkyl groups; aralkyl groups (e.g. benzyl and phenethyl groups) wherein the alkyl groups contain 1 to 10 carbon atoms; substituted aralkyl groups (e.g. haloaralkyl and alkylaralkyl groups); mono and polybenzenoid aryl groups (e.g. phenyl and naphthyl groups); substituted aryl groups (e.g. lower alkaryl, haloaryl, nitroaryl, carboxyaryl and hydroxyaryl groups); heterocyclic groups (e.g. pyridyl, furyl or pyrrolyl groups); substituted heterocyclic groups; cycloalkyl groups containing from 4-6 carbon atoms (e.g. cyclopentyl or cyclohexyl groups); substituted cycloalkyl groups carrying hydroxyl, lower alkoxy or carboxy substituents (e.g. hydroxycycloalkyl or carboxycycloalkyl groups); nitrile groups; imino-ether groups; amidine groups, nitro groups; nitroso groups; hydroxy groups; alkoxy groups containing 1 to 10 carbon atoms (e.g. methoxy, ethoxy or propoxy groups); substituted alkoxy groups containing from 1 to 10 carbon atoms (e.g. hydroxyalkoxy, lower alkoxyalkoxy, carboxyalkoxy, haloalkoxy, aminoalkoxy, lower alkylaminoalkoxy, or lower dialkylaminoalkoxy groups); unsaturated alkoxy groups (i.e. alkenyloxy or alkynyloxy groups); aralkyloxy groups (e.g. a benzyloxy group); aryloxy groups (e.g. phenyloxy or naphthyloxy groups); substituted aryloxy groups; heteroaryloxy groups (e.g. pyridyloxy group); cycloalkyloxy group (e.g. cyclohexyloxy or cyclopentyloxy groups); epoxy-loweralkoxy groups; amino groups; lower alkylamino groups (e.g. ethylamino and propylamino groups); lower dialkylamino groups (e.g. dimethylamino and diethylamino groups); cycloalkylamino groups containing from 4 to 6 carbon atoms; arylamino groups (e.g. phenylamino and naphthylamino groups); diarylamino groups (e.g. a diphenylamino group); halolower alkylamino groups; lower alkenylamino groups; aminoloweralkylamino groups, amine oxide groups; oxime groups; hydroxylamino groups; azo groups; hydrazino groups; hydrazide groups; hydrazone groups; hetero-

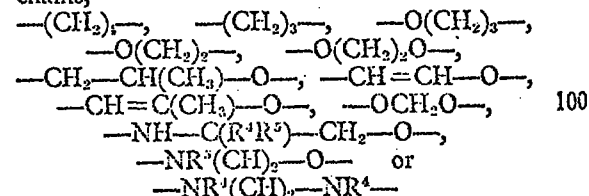
cyclic amino groups; imide groups; ureyl groups; thioureyl groups; guanidino groups; thiol groups; lower alkyl thiol groups; substituted alkyl thiol group; phenyl thiol groups; sulphonic acid groups (including salts, esters or amides thereof); and halogen atoms (e.g. chlorine, bromine, or iodine atoms).

One or more of P, Q, R and T may be a group OY wherein Y is an alkyl or phenyl alkyl group the alkyl portion of which contains from 1 to 10 carbon atoms and in which one or more of the CH₂ groups has been replaced by oxygen, sulphur or a carbonyl group, which alkyl or phenyl alkyl groups may carry one or more hydroxyl or carboxyl substituent groups; a heterocyclic ring containing carbon and oxygen atoms, which ring may carry one or more hydroxyl or alkyl substituent groups; or an alkyl group carrying one or more heterocyclic substituent groups, which heterocyclic groups may carry one or more hydroxyl or alkyl substituent groups.

In addition to the above values, where either P+Q or R+T form the desired

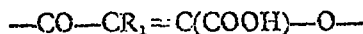


chain, the other adjacent pair of groups (together with the adjacent carbon atoms in the benzene ring) may together form another fused carbocyclic, e.g. benzene, or heterocyclic ring. Thus, the groups may form the chains,



(wherein R⁴ is hydrogen or an lower alkyl or lower alkoxy group and R⁵ is hydrogen, or R⁴ and R⁵ together form a =O group).

Preferred compounds of the invention include those wherein those of P, Q, R and T not forming the $-\text{CO}-\text{CR}_1=\text{C}(\text{COOH})\text{O}-$ chain are hydrogen or halogen, hydroxy, nitro, lower alkyl, lower alkenyl, benzyl, phenyl, lower alkoxy, lower alkenyloxy, phenyloxy, benzyloxy groups or the fused ring substituents specified above, and such groups carrying substituents, such as halogen, hydroxy or lower alkoxy groups. Particularly preferred compounds are those carrying hydrogen or halogen (especially chlorine or bromine), nitro and lower alkyl or alkoxy groups containing from 1 to 6 carbon atoms which may carry hydroxy, lower alkoxy or aryl substituents. It is especially preferred that those of P, Q, R and T not forming the



chain are hydrogen.

The term lower is used herein and in the

claims to 1 to 6 carbons. According to invention pr



or pharma- thereof whe- P', Q', R' -CO-CH bonded to and the oth- the same o- halogen, ni- a lower alk- roxy, lower

It will b- above value and T' inci- mentally af- action conc- groups or t

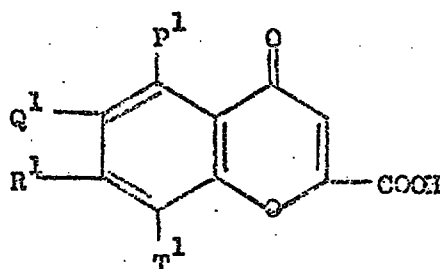
rings into affected g- shielded, f- tion; or by a removable group. Th- P, Q, R, therefore t- claims to in- or blocked sired value

Each R, have the hydrogen; ethyl, pre- alkoxy gr- groups; or group. It group be hydrogen.

Pharma- the comp- clude salts and amide

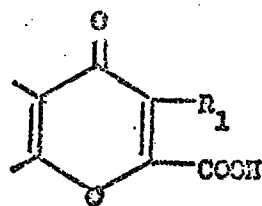
claims to denote a group containing from 1 to 6 carbon atoms.

Accordingly, from a preferred aspect, the invention provides compounds of the formula:



or pharmaceutically acceptable derivatives thereof wherein an adjacent pair of the group P', Q', R' and T' together forms the chain —CO—CH=C(COOH)—O— which may be bonded to the benzene ring in either sense; and the other two P', Q', R' and T' may be the same or different and each is hydrogen, halogen, nitro, lower alkyl, lower alkoxy, or a lower alkyl or alkoxy group carrying hydroxy, lower alkoxy or phenyl substituents.

It will be appreciated that certain of the above values of the P, Q, R, T, P', Q', R' and T' include groups which might be detrimentally affected by the reactants and/or reaction conditions used to introduce other groups or the desired



rings into the molecule. In such cases the affected group or site may be blocked or shielded, for example by alkylation, acetylation; or by the blocking of the reactive site with a removable group such as a cyano or nitro group. The reference to the values for the P, Q, R, T, P', Q', R' and T' groups is therefore to be construed herein and in the claims to include, where permissible, a shielded or blocked precursor or derivative of the desired value for the substituent.

Each R₁ may be the same or different and have the values specified above, particularly hydrogen; lower alkyl, such as a methyl, ethyl, propyl, or pentyl group; a lower alkoxy group corresponding to such alkyl groups; or an aryl group such as a phenyl group. It is usually preferred that each R₁ group be the same and, further, that each is hydrogen.

Pharmaceutically acceptable derivatives of the compound according to the invention include salts, notably water-soluble salts, esters and amides of one or more of the carboxylic

acid functions present and esters of any hydroxylic functions present.

Salts of the compounds which may be mentioned are salts with physiologically acceptable cations, for example, ammonium salts; metal salts, such as alkali-metal salts (e.g. sodium, potassium and lithium salts) and alkaline-earth metal salts (e.g. magnesium and calcium salts); and salts with organic bases, e.g. amine salts such as piperidine, triethanolamine and diethylaminoethylamine salts.

Esters which may be mentioned include simple alkyl esters derived from alcohols containing up to 10 carbon atoms; amides which may be mentioned include simple amides and more complex amides with amino acids such as glycine.

The salts, esters, amides and other pharmaceutically acceptable derivatives of the compounds of the invention may be prepared by conventional techniques. Thus, salts may be prepared by the use of alkaline conditions during the recovery and purification of the compound. Alternatively, the free acid may be obtained and subsequently converted to a desired salt by neutralisation with an appropriate base, e.g. an organic amine, or alkali such as an alkali-metal (e.g. sodium or potassium) or alkaline-earth metal (e.g. calcium or magnesium) hydroxide, carbonate or bicarbonate, preferably a mild base or alkali such as sodium carbonate or bicarbonate. Where the compound is recovered in the form of a salt this salt may be converted to a more desirable salt, for example, by a metathetical process. The esters may be obtained as a result of having used appropriate starting materials, for example by the reaction of a dialkyl oxalate with an acylbenzene of formula V as hereinafter described; or may be formed by the reaction of an appropriate alcohol, alkyl sulphate or halo-compound with free carboxyl groups in the compound. Alternatively transesterification techniques may be used to exchange one ester group for another. The amides may be readily obtained, for example, by dehydration of the ammonium salt or by reaction of an ester or acyl halide of the compound with an appropriate amino compound such as a primary or secondary amine or an amino acid.

The new compounds of the invention have been shown to inhibit the release and/or action of toxic products which arise from the combination of certain types of antibody and specific antigen, e.g. the combination of reaginic antibody with specific antigen. In man, it has been found that both subjective and objective changes which result from the inhalation of specific antigen by sensitised subjects are markedly inhibited by prior administration of the new compounds. Thus, the new compounds are indicated for use in the treatment of "extrinsic" allergic asthma. The new

compounds are also indicated for use in the treatment of so-called "intrinsic" asthma (in which no sensitivity to extrinsic antigen can be demonstrated). In *in vitro* tests, the compounds have been shown to reduce the release of pharmacologically active substances from passively sensitised human lung tissue after exposure to specific antigen using a modification of the *in vitro* technique of Mongar and Schild (J. L. Mongar and H. O. Schild, J. Physiol, Vol. 150 (1960), pp. 546—564). The new compounds may also be of value in the treatment of other conditions in which antigen reactions are responsible for disease, for example, hay fever, urticaria and autoimmune diseases.

According to the further feature of the invention, therefore, there is provided a pharmaceutical composition comprising a benzodipyronone of general formula I, or a pharmaceutically acceptable derivative thereof, preferably in the form of a salt, in association with a pharmaceutically acceptable carrier or diluent. There is also provided a process for the manufacture of such a pharmaceutical composition which comprises mixing a compound of the invention with a carrier or diluent.

The nature of the composition and the pharmaceutically acceptable carrier or diluent will, of course, depend upon the desired mode of administration, which may be for example orally; by inhalation; parenterally, or by topical application.

The compositions may be formulated in the conventional manner with the customary ingredients. For example, the compositions may be put up as aqueous solutions or suspensions, as powders or in tablet, cream, lotion or syrup form.

The compounds of the invention may be inhaled by the user, notably in the treatment of allergic asthma. For such use, the compounds of the invention, preferably in the form of a salt such as the sodium salt, are dissolved or suspended in water and may be applied by means of a conventional nebuliser. However, administration of medicaments by means of a pressurised dispensing container, i.e. an aerosol dispenser, is an alternative to nebuliser administration. For administration from an aerosol dispenser, the medicament is dissolved or suspended in the liquefied propellant medium. Where the medicament is not soluble in the propellant, it may be necessary to add a surface-active agent to the composition in order to suspend the medicament in the propellant medium, and such surface-active agents may be any of those commonly used for this purpose, such as non-ionic surface-active agents. However, we prefer to use the anionic dialkyl sulphosuccinate or alkyl benzene sulphonate surface-active agents. The use of such surface-active agents and the advantages which stem therefrom are more fully described in British Patent Specification No. 1,063,512.

The compositions of the invention may also be administered in the form of powders by means of an insufflator device, such as that described in our French Patent Specification 1471722. In order to improve the properties of the powder, it may be desired to modify the surface characteristics of the powder particles, for example by coating them with a pharmaceutically acceptable material such as sodium stearate. In addition, the fine particle sized powders may be mixed with a coarser diluent material such as lactose.

Whilst the inhalation of medicament has been described above with particular reference to oral administration, it will be appreciated that it may be desirable to administer the medicament nasally. The term inhalation is therefore used herein and in the claims to denote, where the context permits, both oral and nasal administration.

The composition of the invention may also be administered as tablets or syrups or by intradermal or intravenous injection in the conventional manner.

In addition to the internal administration, the compounds of the invention may find use in compositions for topical application, e.g. as creams, lotions or pastes for use in dermatological treatments.

In addition to the compound of the invention and the ingredients required to present the compound in a form suitable for the selected mode of administration, we have found that other active ingredients may be present in the composition of the invention. Thus, in compositions for administration by inhalation, we have found that it is beneficial to include a bronchodilator. Any bronchodilator may, within reason, be used. Suitable bronchodilators include isoprenaline, adrenaline, orciprenaline, isoetharine and derivatives thereof, particularly the salts thereof. The use of isoprenaline sulphate is preferred. The amount of bronchodilator used will vary over a broad range, depending, *inter alia*, upon the nature and activity of the bronchodilator and the compound of the invention used. However, the use of a minor proportion (i.e. less than 50% by weight) of the bronchodilator is preferred. We have found that the use of from 0.1 to 10% by weight of the bronchodilator based on the weight of the compound of the invention is satisfactory.

From a further aspect, the invention therefore provides a composition which comprises a compound of the formula I or a pharmaceutically acceptable derivative thereof in admixture with a bronchodilator, which latter is preferably present in less than 50%, especially 0.1 to 10%, by weight of the former.

As indicated above, the compounds of the invention may be used to inhibit the effects of antibody-antigen reactions and are indicated

for use in the pre-airway diseases. pound or compound administered by one of the antibody-peptically effect may be one of the medicament amount and administered will and no concise generally stated found that, administered by from acute allergic results are administered 0.1 to 50 mg administered may be given.

The invention for inhibiting reaction which to the known body-antigen peptically effect a pharmaceutical formula I.

The compound prepared from

B₂

B₂

wherein A₁
—CO—CR₂
thereof, or

chain (where group V an to a —CO R₂ is hydr from 1 to groups, one are converted chain or p

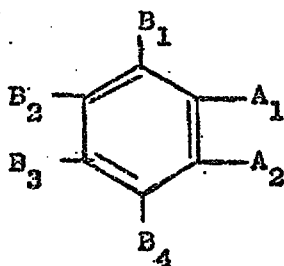
—C

chain or pair of the groups A₁ and values end form —C the other

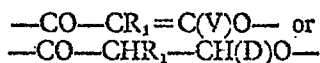
for use in the prophylactic treatment of allergic airway diseases. In such treatments the compound or composition of the invention is administered by the chosen method to the site of the antibody-antigen reaction in the therapeutically effective amount. The treatment may be one which requires repeated dosages of the medicament at regular intervals. The amount and frequency of medicament administered will depend upon many factors and no concise dosage rate or regimen can be generally stated. However, as a guide we have found that, where the compounds are administered by inhalation to a patient suffering from acute allergic asthma, therapeutically useful results are achieved when the compounds are administered at a dosage rate of from 0.1 to 50 mgs. Where the compounds are administered by the oral route, larger dosages may be given.

The invention thus also provides a method for inhibiting the effects of an antibody-antigen reaction which comprises the prior application to the known or expected area of the antibody-antigen reaction mechanism of a therapeutically effective amount of a compound or a pharmaceutically acceptable derivative of formula I.

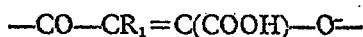
The compounds of the invention may be prepared from compounds of the formula



wherein A_1 and A_2 together form the chain $-\text{CO}-\text{CR}_1=\text{C}(\text{COOH})\text{O}-$ or a derivative thereof, or form a chain such as a



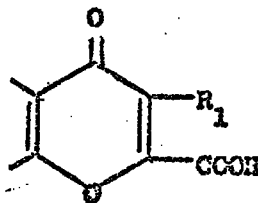
chain (wherein D is a COOR_2 group or a group V and V is a group which is convertible to a $-\text{COOH}$ group convertible thereto and R_2 is hydrogen or an alkyl group containing from 1 to 10 carbon atoms), or a pair of groups, one of which may be hydrogen, which are convertible either directly or via another chain or pair of groups to the desired



chain or a derivative thereof; an adjacent pair of the groups B_1 , B_2 , B_3 and B_4 are the groups A_1 and A_2 , the two pairs of groups A_1 and A_2 may have the same or different values except that both pairs of groups cannot form $-\text{CO}-\text{CR}_1=\text{C}(\text{COOH})\text{O}-$ chains; and the other two of the groups B_1 , B_2 , B_3 and

B_4 are hydrogen or substituents other than hydrogen.

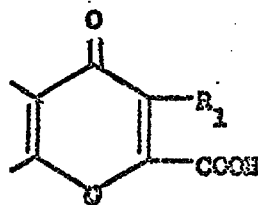
It will be appreciated that the compounds of the invention possess two



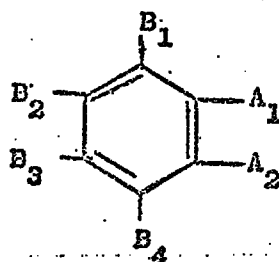
rings and that these may be the same. Each of these rings may be introduced in separate stages by different or similar methods or may be introduced together in a single reaction stage. It is also possible to introduce in separate stages precursors of one of the desired rings, for example a chain



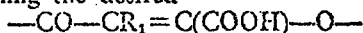
by one method, to introduce the same or another precursor for the other ring, e.g. a chain $-\text{CO}-\text{CH}(\text{CH}_3)-\text{CH}(\text{COOH})-\text{O}-$ by a different method, and then to convert the two precursors into the desired rings in a final common reaction stage, e.g. by dehydrogenation. For convenience, the preparation of the compounds of the invention will be described in terms of the conversion of only one of the two pairs of groups A_1 and A_2 to the desired



ring. The other ring may be present initially, be formed during the formation of the first ring, or be introduced later by the same or a different process. Where both rings are to be introduced one after another it may be necessary to shield or block the sites at which the second ring is to be introduced. Such shielding or blocking may be achieved by conventional methods as indicated above. The general formula for the starting material.

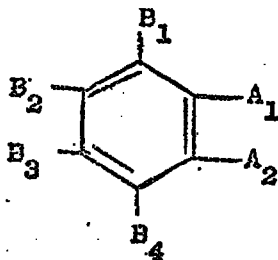


is therefore to be construed as covering compounds which may be converted to those containing the desired

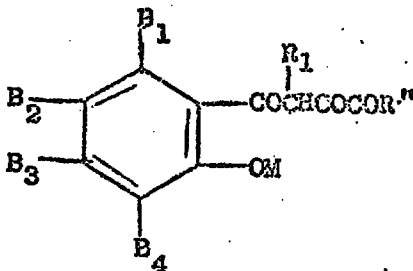


- 5 chain by the same or different methods. It is however preferred that the two pairs of groups A_1 and A_2 have the same values and that each pair is converted to the desired chain by the same method in the same reaction process.

- 10 The conversion of the A_1 and A_2 group in the compound

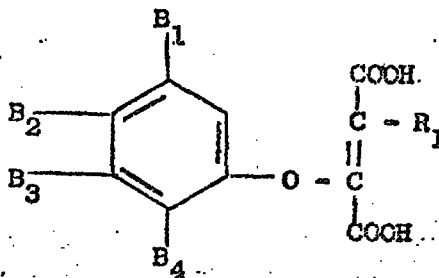


II

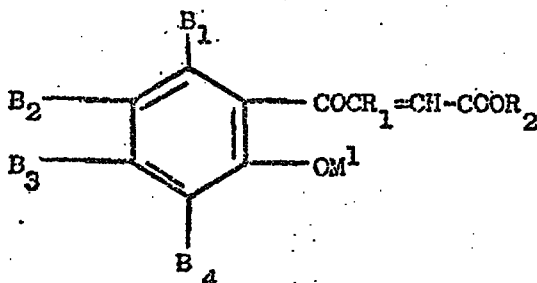


- 20 wherein R'' is an OH group or a group convertible thereto and M is hydrogen, an alkali-metal cation or an alkyl group;

III



and

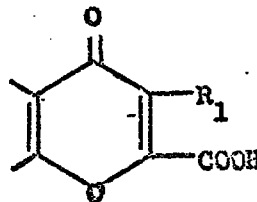


IV

- 25 wherein M^1 is hydrogen or an alkali-metal cation, with oxidation or dehydrogenation of the product if required. The desired ring may also be formed by modification of an already formed chromone or chromanone ring [i.e.

may be achieved by a variety of methods. For example the desired

15



ring may be formed by cyclising compounds of the general formulae:

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Cycl
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As i
10 compo
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Suitable
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45 R1 is a
the nitr
F where
alkyl, a
50 or haloa
gen cari
stituent
a sulph
group.
55 present
formulac
R2 is a
propyl,
alkaryl
60 alkenyl
R3O-C

compounds wherein A_1 and A_2 together form the chain $-\text{CO}-\text{CR}_1=\text{C}(\text{V})-\text{O}-$ or $-\text{CO}-\text{CHR}_1-\text{CH}(\text{D})-\text{O}-$, for example by oxidation of substituents in the 2- position of the ring or by dehydrogenation.

The compounds of formula II may be readily cyclised, for example by heating under non-basic conditions. It is preferred to carry out the cyclisation reaction in a solvent such as ethanol or dioxan. It is also preferred to carry out cyclisation in the presence of a cyclisation catalyst, ideally an acid cyclisation catalyst such as a polyphosphoric acid, sulphuric acid, hydrochloric acid, acetic acid or mixtures thereof. When a compound is used wherein M is an alkyl group, simultaneous cyclisation and dealkylation may be achieved

by the use of hydroiodic or hydrobromic acid as the cyclisation catalyst.

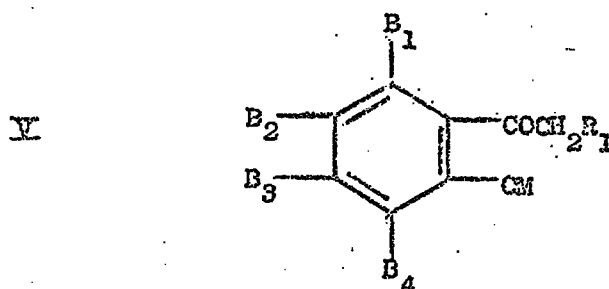
Cyclisation may be carried out at from ambient temperature to about 100° C, for example by heating the reaction mixture on a steam bath and, where the nature of the reaction medium permits it, under atmospheric reflux.

As indicated earlier, the group R'' in the compound of formula II is an OH group, or a group which is convertible to an OH group. Such conversion may have already occurred in the cyclisation of the compound or may

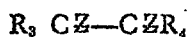
have taken place prior to cyclisation. However, where this is not the case, such conversion may be readily achieved using conventional methods.

Alternatively, the R'' group may be converted into a more desirable derivative, for example an alkoxy group, and such further conversion is also within the scope of this invention.

The compounds of formula II may themselves be prepared by a number of methods. For example, an acylbenzene of the formula:



(Wherein R₁ has the values given above and M is hydrogen, an alkali-metal cation or an alkyl group, such as a lower alkyl group, e.g. a methyl, ethyl, propyl or pentyl group), may be condensed with a compound of the formula



wherein R₃ and R₄ may be the same or different, one being a group reactive with an hydrogen in the $-\text{CO}-\text{CH}_2\text{R}_1$ group of the acylbenzene, the other being an R'' group, and each Z is a carbonyl oxygen or one is an (Hal)₂ group wherein Hal is halogen. Suitable groups which react with a $-\text{CO}-\text{CH}_2\text{R}_1$ group include alkoxy, amino, alkyl amino, substituted amino or substituted alkyl amino groups. It will be appreciated that these groups include groups which are also convertible to OH groups. Where R₃ and/or R₄ is an amino or substituted amino group, the nitrogen atom may carry groups E and F wherein E and/or F is hydrogen, a lower alkyl, a substituted or unsubstituted aryl, alkaryl or haloaryl group. In the case where the nitrogen carries only one group E or F, the substituent may be linked to the nitrogen through a sulphur atom or an $-\text{SO}-$ or $-\text{SO}_2-$ group. Examples of suitable compounds for present use include those of the general formulae $\text{R}_5\text{OOC}-\text{COOR}_5$ (wherein each R₅ is an alkyl group, such as methyl, ethyl, propyl, butyl group, or pentyl group; an alkaryl group such as a benzyl group; or an alkenyl group such as an allyl group), and $\text{R}_5\text{O}-\text{C}(\text{Hal})_2-\text{COOR}_5$ (wherein Hal is

halogen, preferably chlorine or bromine). Preferred compounds of formula



for present include diethyloxalate, ethyl ethoxydichloroacetate, ethyl oxamate, ethyl oxalylanilide and ethyl oxalyl-*p*-toluene sulphonamide.

The condensation of the acylbenzene V with the compound of formula



may be carried out merely by mixing the reactants together and heating, if desired, to a temperature of from 25 to 150° C, preferably about 70 to 80° C. In the case of the oxalate esters, the reaction is desirably carried out in the presence of a condensation agent. Suitable agents include, for example, metal alkoxides, such as sodium ethoxide, sodium hydride, sodamide or metallic sodium. The condensation agent may be formed *in situ*, for example by the use of ethanol as the reaction medium and the addition of metallic sodium. In some cases the alkali metal salt of the compound of formula V (that is when M is alkali metal) may act as part of the condensation agent required. Where a substituted dihalo-acetate is used, it is preferred to carry out the reaction in the presence of a finely divided metal catalyst, such as finely divided platinum group metal.

If desired, the reaction may be carried out in an inert solvent or diluent medium, such as diethyl ether, dioxan, ethanol, benzene,

toluene, tetrahydrofuran, or mixtures thereof.

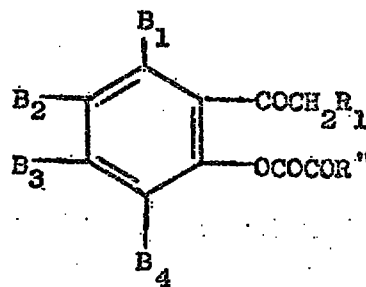
The reactants are conveniently employed in substantially stoichiometric proportions. If desired, an excess of either may be employed, for example in from 100 to 300 molar % excess. When used, the condensation agent is desirably used in from 200 to 750 molar percent based on the amount of the acylbenzene of formula V used, preferably from 200 to 500 molar percent.

It will be appreciated that the condensation reaction is desirably carried out under substantially anhydrous conditions, that is in the absence of initial or added water.

The reaction mixture of the above reaction will usually contain the compound of formula II, or a precursor thereof, though in some cases cyclisation of the product to the compound of formula I, or a salt or derivative thereof, may take place spontaneously. Cyclisation of the compound of formula II may also be achieved *in situ* by acidifying the reaction mixture. It is usually preferred to recover the compound of formula II from the reaction mixture and to cyclise it in the presence of a cyclisation agent optionally in the presence of water as when a concentrated aqueous acid is used as the cyclisation catalyst as described above. The compound may be recovered from the crude reaction mixture wherein it was prepared by conventional techniques. Thus, for example, the reaction mixture may be treated with ether to precipitate the intermediate, if this precipitation had not already been achieved by the use of ether as the reaction medium. The precipitate, after any further washing with ether, may be dissolved in water and acidified to yield the compound of formula II which usually separates out and may be recovered by, for example, filtration, centrifuging, or by extraction with a suitable solvent such as as chloroform or ethyl acetate and evaporation of the solvent. It may be preferred to omit the ether precipitation step and merely acidify the reaction mixture and recover the product by solvent extraction.

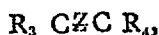
The compound of formula II may also be prepared by the reaction of an acylbenzene of formula V wherein M is hydrogen or an alkali-metal cation with a dicarbonyl compound of formula R_3COCOR_4 , wherein R_3 and R_4 have the values given above, except that one or both of R_3 and R_4 are halogen. Suitable dicarbonyl compounds for use in this case include oxalyl chloride and compounds wherein R_3 is chlorine or bromine and R_4 is an OH, alkoxy (e.g. methoxy or ethoxy), NH_2 , phenylamino or *p*-toluene sulphonyl-amino group. The reaction using these halo compounds may be carried out in a manner similar to that described in relation to the use of the other compounds

except that an acid-binding agent is used in place of the condensation agent and that the use of an anhydrous organic solvent is desirable. Suitable acid-binding agents include alkalis, such as sodium or potassium carbonate, sodium, sodamide and alkali metal alkoxides; and organic amines such as pyridine or triethylamine. The acid-binding agent is present in at least the theoretically stoichiometric amount to bind all the halogen in the dicarbonyl compound. It may be desired to use an excess of acid-binding agent, and, if desired, the acid-binding agent may be added to the reaction mixture in a series of additions over a period of time. In some cases the acid-binding agent may be used as the reaction medium. The reaction mixture from this process will usually contain the intermediate product of the formula



or a precursor or derivative thereof, though in some cases rearrangement of this intermediate to yield the compound of formula II may have occurred spontaneously. Rearrangement of the intermediate may also be achieved *in situ* by the addition of an alkali and heating. However it is usually preferred to recover the intermediate product from the reaction mixture and rearrange it, after any purification that may be desired, in a separate reaction step. The recovery and purification of the intermediate product may be achieved by conventional methods.

Rearrangement of the intermediate product may be achieved by heating the crude, or purified, recovered material under non-acidic conditions and preferably in an inert solvent or diluent medium such as benzene, dioxan or anisole. The non-acidic conditions may be achieved by the presence of an organic base, such as pyridine and potassium hydroxide or monoethylamine, or of a mineral alkali such as sodium carbonate or potassium carbonate, sodium hydride, sodium alkoxides e.g. sodium methoxide, or metallic sodium. If desired, the rearrangement may be carried out under the influence of heat, for example at from ambient temperature to 100° C, e.g. by heating on a steam bath and, where the reaction mixture permits it, under atmospheric reflux. Preferably the rearrangement is carried out under anhydrous conditions i.e. in the absence of appreciable amounts of initial or added water. The amount of alkali present may be from 100 to 1000 molar %, based on



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the amount of the intermediate product being rearranged and may, if desired, be added in a single addition or in a series of additions over a period of time.

5 The compound of formula II or a derivative or precursor thereof, may be recovered from the reaction mixture in which it was formed by conventional methods with, if necessary, conversion of the R'' group into a more desired substituent.

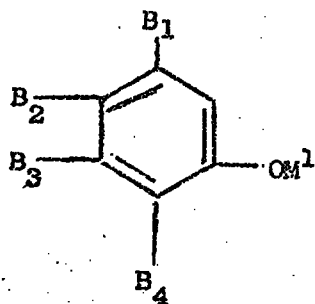
10 In a further process for preparing the compounds of formula II, an appropriately substituted salicylic acid or ester thereof is reacted with a compound of the formula $\text{CH}_3\text{CO COOR}_1$ wherein R_1 has the values given above. The reaction is desirably carried out in an inert medium such as ethanol, anisole, benzene or dioxan and it is preferred to employ a condensation agent such as an alkali metal alkoxide (e.g. sodium ethoxide), sodamide, sodium hydride or metallic sodium.

20 The compounds of formula III may be cyclised by treating the compound with a cyclisation agent at ambient temperature or above. Suitable cyclising agents include dehydrating agents such as phosphorus pentoxide, polyphosphoric acid, sulphuric acid, chlorosulphonic acid and other Lewis acids. In certain cases it is also possible to use glacial acetic acid containing a small amount of hydrochloric or hydrobromic acid. It will be appreciated that, since cyclisation is achieved in these cases by the use of dehydrating agents, the presence of added or initial water in the reaction mixture is undesirable.

30 It is usually preferred to subject the compounds of formula III to an initial drying step and to carry out the cyclisation reaction under substantially anhydrous conditions.

40 Alternatively, cyclisation may be achieved by converting the free carboxyl groups of the compound of formula III into acyl chloride groups, for example, by treatment with PCl_5 or PCl_3 , and subjecting the resultant acyl chloride to an internal Friedel Crafts reaction.

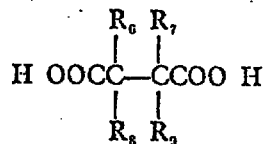
45 The compounds of formula III when R_1 is hydrogen may be obtained by the reaction of the phenol of formula:



50 (wherein M^1 is hydrogen or an alkali metal cation) with an acetylene dicarboxylic acid or ester thereof under alkaline conditions to produce a product which, upon hydrolysis, yields

the compound of formula III. The acetylene dicarboxylic acid esters may be derived from alcohols having from 1 to 10 carbon atoms. However, since the ester moiety is to be eliminated, it is preferred to use simple esters derived, for example, from methyl, ethyl, propyl, or butyl alcohols. It is preferred that both carboxylic acid groups on the acetylene dicarboxylic acid be esterified. In this process the ester and phenol are reacted, preferably in approximately stoichiometric amounts, under alkaline conditions. These may be achieved by the presence of an organic base such as benzyl trimethyl ammonium hydroxide, or of an alkali metal hydroxide. However, it is convenient to have the alkali present in the form of an alkali metal salt, especially the sodium salt, of the reactant phenol, such a salt being considered as free phenol when assessing the amount of phenol present in the reaction mixture. Where this is done, the alkali metal phenate may conveniently be made *in situ* in the reaction mixture by the addition of metallic sodium. The alkali is believed to act catalytically and it is possible to use less than 100 molar percent thereof based on the phenol present. We prefer to use substantially 10 molar percent. It will be appreciated that the reaction, especially where the alkali metal phenate is formed *in situ*, is desirably carried out under substantially anhydrous conditions. It is also preferred to carry out the reaction in a solvent or diluent medium. Suitable media included, for example, excess of the reactant phenol, diphenyl ether, dioxan and anisole. These media have the advantage that the reaction may be carried out at elevated temperatures at atmospheric pressure. It is generally preferred to carry out the reaction at temperatures of from 50° to 100° C.

In place of the acetylene dicarboxylic acid ester used in the above process for the preparation of the compound of formula III, an ester of a mono-halofumaric acid, or a precursor thereof may be used, i.e. esters of acids of the general formula



wherein R_6 is halogen and R_7 is an R_1 group when R_6 and R_7 together form a carbon to carbon bond; or, any two of R_6 , R_7 , R_8 and R_9 are halogen, one of the other two is hydrogen and the second is an R_1 group.

In this case the reaction is not an addition reaction but a condensation reaction which involves at some stage the elimination of the elements of a halogen acid from between the phenol and the halofumaric ester. This acid must be eliminated from the system and the

reaction is therefore carried out in the presence of at least sufficient of an acid-binding agent to eliminate the elements of the halogen acid which will be formed during the overall process. The elements of the halogen acid are not necessarily eliminated in one step, but may be eliminated firstly as a proton and then as a halogen anion. The term acid-binding agent is therefore used in this context to denote both conventional acid-binding agents, such as pyridine and triethylamine, and materials which eliminate for example, first the hydrogen from the phenol (to form a phenate salt) and then are displaced from the phenate salt to form a salt with the halogen of the halofumaric acid ester. Apart from the use of a different acid ester reactant and the presence of the acid-binding agent, the process may be carried out in similar manner to that when an acetylene dicarboxylic acid ester is used. Since the acid-binding agent is usually also a strong alkali, there is generally no need to provide a separate strong alkali in the reaction mixture. As will be appreciated from the general formula for the acids which may be used to react with the phenol, the use of the monohalofumaric acid or precursors thereof permits the introduction of an R_1 group into the molecule.

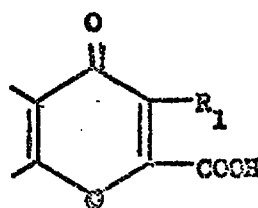
As indicated above, it is also possible to use compounds which yield the desired halofumaric acid esters under the conditions of the reaction with the phenol. Such other compounds or precursors, include halomaleic acid esters and dihalosuccinic acid esters. When precursors are used, it may be necessary to provide extra alkali to ensure conversion of the precursor to the desired halofumaric acid ester. Such alkali may be merely an excess of the acid-binding agent.

The products obtained from the reactions outlined immediately above usually contain the compounds of formula III in the form of their esters. The compounds of formula III may be recovered from these products by acidification of the reaction mixture; subsequent hydrolysis of the esters by boiling with alkali and acidification to liberate the free acid, removal of organic solvent or diluent medium (if any) and extraction of the aqueous solution with, for example, ether which may thereafter be evaporated. The solvent extraction of the acid may be carried out as indicated, or may occur after hydrolysis of the ester of compound III if desired. The product may, if necessary, be subjected to further purification, for example by extracting the ethereal solution with sodium bicarbonate and then precipitating the acid of formula III by addition of dilute sulphuric acid.

The compounds of formula IV may be cyclised by treatment with an alkali or organic base in a suitable inert solvent to give the 2-carboxychromanone compound. This may subsequently be converted into the 2-carboxy-

chromone compound by heating with selenium dioxide or other suitable dehydrogenation agents such as palladium black in an inert solvent as is detailed below. Simultaneous oxidation and cyclisation to the desired 2-carboxychromone compound may be brought about by the introduction of a suitable oxidant into the cyclisation stage (e.g. selenium dioxide in an inert solvent using benzyltrimethylammonium hydroxide as the cyclising base).

Where non-oxidising conditions are used for the cyclisation step, the product will be the analogous chromanone compound from which the desired



ring compound may be prepared as detailed later.

The compounds of formula IV may be prepared by reacting an acylbenzene of formula V wherein M is hydrogen or an alkali-metal cation with glyoxalic acid or an ester thereof in the presence of a base (e.g. aqueous sodium hydroxide) or a mineral acid. A water miscible solvent, e.g. alcohol, may be added to facilitate the reaction.

Alternatively a phenol of formula VI wherein M' is hydrogen is heated at a temperature of, for example, 25 to 150° C with maleic anhydride in a solvent or diluent medium, such as nitrobenzene or carbon disulphide, in the presence of a Lewis acid such as an excess of aluminium trichloride. The complex which is produced by this process may then be decomposed with a dilute mineral acid, such as hydrochloric acid, and the solvent removed, for example by distillation. The residue, which contains the compound of formula IV wherein R_2 is H, may be recovered using conventional techniques and then purified by, for example, recrystallisation. However, as indicated below the reaction may proceed to give a 2-carboxychromanone directly without isolation of an intermediate.

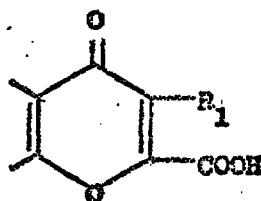
In the processes outlined above, we believe that the compounds II to IV are all necessary intermediates in the conversion of the various starting materials to the compounds of formula I. However, in many cases the intermediates are formed under those conditions required to achieve cyclisation and therefore exist only transitorily. Whilst, for clarity, these processes have been described as if the compounds II to IV were necessarily isolated prior to cyclisation, the invention embraces those processes wherein the intermediate undergoes cyclisation without separation or

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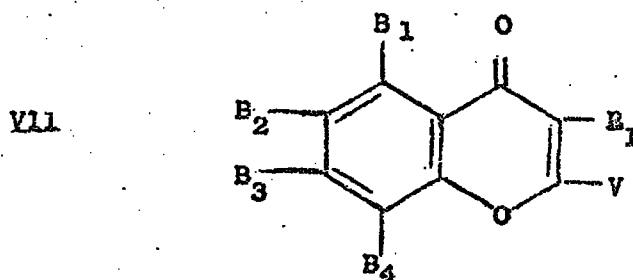
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isolation from the reaction mixture in which it has been prepared.
As indicated above, the desired



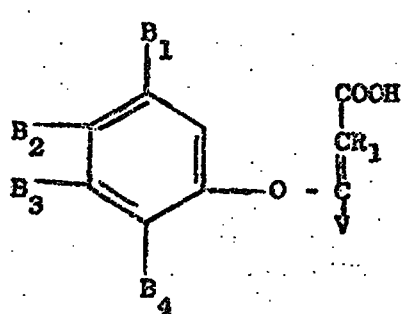
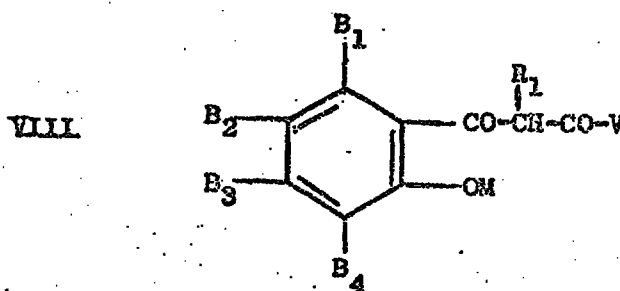
ring may also be formed from an already present chromone ring, i.e. from a compound of formula



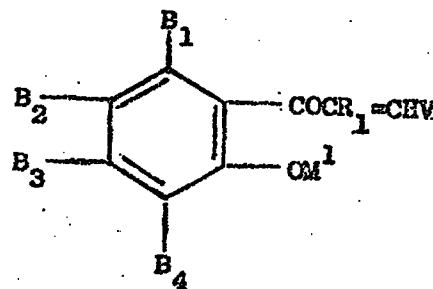
wherein V is a group which is convertible to a —COOR_2 group. Examples of suitable V groups include nitrile and ester groups which may be hydrolysed to a carboxylic acid group; alkyl or substituted alkyl groups such as methyl, hydroxymethyl, halomethyl (e.g. chloromethyl, bromomethyl, dichloromethyl, trichloromethyl), acyl groups such as formyl or acetyl groups, and alkenyl and aryl alkenyl groups such as vinyl, ω -trichloromethylvinyl and styryl groups, all of which are groups

oxidisable or hydrolysable to a carboxylic acid group. The conversion of the V group to a COOH group or derivative thereof may be achieved using any of the known methods.

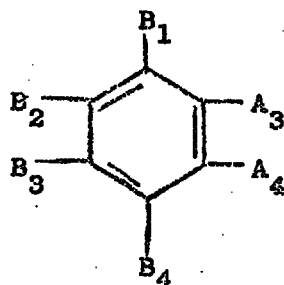
The compounds of formula VII may be prepared by a variety of methods, many of which are closely analogous to the processes described above for the preparation and cyclisation of the compounds of formulae II to IV except that in place of the starting materials II, III and IV, compounds of the formulae



X



are used and that the final product requires conversion of the V group to the —COOH group or derivative thereof. Such analogous processes may together be broadly described as a process for preparing a compound of formula I by conversion of a compound of the formula



(wherein A_3 and A_4 are the pairs of groups $\text{—CO—CHR}_1\text{COD}$ and OM ; H and

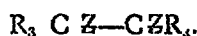
$\text{—O—C(D)=CR}_1\text{COOH}$; or

$\text{—CO—CR}_1\text{=CHD}$

and OM^1 respectively wherein D is a COOR_2 group or a group V convertible thereto, M is H, an alkali-metal cation or an alkyl group, M^1 is H or an alkali metal cation and R_1 and R_2 have the values given above; one adjacent pair of the substituents B_1 , B_2 , B_3 and B_4 is the pair of groups A_3 and A_4 which may have the values given above for A_1 and A_2 or may be the pair of groups A_3 and A_4 , and the other two of the groups B_1 , B_2 , B_3 or B_4 are hydrogen or substituents other than hydrogen) during which cyclisation of the groups A_3 and A_4 and, if necessary, A_5 and A_6 takes place.

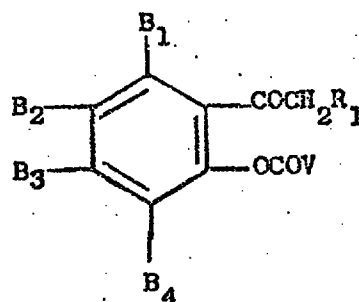
Thus the compounds of formula VIII may be prepared by cyclising a compound of formula VIII under the conditions described above for the cyclisation of the compound of formula II. In some instances cyclisation may occur spontaneously.

The compounds of formula VIII may themselves be prepared by condensing an acylbenzene of formula V with a compound of formula VCOR_3 , wherein V has the values given above and R_3 is a group reactive with a hydrogen in the $\text{—COCH}_2\text{R}_1$ group of the acylbenzene. Suitable compounds VCOR_3 include esters of substituted or unsubstituted acetic, acrylic and cinnamic acids, and amides or substituted amides thereof. The condensation may be achieved by the method outlined earlier for the production of the compounds of formula II from the acylbenzene V and the compounds



The compounds VIII may also be prepared from the acylbenzene V and the compounds VCOR_3 wherein R_3 is halogen via, if necessary,

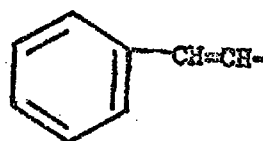
the rearrangement of a compound of the formula:



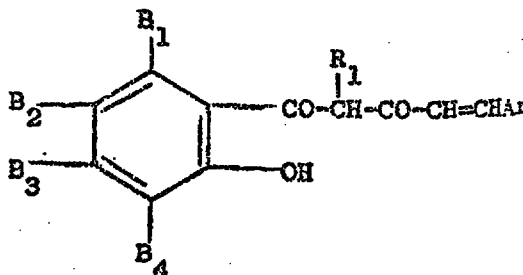
using conditions similar to those set out above for the preparation of the compounds of formula III by the analogous route.

Particular examples of the preparation of compounds VIII include the preparation of those compounds wherein V is a methyl or vinyl group by reaction of an alkyl acetate or acrylate, i.e. the compounds VCOR_3 wherein V is a methyl or vinyl group and R_3 is an alkoxy group, with an acylbenzene V under the condensation conditions outlined above for the preparation of compound II.

The 2-styryl compound, that is the compound of formula VIII wherein V is

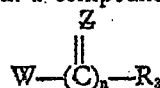


may be prepared from the acylbenzene V by reaction with sodium cinnamate and cinnamic anhydride or by reaction with a cinnamoyl halide, e.g. cinnamoyl chloride, in the presence of an acid-binding agent to yield the cinnamate ester of the acylbenzene, followed by rearrangement with a base, e.g. potassium carbonate, in the presence of an inert solvent such as toluene or benzene, to give a 1,3-diketone of the formula:



wherein Ar denotes a benzene ring.

From these examples of the preparation of the compounds of formula VIII it will be appreciated that certain of the processes for preparing the compounds of formulae II and VIII may together be broadly described as processes wherein an acylbenzene of formula V is reacted with a compound



wherein R_3 is a hydrogen in the benzene, or a $(\text{Hal})_2$ group or 2 and a COOR_2 group and when a OH group is

The compound VI with a silicic acid, or used to prepare above. The

or esters of general form and R_2 has preferred values as a methyl to use precursors or ethylenic and

The compound cyclised in with the compound preparation III and IX as a process reacted with

wherein R_2 values given that when a carbon to a carbon to

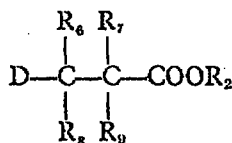
The compound can be prepared to that use of formula of cinnamaldehyde conditions compound of However, in benzenes of group and to obtain the

As with certain compounds of be broadly action of a compound D has the In addition formula V

wherein R_3 is a group reactive with an hydrogen in the $-\text{COCH}_2R_3$ group of the acylbenzene, each $\frac{1}{2}$ is 0 or one may be a (Hal) $_2$ group, Hal represents halogen, n is 1 or 2 and when n is 1, W is a D group i.e. a COOR_2 group or a group V convertible thereto and when n is 2, W is an R'' group, i.e. an OH group or a group convertible thereto.

The compounds of formula IX may be prepared by the reaction of a phenol of formula VI with a substituted acetylene monocarboxylic acid, or ester in manner similar to that used to prepare the compounds of formula III above. The acetylene monocarboxylic acids, or esters thereof, for present use have the general formula $\text{VC}\equiv\text{C}-\text{COOR}_2$ wherein V and R_2 have the values given above. It is preferred that R_2 be a lower alkyl group such as a methyl or ethyl group. It is also possible to use precursors of acetylene monocarboxylic acids or esters, for example the mono-halo-ethylenic and dihalo-ethane analogues thereof.

The compounds of formula IX may be cyclised in a manner similar to that employed with the compounds of formula III. As with the compounds of formula II and VIII, the preparation of the compounds of formula III and IX may together be broadly described as a process wherein a phenol of formula VI is reacted with a compound of the formula



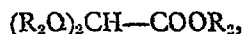
wherein R_2 , R_6 , R_7 , R_8 , R_9 and D have the values given above and also the further value that when R_6 and R_7 together form a carbon to carbon bond, R_8 and R_9 may also form a carbon to carbon bond.

The compounds of formula X may also be prepared and cyclised in a manner similar to that used to prepare and cyclise the compound of formula IV. Thus, an acylbenzene of formula V may be reacted with an aldehyde of the formula OHCV , for example cinnamaldehyde, under substantially the same conditions as are used to prepare the compound of formula IV from glyoxalic acid. However, it may be preferred to employ acylbenzenes of formula V wherein M is an alkyl group and to dealkylate the reaction product to obtain the compound of formula X.

As with the other intermediate compounds, certain routes for the preparation of the compounds of formula IV and X may together be broadly described as comprising the reaction of an acylbenzene of formula V with a compound of the formula OHCD wherein D has the values given above.

In addition to producing the compounds of formula VII by the methods outlined above,

a number of other methods may be readily devised which do not necessarily pass through the intermediate compounds VIII, IX or X. Thus, the 2-formyl compound may be prepared by the reaction of an acylbenzene of formula V with a substituted acetic acid or ester thereof of the formula



for example ethyl diethoxy acetate. In this case an acetal compound is produced as an intermediate, which may be hydrolysed with, for example, a dilute mineral acid to yield the desired $-\text{CHO}$ group. Other routes which may be specified include: the condensation of a diketene with an appropriate enamine; and the condensation of an alkyl alkoxalylacetate with an appropriate phenol or resorcinol in the presence of phosphorus pentoxide.

In addition to the direct conversion of a compound of formula VII into the desired compound of formula I, the V group in compounds of formula VII may be converted in known manner from one form of substituent into another more preferred substituent, e.g. into a group V' which may then be converted to a carboxylic acid group or derivative thereof.

Thus, the compound of formula VII wherein V is a methyl group also serves as an intermediate in the preparation of a number of other oxidisable derivatives. For example, the methyl group may be converted into the corresponding 2-halomethyl compound, e.g. by reaction with hydrogen chloride and manganese dioxide in boiling acetic acid to produce the 2-chloromethyl compound; or by reaction with bromine in acetic acid to yield the 2-bromomethyl compound. The 2-halomethyl compound may be oxidised to the corresponding 2-carboxylic acid using, for example, chromium trioxide as oxidising agent in the presence of acetic acid.

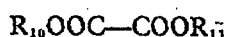
The 2-methyl compound may also be reacted with p-nitrosodimethylaniline and the reaction product hydrolysed with dilute mineral acid to give the corresponding 2-formyl compound which may be oxidised to the corresponding 2-carboxylic acid using, for example, chromium trioxide as reagent.

Condensation of the 2-methyl compound with a benzaldehyde in the presence of a condensation catalyst gives the 2-styryl compound which may be oxidised to the corresponding 2-carboxylic acid using, for example, potassium permanganate. The 2-formyl compound may also serve as a starting point for the preparation of the 2-cyano compound. Thus, the 2-formyl compound may be reacted with hydroxylamine to yield the 2-oximino compound which may, after dehydration to give the 2-cyano compound, be hydrolysed to the 2-carboxylic acid or amide thereof, under acid conditions.

As stated earlier the compounds of formula I may also be prepared by conversion of chain $-\text{CO}-\text{CHR}_1-\text{CH}(\text{D})-\text{O}-$ to the desired $-\text{CO}-\text{CR}_1=\text{C}(\text{COOH})\text{O}-$ chain. This

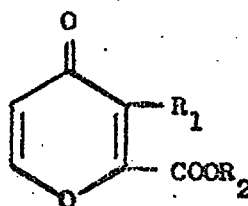
conversion may go via a compound of formula VII when the group D is a group V, or may proceed directly to the compound of formula I or a derivative thereof. Thus, the compounds of formula I may also be prepared from corresponding chromanone compounds by dehydrogenation followed, or preceded, by oxidation or hydrolysis of any substituent in the 2-position if this is necessary. The dehydrogenation may be effected by, for example, the use of selenium dioxide, palladium black or chloranil. Alternatively, dehydrogenation may be carried out by bromination followed by dehydrobromination. Thus, the chromanone may be brominated using N-bromosuccinimide in an inert solvent or by treatment with pyridinium perbromide in an inert solvent such as chloroform in the presence of a free radical catalyst such as benzoyl peroxide, to yield the 3-bromo derivative which may be subsequently dehydrobrominated. The chromanones themselves may be obtained by the action of an β -substituted β -chloropropionic acid or derivative thereof on resorcinol in the presence of a basic reagent followed by conversion of the acid function to the acid chloride and treatment with aluminium chloride in the presence of a suitable solvent (e.g. nitrobenzene); or by the action of a phenol on a β -substituted acrylonitrile, e.g. propenyl nitrile, with subsequent hydrolysis and cyclisation of the product. As indicated above, cyclisation of the intermediates IV and X may lead to the production of a corresponding chromanone compound, which may then be converted as outlined above to the desired chromone compound.

In addition to the above outlined methods for preparing the compounds of formula I via the intermediates II to IV and VII to X other methods may be devised which do not necessarily produce any of these intermediates. Thus, an oxalate ester of the type

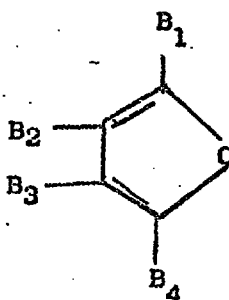


wherein R_{10} is an appropriately substituted benzene ring and R_{11} is an alkyl or an aryl group, may be cyclised by condensing it with an acetyl halide, acetic anhydride or acetic acid in the presence of a Lewis acid. The oxalate ester may itself be obtained by the esterification of a phenol of formula VI with the appropriate oxalyl halide. Alternatively the compounds of formula I may be obtained by reacting a phenol of formula VI with ethyl ethoxalyl acetate and subsequently cyclising the product, if necessary, e.g. by heating in a solvent medium. In a further process a

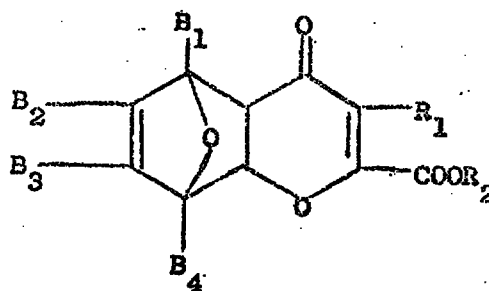
2-carboxy-pyrone of the formula



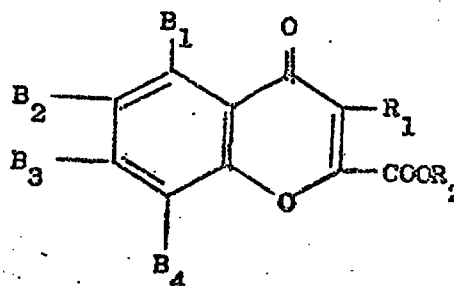
is reacted with a furan of the formula



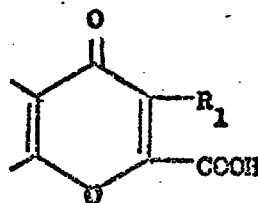
to yield the intermediate



which may be converted, for example by dehydration, to the compound.



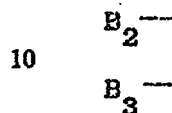
As stated earlier, the desired



rings may be introduced in separate steps or in the same step. Where they are both to be introduced together, the two pairs of groups A_1 and A_2 will have the same values, appro-

priate to the rings. Thus benzene for group in A_1 group and A_2 From the of the star

into the d



compound routes ma the conve A_2 together $-\text{D}$ or $-\text{OC}$ and H or a group $-\text{CR}_1=$ have the and A_2 to

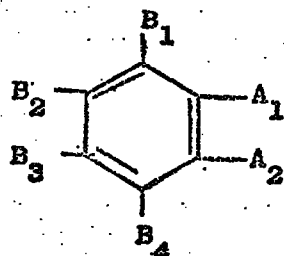
$\text{B}_1, \text{B}_2, \text{B}_3$ above.

The p the free a tives ther present i of the al purificati order to convert The me one deri purify al ally used

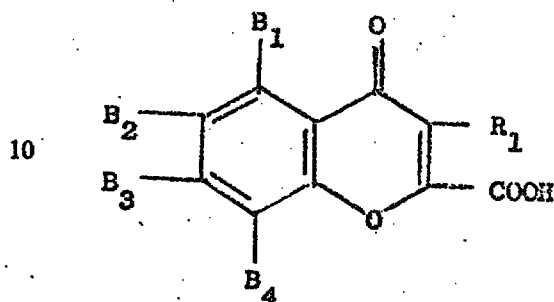
Furthe this in P, Q, R tion of

appropriate to the method used to introduce the rings. Thus, where condensation with an acylbenzene forms one of the steps required, one group in each pair will be a $-\text{COOCH}_2\text{R}_1$ group and the other will be an OM group.

From the above examples of the conversion of the starting materials



into the desired



compounds, it will be seen that many of these routes may be together broadly described as the conversion of compounds wherein A₁ and A₂ together form the groups $-\text{OM}$ and $-\text{H}$, $-\text{D}$ or $-\text{COJ}$; $-\text{H}$ and

$-\text{OCD}=\text{CR}_1\text{COOR}_2$; $-\text{OCOCOR}''$

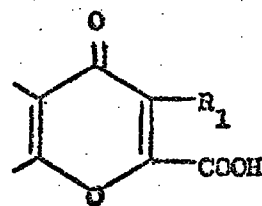
and H or COCH_2R_1 respectively wherein J is a group $-\text{CH}_2\text{R}_1$, $-\text{OR}_2$, $-\text{CHR}_1\text{COD}$ or $-\text{CR}_1=\text{CHD}$ and R'', R₁, R₂, D and M have the values given above; or wherein A₁ and A₂ together form the chains

$-\text{CO}-\text{CR}_1=\text{C(V)}\text{O}-$ or
 $-\text{CO}-\text{CHR}_1-\text{CH(D)}\text{O}-$;

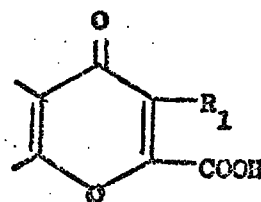
B₁, B₂, B₃ and B₄ having the values set out above.

The processes outlined above may produce the free acids of formula I or may yield derivatives thereof. It is also within the scope of the present invention to treat the product of any of the above processes, after any isolation and purification steps that may be desired, in order to liberate the free acid therefrom or to convert one form of derivative into another. The methods used to free the acid, convert one derivative into another and to isolate and purify any product may be those conventionally used.

Furthermore, it is also within the scope of this invention to introduce the substituents P, Q, R, T, P', Q', R', and T' after formation of one or both the



rings has taken place. Such introduction may be achieved by any of the known methods. As indicated earlier, it is also within the scope of this invention to block or shield sites or groups which might be detrimentally affected during the introduction of the



ring or rings. Such shielding or blocking groups include, for example, amino, substituted amino, e.g. acylated amino, carboxyl, SO_3H , tert. butyl, cyano or nitro groups. These groups may be removed after introduction of the ring or rings to leave unsubstituted positions which may, if desired, thereafter be substituted.

The invention will be illustrated by the following Examples in which all parts and percentages are by weight unless otherwise stated:

EXAMPLE 1

4, 10 - Dioxo - 5 - methoxy - 2,8 - dicarboxy-4H,10H - benzo (1,2 - b:3,4 - b') dipyran

(a) 4,10 - Dioxo - 5 - methoxy - 2,8 - dicarboxy - 4H,10H - benzo (1,2 - b:3,4 - b') dipyran, monohydrate

To a stirred solution of sodium ethoxide in ethanol, prepared from 3.04 parts of sodium and 40 parts of ethanol, was added a slurry of 3.7 parts of 2,4 - diacetyl - 5 - methoxyresorcinol and 12.05 parts of diethyl oxalate in 20 parts of ethanol and 50 parts of diethyl ether. The mixture was stirred and heated under reflux for 4 hours.

Diethyl ether and water were added, and the aqueous layer was separated and acidified with dilute hydrochloric acid. The aqueous solution was extracted with ethyl acetate dried over sodium sulphate, filtered and evaporated to dryness to leave a brown oil.

This oil was dissolved in boiling ethanol and 0.5 parts of concentrated hydrochloric acid were added. The solution was heated under reflux for 10 minutes and the solvent was then removed under reduced pressure to leave a brown oil.

This oil was triturated with ether to give

a solid which was shown by thin layer chromatography to be a mixture of acid and ester. The solid was heated in aqueous sodium bicarbonate solution until it had all dissolved. This solution was cooled and acidified with dilute hydrochloric acid to give 0.96 parts of 4, 10 - dioxo - 5 - methoxy - 2,8 - dicarboxy-4H,10H-benzo(1,2-b: 3,4-b') dipyrans, monohydrate as a pale brown solid, melting point 262—3° C (d).

Analysis:

Found: C 51.7% H 3.02%
C₁₅H₈O₉·H₂O requires: C 51.5% H 2.86%

(b) 4,10 - Dioxo - 5 - methoxy - 2,8 - dicarboxy - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans, disodium salt

A solution of 0.83 parts of 4,10 - dioxo - 5 - methoxy - 2,8 - dicarboxy - 4H,10H-benzo (1,2 - b: 3,4 - b') dipyrans monohydrate and 0.4 parts of sodium bicarbonate in 50 parts of water was freeze-dried to give 0.83 parts of 4,10 - dioxo - 5 - methoxy - 2,8 - dicarboxy - 4H, 10H - benzo (1,2 - b: 3,4 - b') dipyrans disodium salt as a pale yellow solid.

EXAMPLE 2

4,10 - Dioxo - 2,8 - dicarboxy - 5 - hydroxy-4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans

(a) 4,10 - Dioxo - 2,8 - dicarboxy - 5 - hydroxy - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans monohydrate.

A solution of 0.55 parts of 4,10 - dioxo - 2,8 - dicarboxy - 5 - methoxy - 4H,10H-benzo (1,2 - b: 3,4 - b') dipyrans monohydrate (Prepared as in Example 1) in a mixture of 7 parts of hydrogen bromide-acetic acid (45% w/v) and 7 parts of glacial acetic acid was refluxed for 1½ hours. During this time, a solid separated out of the reaction mixture. The mixture was poured into 200 parts of water and the solid precipitate was filtered off.

The solid was dissolved in aqueous bicarbonate solution and the solution treated with charcoal and filtered. Acidification of the bicarbonate solution with dilute hydrochloric acid gave 0.3 parts of 4,10 - dioxo - 2,8 - dicarboxy - 5 - hydroxy - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans monohydrate as a pink solid, melting point 300—2° C (d).

Analysis:

Found: C, 49.8% H, 2.14%
C₁₄H₈O₉·H₂O requires: C, 50.01% H, 2.4%

(b) 4,10 - Dioxo - 2,8 - dicarboxy - 5 - hydroxy - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans disodium salt

A solution of 0.238 parts of 4,10 - dioxo - 2,8 - dicarboxy - 5 - hydroxy - 4H,10H-benzo (1,2 - b: 3,4 - b') dipyrans monohydrate

and 0.113 parts of sodium bicarbonate in 30 parts of water was freeze-dried to give 0.23 parts of 4,10 - dioxo - 2,8 - dicarboxy - 5 - hydroxy - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans disodium salt as a buff coloured solid.

EXAMPLE 3

4, 10 - Dioxo - 5 - methyl - 2,8 - dicarboxy-4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans

To a solution of 3.1 parts of anhydrous orcinol in 50 parts of anhydrous dioxan were added 0.23 parts of sodium. The mixture was stirred and heated until the sodium had dissolved. The stirred solution was then treated dropwise with a solution of 7.5 parts of dimethyl acetylene dicarboxylate in 20 parts of anhydrous dioxan. After stirring and heating on a steam-bath for 15 minutes, the mixture was cooled and acidified with 9 parts of 10% w/v sulphuric acid solution. It was then treated with 25 parts of 25% w/v sodium hydroxide solution; heated on a steam-bath for one hour; cooled; acidified with 10% w/v sulphuric acid solution; and the dioxan was then distilled off. The mixture was extracted with ether and the ether evaporated to leave a yellow solid which was crystallised from water to give 1.0 parts of orcinol di(trans - 1,2 - dicarboxyvinyl) ether, melting point, 260—1° C.

Analysis

Found: C, 50.92% H, 3.59%
C₁₅H₁₂O₁₀ requires: C, 51.15% H, 3.41%

The structure was confirmed by nuclear magnetic resonance spectrum.

A mixture of 0.5 parts of orcinol di(trans - 1,2 - dicarboxyvinyl) ether and 15 parts of polyphosphoric acid was stirred and heated at 110—20° C for three hours. The mixture was cooled and diluted with ice-water. The supernatant liquid was decanted off and the precipitated solid was filtered off, washed with water and dried in the oven to leave 0.3 parts of 4,10 - dioxo - 5 - methyl - 2,8 - dicarboxy-4H, 10H - benzo (1,2 - b: 3,4 - b') dipyrans sesquihydrate, melting point, 285—6° C. (Decomp).

Analysis

Found: C, 52.22% H, 3.02%
C₁₅H₈O₉·1½H₂O requires:

C, 52.49% H, 3.2%

The material was shown to be identical with the free acid obtained by reaction of diethyl oxalate and 2,4 - diacetylresorcinol using the method of Example 1 by comparison of melting points and infra-red spectra. The mixed melting point gave no depression.

EXAMPLE 4

2,8 - Dicarboxy - 4,10 - dioxo - 5 - methoxy-4H, 10H - benzo (1,2 - b: 3,4 - b') dipyrans

A mixture of 5 - methoxy - 2,4 - diacetylresorcinol (20 parts) and ethyl ethoxydichlor-

acetate for 5 h material obtained in glass concentrate and red solid was washed dissolving treating and chloric 4,10 - (1,2 - b: 3,4 - b') shown Example

2,8 - Dioxo - 4H - dipyrans

A solution of resorcinol sulphuric acid

volume of dioxan of solid

The reflux for a large and the

The extracted by-product

phenyl was dried a sticky with ethyl

ated by of NaOH

ide. The oil was contain

chloric 15 min to yield

This oil was and in hydro

Heating, The filtered

55 4,10 - (1,2 - b: 3,4 - b') was obtained

60 2,8 - Dioxo - 4H - dipyrans

ethyl slowly

(23)

acetate (52 parts) was heated at 150 to 170° C for 5 hours. After evaporating off any volatile material under reduced pressure, a mixture was obtained which was hydrolysed by dissolving in glacial acetic acid containing 17% of concentrated hydrochloric acid (500 parts total) and refluxing for 4 hours. After cooling, a solid was obtained. This solid was filtered off, washed well with water and purified by dissolving in aqueous sodium bicarbonate, treating the hot solution with charcoal, filtering and precipitating with concentrated hydrochloric acid. The product, 2,8 - dicarboxy-4,10 - dioxo - 5 methoxy - 4H,10H - benzo (1,2 - b; 3,4 - b') dipyrans monohydrate, was shown to be identical with the product of Example 1a.

EXAMPLE 5

2,8 - Dicarboxy - 4,10 - dioxo - 5 - methoxy-4H,10H - benzo (1,2 - b; 3,4 - b') dipyrans monohydrate

A solution of 5 - methoxy - 2,4 - diacetylresorcinol (1 part) and ethyl *N* - toluene - *p* - sulphonyloxamate (10 parts) in 80 parts by volume of dry ethanol and 10 parts by volume of dioxan, was added to a solution of 1.3 parts of sodium in 100 parts by volume of ethanol. The resultant mixture was heated under reflux for 20 hours. After cooling the mixture, a large excess of ether (500 parts) was added and the mixture was extracted with water. The aqueous extract was acidified and extracted into chloroform and filtered to remove by-product *N,N'* - bis(toluene - *p* - sulphonyl) oxamide. The chloroform solution was dried and evaporated to dryness, yielding a sticky solid which was washed several times with ether, the ethereal extracts being separated by decantation, to leave a further amount of *N, N'* - bis(toluene - *p* - sulphonyl) oxamide. The ethereal extracts on evaporation gave an oil which was dissolved in ethanol (20 parts) containing a few drops of concentrated hydrochloric acid. This solution was refluxed for 15 minutes and the solvent removed *in vacuo* to yield a brown oil.

Thin layer chromatography showed that this oil was probably a mixture of the desired acid and its ester. The mixture was therefore hydrolysed with aqueous sodium bicarbonate. Heating of the hydrolysis mixture was continued until complete solution was achieved. The solution was then treated with charcoal, filtered and acidified to yield 2,8 - dicarboxy-4,10 - dioxo - 5 - methoxy - 4H,10H - benzo (1,2 - b; 3,4 - b') dipyrans monohydrate which was shown to be identical to the product obtained in Example 1a.

EXAMPLE 6

2,8 - Dicarboxy - 4,10 - dioxo - 5 - methoxy-4H,10H - benzo (1,2 - b; 3,4 - b') dipyrans monohydrate.

Ethyl oxalylchloride (8 parts) was added slowly to a mixture of 2,4 - diacetyl - 5 -

methoxyresorcinol (2.5 parts) and anhydrous pyridine (10 parts) cooled in ice. The mixture was kept at room temperature for 24 hours and then heated for 30 minutes on a steam bath. After cooling and pouring onto a mixture of ice and hydrochloric acid, an oil was obtained which was extracted with chloroform, washed and the chloroform solution then dried over sodium sulphate. After filtration and removal of the solvent, the residue was crystallised from ethanol to give 2,8 - dicarboxy - 4,10 - dioxo - 5 - methoxy - 4H,10H - benzo (1,2 - b; 3,4 - b') dipyrans monohydrate which was shown to be identical with the product of Example 1a.

EXAMPLE 7

2,8 - Dicarboxy - 4,10 - dioxo - 5 - methoxy-4H,10H - benzo (1,2 - b; 3,4 - b') dipyrans monohydrate.

A mixture of phloroglucinol monomethyl ether (2 parts) and ethyl ethoxalylacetate (10 parts) in diphenyl ether (30 parts) was heated for 4 hours at 150° C. The reaction vessel was fitted with an air condenser, so that volatile reaction products, such as water and ethanol, could escape from the reaction mixture. After cooling, the reaction mixture was triturated with an excess of petroleum ether (b.p. 60—80° C) several times, to leave a sticky gum. Aqueous sodium bicarbonate was added to this gum and the mixture heated on a steam bath until solution of the gum was achieved. Acidification of the solution gave 2,8 - dicarboxy - 4,10 - dioxo - 5 - methoxy-4H,10H - benzo (1,2 - b; 3,4 - b') dipyrans monohydrate which was shown to be identical with the product of Example 1a.

EXAMPLE 8

2,8 - Diethoxycarbonyl - 4,10 - dioxo-4H,10H - benzo (1,2 - b; 3,4 - b') dipyrans.

Resacetophenone (7.6 parts) and dimethyl acetylene dicarboxylate (15 parts) were mixed together and 3 drops of benzyltrimethylammonium hydroxide (40% aqueous solution) were added. The resulting solution was heated on a steam bath for 1 hour and then cooled, treated with sodium hydroxide (45 parts of 25% aqueous solution) and heated on a steam bath for 3 hours. The mixture was then cooled and acidified with sulphuric acid (20% H₂SO₄). A precipitate was slowly deposited, which was filtered off, washed with water and crushed to leave a fawn powder. This powder was crystallised from water to give 3.5 parts of 3 - hydroxy - 4 - acetylphenoxyfumaric acid hemi - hydrate, melting point 217° C (d).

Analysis:

Found: C, 52.8% H, 3.89%

C₁₂H₁₀O_{7.5} H₂O required:

C, 52.4% H, 4.00%

A mixture of this material and concentrated sulphuric acid (18 parts) was stirred until a clear solution was obtained. The solution was then heated on a steam bath for 10 minutes, cooled and poured onto ice. A fine green precipitate was obtained which settled under gravity. This precipitate was filtered off, washed with water and dried. The dried powder was crystallised from ethanol to give 0.9 parts of 5 - hydroxy - 6 - acetylchromone-2 - carboxylic acid, whose structure was confirmed by NMR evidence, melting point 262° C (d).

Analysis:

Found: C, 58.0% H, 3.26%

C₁₂H₈O₆ requires:

C, 58.1% H, 3.23%

This product (0.5 parts) was mixed with diethyl oxalate (5 parts by volume) in dry ethanol (20 parts by volume) and the mixture added to a solution of sodium (0.5 parts) in dry ethanol (50 parts by volume). The resultant solution was stirred and heated under reflux for 16 hours, cooled and poured into a large volume of ether. The mixture was extracted several times with water and the aqueous extracts acidified. The acidified aqueous extracts were then extracted with chloroform (three 50 part lots). The chloroform extracts were washed with water, dried and evaporated to dryness leaving an oil. This oil was dissolved in dry ethanol (20 parts) and the solution saturated with hydrogen chloride by passing a stream of dry hydrogen chloride through the solution. This mixture was kept overnight and then refluxed for 1 hour. The ethanol was evaporated and iced water added to the residue to give a sticky solid. The water was decanted and the solid crystallised from ethanol to give 2,8 - diethoxycarbonyl - 4,10-dioxo - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans which was shown to be identical to the ester obtained when 2,4 - diacetylresorcinol was reacted with diethyl oxalate using the process of Example 1.

EXAMPLE 9

2 - 8 - Dicarboxy - 4,6 - dioxo - 10 - nitro-4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.

Powdered aluminium chloride (15 parts) was added with stirring to a solution of 2-nitroresorcinol (3.5 parts) and maleic anhydride (5.5 parts) in ethylene dichloride (200 parts). After standing at room temperature for 20 hours, the mixture was warmed to 80° C for 1 hour, cooled and filtered to give a yellow residue. This residue was added with stirring to a mixture of crushed ice (20 parts), concentrated hydrochloric acid (10 parts) and chloroform (100 parts). The mixture was allowed to separate into two layers. After 30 minutes the organic layer was removed, the

aqueous layer extracted with further lots of chloroform and the chloroform extracts combined with the organic layer. The combined organic layer was dried over sodium sulphate and the chloroform evaporated off *in vacuo* to give a reddish brown oil which was taken up in amyl alcohol (50 parts) and selenium dioxide (3 parts) was added. The mixture was refluxed for 18 hours. The inorganic materials were then removed by centrifuging and decanting. The organic layer was then steam distilled to remove the solvent and purified by dissolution in sodium bicarbonate, treatment with charcoal, filtration and precipitation with concentrated hydrochloric acid to give 2,8 - dicarboxy - 4,6 - dioxo - 10 - nitro - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans which was identical to the compound obtained when 2,4 - diacetyl - 6 nitroresorcinol was reacted with diethyl oxalate using the method of Example 1.

EXAMPLE 10

2,8 - Dicarboxy - 4,6 - dioxo - 10 methyl-4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.

(a) 3,7 - Diacetyl - 2,8 - dimethyl - 4,6-dioxo - 10 - methyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.

A mixture of 4,6 - diacetyl - 2 - methylresorcinol (10.4 parts), sodium acetate (15 parts) and acetic anhydride (90 parts) was heated under reflux for 4 hours. The mixture was cooled and then poured onto ice. A brown oil was precipitated and the aqueous layer was decanted therefrom. The oil was washed with water. Hydrochloric acid (150 parts, 15% HCl) was added to the oil and the mixture heated to boiling. On cooling, a brown crystalline solid was obtained which was filtered off, suspended in boiling ethanol for 15 minutes and, after cooling, filtered off to yield 3,7-diacetyl - 2,8 - dimethyl - 4,6 - dioxo - 10-methyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans, melting point 280—5° C.

Analysis:

Found: C, 67.5% H, 4.56%

C₁₉H₁₆O₆ requires:

C, 67.0% H, 4.71%

(b) 2,8 - Dimethyl - 4,6 - dioxo - 10-methyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.

A mixture of 3,7 - diacetyl - 2,8 - dimethyl-4,6 - dioxo - 10 - methyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans (0.9 parts as prepared above), sodium carbonate (2.0 parts) and water (40 parts) was heated under atmospheric reflux for 1.5 hours. The resulting solution was acidified and the precipitated solid was filtered off, washed with water, and crystallised from ethanol to give 2,8 - dimethyl - 4,6 - dioxo - 10 - methyl - 4H,6H -

benzo (1,2 - as a yellow

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benzo (1,2 - b: 5,4 - b') dipyrans (0.5 parts)
as a yellow solid.

(c) 2,8 - Dicarboxy - 4,6 - dioxo - 10-
methyl - 4H,6H - benzo (1,2 - b:
5,4 - b') dipyrans hemihydrate.

Finely divided selenium dioxide (1.2 parts)
was added to a mixture of 2,8 - dimethyl-
4,6 - dioxo - 10 - methyl - 4H,6H - benzo
(1,2 - b: 5,4 - b') dipyrans (1.0 parts as pre-
pared above) and dioxan (20 parts). The
resulting mixture was heated under atmos-
pheric reflux for 8 hours. After cooling the
reaction mixture, the selenium precipitate was
filtered off and the solvent removed from the
filtrate by evaporation *in vacuo*. The solid resi-
due was extracted with aqueous sodium bicar-
bonate. The extract was acidified with dilute
hydrochloric acid and the precipitated solid
filtered off to give 2,8 - dicarboxy - 4,6 - di-
oxo - 10 - methyl - 4H,6H - benzo (1,2 - b:
5,4 - b') dipyrans hemihydrate. The product
had a melting point of 292°-4° C and was
shown to be identical to the product obtained
by the reaction of 2,4 - diacetyl - 6 methyl-
resorcinol with diethyl oxalate using the pro-
cess of Example 1.

EXAMPLE 11

2,8 - Dicarboxy - 4,6 - dioxo - 10 - methyl-
4H,6H - benzo (1,2 - b: 5,4 - b') di-
pyran.

(a) 2,8 - Dimethyl - 4,6 - dioxo - 10-
methyl - 4H,6H - benzo (1,2 - b:
5,4 - b') dipyrans.

A mixture of powdered sodium (2.3 parts),
4,6 - diacetyl - 2 - methylresorcinol (2.08
parts) and ethyl acetate (70 parts) was stirred
and heated under gentle atmospheric reflux
for 4 hours. The resulting solution was cooled
and diluted with diethyl ether (100 parts). A
solid was precipitated, filtered off, and extrac-
ted with water. The aqueous extract was
acidified with dilute hydrochloric acid and an
oil precipitated. The oil was extracted into
ethyl acetate. The organic solution was dried
over sodium sulphate, filtered and the solvent
removed to yield an oil. This oil was heated
under atmospheric reflux for 15 minutes with
ethanol (20 parts) and concentrated hydro-
chloric acid (0.5 parts). The solid which
crystallised out from the reaction mixture on
cooling was filtered off to give 2,8 - dimethyl-
4,6 - dioxo - 10 - methyl - 4H,6H - benzo
(1,2 - b: 5,4 - b') dipyrans which was identi-
cal to that obtained in step (b) of Example
10.
(b) The 2,8 - dimethyl - 4,6 - dioxo - 10-
methyl - 4H,6H - benzo (1,2 - b: 5,4 - b')
dipyrans was oxidised to the corresponding 2,8-
dicarboxyl - 4,6 - dioxo - 10 - methyl-
4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans by
the method of step (c) of Example 10.

EXAMPLE 12

2,8 - Dicarboxyl - 4,6 - dioxo - 10 - methyl-
4H,6H - benzo (1,2 - b: 5,4 - b') di-
pyran.

(a) 2,8 - Distyryl - 4,6 - dioxo - 10 - methyl-
4H,6H - benzo (1,2 - b: 5,4 - b')
dipyrans.

A slurry of 2,8 - dimethyl - 4,6 - dioxo-
10 - methyl - 4H,6H - benzo (1,2 - b: 5,4-
b') dipyrans (2.6 parts, prepared as in Example
10 or 11) and benzaldehyde (2.12 parts) in
ethanol (20 parts) was added to a stirred solu-
tion of sodium ethoxide in ethanol, which had
been prepared by dissolving sodium (0.46
parts) in ethanol (20 parts). The mixture was
stirred and heated under atmospheric reflux
for 4 hours and then left to stand at room
temperature for 18 hours. The supernatant
liquor was decanted from the brown oil which
had precipitated. The oil was washed by
trituration with ether and not purified further,
to yield 2,8 - distyryl - 4,6 - dioxo - 10-
methyl - 4H,6H - benzo (1,2 - b: 5,4 - b') di-
pyran.

(b) 2,8 - Dicarboxyl - 4,6 - dioxo - 10-
methyl - 4H,6H - benzo (1,2 - b:
5,4 - b') dipyrans hemihydrate.

The crude 2,8 - distyryl - 4,6 - dioxo - 10-
methyl - 4H,6H - benzo (1,2 - b: 5,4 - b')
dipyrans obtained by the above process was
dissolved in pyridine (50 parts) and aqueous
potassium permanganate solution (105 parts of
5% solution) was added. The mixture was
stirred at room temperature for several hours.
The presence of excess permanganate was
checked from time to time and further
amounts of 5% solution were added as re-
quired. When no further oxidation took place,
the solution was acidified with dilute hydro-
chloric acid and decolourised with sulphur di-
oxide. The precipitate was filtered off, washed
with water and extracted into aqueous sodium
bicarbonate solution. Upon acidification of the
solution, a precipitate was formed which was
filtered off and dried to yield 2,8 - dicarboxy-
4, 6 - dioxo - 10 - methyl - 4H,6H - benza
(1,2 - b: 5,4 - b') dipyrans hemihydrate,
which was shown to be identical with the di-
pyran product of Examples 10 and 11.

EXAMPLE 13

6 - Bromo - 2,8 - dicarboxy - 4,10 - dioxo-
5 - hydroxy - 4H,10H - benzo 1,2 - b:
3,4 - b') dipyrans.

(a) 2,8 - Diethoxycarbonyl - 4,10 - dioxo - 5-
hydroxy - 4H,10H - benzo (1,2 - b:
3,4 - b') dipyrans.

A solution of 2,8 - dicarboxy - 4,10 - di-
oxo - 5 - hydroxy - 4H,10H benzo (1,2 - b:
3,4 - b') dipyrans monohydrate (1.76 parts,
prepared as in Example 2) and concentrated
sulphuric acid (0.5 parts) in ethanol (150
parts) was refluxed for 4 hours. The solid
obtained on cooling was filtered off to give

The processes described in Examples 1 to 13 were repeated using different reactants and Table I sets out the products obtained, the Example number of the process route employed and the physical characteristics of the products, where measured.

	Example Number of	Physical data, where measured	
		Melting Point	Analysis Found

TABLE I

Name of Compound	Example Number of Preparative Route	Physical data, where measured		
		Melting Point in °C.	Analysis Found	Other %
			C %	H %
4,6-Dioxo-2,8-diethoxycarbonyl-4H,6H-benzo (1,2-b;5,4-b') dipyrans	1	225—6	60.34	3.85
4,6-Dioxo-2,8-dicarboxy-4H,6H-benzo (1,2-b;5,4-b') dipyrans, disodium salt	1		46.6	1.67
4,10-Dioxo-2,8-diethoxycarbonyl-4H,10H-benzo (1,2-b;3,4-b') dipyrans	1	183—4	60.79	3.74
4,10-Dioxo-2,8-dicarboxy-4H,10H-benzo (1,2-b;3,4-b'), dipyrans disodium salt	1		44.6	2.09
5-Benzoyloxy-4,10-dioxo-2,8-diethoxycarbonyl-4H,10H-benzo (1,2-b;3,4-b') dipyrans	1	210—212	64.8	4.21
5-Benzoyloxy-4,10-dioxo-2,8-dicarboxy-4H,10H-benzo (1,2-b;3,4-b') dipyrans sesquihydrate	1	272—5	57.6	3.42
5-Benzoyloxy-4,10-dioxo-2,8-dicarboxy-4H,10H-benzo (1,2-b;3,4-b') dipyrans, disodium salt	1			
4,10-Dioxo-5-methyl-2,8-dicarboxy-4H,10H-benzo (1,2-b;3,4-b') dipyrans sesquihydrate	1 (via ethyl ester)	287 (decomp)	52.22	3.02
4,10-Dioxo-5-methyl-2,8-dicarboxy-4H,10H-benzo (1,2-b;3,4-b') dipyrans disodium salt	1			
5-Methoxy-4,6-dioxo-2,8-diethoxycarbonyl-4H,6H-benzo (1,2-b;5,4b') dipyrans	1	227—8	59.0	4.20
5-Methoxy-4,6-dioxo-2,8-dicarboxy-4H,6H-benzo (1,2b;-5,4b') dipyrans disodium salt	1			
4,10-Dioxo-6-ethyl-2,8-dicarboxy-4H,10H-benzo (1,2-b;3,4-b') dipyrans monohydrate	1 (via ethyl ester)	282	55.6	3.23
4,10-Dioxo-6-ethyl-2,8-dicarboxy-4H,10H-benzo (1,2-b;3,4-b') dipyrans disodium salt	1			

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TABLE I Continued

Name of Compound	Example Number of Preparative Route	Physical data, where measured			
		Melting Point in °C.	Analysis Found		
			C %	H %	Other %
4,6-Dioxo-2,8-dicarboxy-10-methyl-4H,6H-benzo (1,2-b:5,4-b') dipyrro hemihydrate	1 (via ethyl ester)	293—4	55.78	2.51	
4,6-Dioxo-2,8-dicarboxy-10-methyl-14H,6H-benzo (1,2-b:5,4-b') dipyrro disodium salt	1				
4,6-Dioxo-2,8-dicarboxy-10-ethyl-4H,6H-benzo (1,2-b:5,4-b') dipyrro hemihydrate	1	315	57.2	2.95	
4,6-Dioxo-2,8-dicarboxy-10-ethyl-4H,6H-benzo (1,2-b:5,4-b') dipyrro disodium salt	1				
4,6-Dioxo-2,8-dithoxycarbonyl-10-ethyl-4H,6H-benzo (1,2-b:5,4-b') dipyrro	1	189—91	61.9	4.98	
4,6-Dioxo-2,8-dithoxycarbonyl-10-nitro-4H,6H-benzo (1,2-b:5,4-b') dipyrro	1	215	53.9	3.14	3.36N
4,6-Dioxo-2,8-dicarboxy-10-nitro-4H,6H-benzo (1,2-b:5,4-b') dipyrro hemihydrate	1	225—7	44.1	2.31	3.5N
4,6-Dioxo-2,8-dicarboxy-10-nitro-4H,6H-benzo (1,2-b:5,4-b') dipyrro disodium salt	1				
6,10-Dicarboxy-4-methyl-2,8, 12-trioxo-2H,8H,12H-benzo (1,2-b:3,4-b':5,6-b') tripyran trihydrate	1	263—7	49.6	2.96	
6,10-Dicarboxy-4-methyl-2,8,12-trioxo-2H,8H,12H-benzo (1,2-b:3,4-b':5,6-b') tripyran disodium salt	1				
6-Bromo-2,8-dithoxycarbonyl-4,10-dioxo-5-hydroxy-4H,10H-benzo (1,2-b:3,4-b') dipyrro	1	199—202	46.5	2.87	
6-Bromo-2,8-dicarboxy-4,10-dioxo-5-hydroxy-4H,10H-benzo (1,2-b:3,4-b') dipyrro dihydrate	1	312 (d)	37.0	1.82	

(39)

TABLE I Continued

	Example Number	Physical data, where measured			

6-Bromo-2,8-diethoxycarbonyl-4,10-dioxo-5-hydroxy-4H,10H-benzo (1,2-b:3,4-b') dipyrans

6-Bromo-2,8-dicarboxy-4,10-dioxo-5-hydroxy-4H,10H-benzo (1,2-b:3,4-b') dipyrans dihydrate

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TABLE I Continued

Name of Compound	Example Number of Preparative Route	Physical data, where measured			
		Melting Point in °C.	Analysis Found		
			C %	H %	Other %
6-Bromo-2,8-dicarboxy-4, 10-dioxo-5-hydroxy-4H,10H-benzo (1,2-b:3,4-b') dipyrans disodium salt	1				
4,10-Dioxo-6-chloro-2,8-dicarboxy-4H,10H-benzo (1,2-b:3,4-b') dipyrans monohydrate	2	286—7	47.1	1.62	
4,10-Dioxo-6-chloro-2,8-dicarboxy-4H,10H-benzo (1,2-b:3,4-b') dipyrans disodium salt	2				
4,10-Dioxo-2,8-dicarboxy-5-allyloxy-4H,10H-benzo (1,2-b:3,4-b') dipyrans hemihydrate	1	250—3(d)	55.8	3.30	

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The following compounds may also be prepared by the process of Example 1:

- 5 4,10 - Dioxo - 2,8 - dicarboxy - 5,6 - dimethyl - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
- 10 4,10 - Dioxo - 2,8 - dicarboxy - 5,6 - dipentyl - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
- 15 4,10 - Dioxo - 2,8 - dicarboxy - 5,6 - diethoxy - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
- 20 4,10 - Dioxo - 2,8 - dicarboxy - 6 - butyloxy-4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
- 25 4,10 - Dioxo - 2,8 - dicarboxy - 6 - nitro-4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
- 30 4,10 - Dioxo - 2,8 - dicarboxy - 5,6 - di(2 - hydroxyethoxy) - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
- 35 4,10 - Dioxo - 2,8 - dicarboxy - 5,6 - di(2 - chloroethoxy) - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.

(3)



- 4,10 - Dioxo - 2,8 - dicarboxy - 5 - methoxy-
6 - bromo - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
- 5 4,10 - Dioxo - 2,8 - dicarboxy - 5 - methoxy-
6 - ethyl - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
- 4,10 - Dioxo - 2,8 - dicarboxy - 6 - amino-
4H,10H - benzo (1,2 - b: 3,4 - b') di-
pyran.
- 10 4,10 - Dioxo - 2,8 - dicarboxy - 6 - acetyl-
amino - 4H,10H - benzo (1,2 - b: 3,4 -
b') dipyrans.
- 4,10 - Dioxo - 2,8 - dicarboxy - 5 - methoxy-
6 - allyl - 4H,10H - benzo (1,2 - b: 3,4 -
b') dipyrans.
- 15 4,10 - Dioxo - 2,8 - dicarboxy - 5 - methoxy-
6 - diethylaminomethyl - 4H,10H - benzo
(1,2 - b: 3,4 - b') dipyrans.
- 4,10 - Dioxo - 2,8 - dicarboxy - 5 - (2-
hydroxypropoxy) - 4H,10H - benzo
(1,2 - b: 3,4 - b') dipyrans.
- 20 4,6 - Dioxo - 2,8 - dicarboxy - 5 - methyl-
4H,6H - benzo (1,2 - b: 5,4 - b') di-
pyran.
- 4,6 - Dioxo - 2,8 - dicarboxy - 5 - methyl-
3,7 - dimethyl - 4H,6H - benzo (1,2 -
b: 5,4 - b') dipyrans.
- 25 4,6 - Dioxo - 2,8 - dicarboxy - 10 - amino-
4H,6H - benzo (1,2 - b: 5,4 - b') di-
pyran.
- 30 4,6 - Dioxo - 2,8 - dicarboxy - 10 - acetyl-
amino - 4H,6H - benzo (1,2 - b: 5,4 -
b') dipyrans.
- 4,6 - Dioxo - 2,8 - dicarboxy - 5 - methyl-
10 - ethyl - 4H,6H - benzo (1,2 - b: 5,4 -
b') dipyrans.
- 35 4,6 - Dioxo - 2,8 - dicarboxy - 10 - methoxy-
4H,6H - benzo (1,2 - b: 5,4 - b') di-
pyran.
- 4,6 - Dioxo - 2,8 - dicarboxy - 10 - hydroxy-
4H,6H - benzo (1,2 - b: 5,4 - b') di-
pyran.
- 40 4,6 - Dioxo - 2,8 - dicarboxy - 10 - bromo-
4H,6H - benzo (1,2 - b: 5,4 - b') di-
pyran.
- 45 4,6 - Dioxo - 2,8 - dicarboxy - 5 - methyl-
10 - ethoxyl - 4H,6H - benzo (1,2 - b: 5,4 -
b') dipyrans.
- 4,6 - Dioxo - 2,8 - dicarboxy - 5 - hydroxy-
10 - ethyl - 4H,6H - benzo (1,2 - b: 5,4 -
b') dipyrans.
- 50 4,6 - Dioxo - 2,8 - dicarboxy - 5,10 - diethyl-
4H,6H - benzo (1,2 - b: 5,4 - b') di-
pyran.
- 55 4,6 - Dioxo - 2,8 - dicarboxy - 10 - butyl-
4H,6H - benzo (1,2 - b: 5,4 - b') di-
pyran.
- 4,6 - Dioxo - 2,8 - dicarboxy - 5,10 - di-
pentyl - 4H,6H - benzo (1,2 - b: 5,4 -
b') dipyrans.
- 60 4,6 - Dioxo - 2,8 - dicarboxy - 5,10 - di-
ethoxy - 4H,6H - benzo (1,2 - b: 5,4 -
b') dipyrans.
- 4,6 - Dioxo - 2,8 - dicarboxy - 5 - butoxy-
butoxy - 10 - methyl - 4H,6H - benzo
- 65

- (1,2 - b: 5,4 - b') dipyrans.
- 4,6 - Dioxo - 2,8 - dicarboxy - 5 - phenyl-
ethoxy - 4H,6H - benzo (1,2 - b: 5,4 -
b') dipyrans.
- 4,6 - Dioxo - 2,8 - dicarboxy - 5,10 - di(2-
hydroxyethoxy) - 4H,6H - benzo (1,2 -
b: 5,4 - b') dipyrans.
- 70 4,6 - Dioxo - 2,8 - dicarboxy - 3,7 - dimethyl-
4H,6H - benzo (1,2 - b: 5,4 - b') di-
pyran.
- 75 4,6 - Dioxo - 2,8 - dicarboxy - 3,7 - diethoxy-
4H,6H - benzo (1,2 - b: 5,4 - b') di-
pyran.
- 4,6 - Dioxo - 2,8 - dicarboxy - 5,10 - di-
bromo - 4H,6H - benzo (1,2 - b: 5,4 -
b') dipyrans.
- 80 4,6 - Dioxo - 2,8 - dicarboxy - 5 - methoxy-
10 - (1 - hydroxyethyl) - 4H,6H - benzo
(1,2 - b: 5,4 - b') dipyrans.
- 4,6 - Dioxo - 2,8 - dicarboxy - 10 - ethoxy-
methyl - 4H,6H - benzo (1,2 - b: 5,4 -
b') dipyrans.
- 85 4,6 - Dioxo - 2,8 - dicarboxy - 10 - hydroxy-
methyl - 4H,6H - benzo (1,2 - b: 5,4 -
b') dipyrans.
- 4,6 - Dioxo - 2,8 - dicarboxy - 5 - (2-
hydroxypropoxy) - 10 - ethyl - 4H,6H -
benzo (1,2 - b: 5,4 - b') dipyrans
- 90

EXAMPLE 15

The compounds described in Table II hereof, were tested to assess their acute toxicity and their effectiveness in inhibiting antibody-antigen reactions.

In most cases the compounds of the invention were found to possess very low toxicity values, that is they had LD₅₀ values of at least 1000 mg/Kg of the compound (expressed in terms of the free acid).

In the antibody-antigen tests, the effectiveness of the compounds of the invention in inhibiting the passive cutaneous anaphylaxis in rats was assessed. It has been proved that this form of test gives reliable qualitative indications of the ability of the compounds under test to inhibit antibody-antigen reactions in man.

In this test method Sprague-Dawley rats (male or female) having a body weight of from 100 to 150 gms. were infected subcutaneously at weekly intervals with *N. muris* larvae in doses increasing from about 200 larvae per animal to 2000 larvae per animal in order to establish the infection in rats. After 8 weeks the rats were bled by heart puncture and 15-20 mls. of blood collected from each animal. The blood samples were then centrifuged at 3500 rpm. for 30 minutes in order to remove the blood cells from the blood plasma. The blood was collected and used to provide a serum containing *N. muris* antibody. A pilot sensitivity test was carried out to determine the least quantity of serum required to give a skin weal in control animals in the test described below of >2 cm diameter. It

was found in the blood obtained parts of antibody

The antiserum A worms from fusing the supernatant with water 1 mg./ml

10 Sprague range 10

15 intra der A into allowed to were then 100 gms.

20 B (0.25 mls.) and test (0.5

45 % in

The dose level compound required

was found that optimum sensitivity of rats in the body weight range 100—130 gms was obtained using a serum diluted with eight parts of water. This diluted solution is called antibody serum A.

The antigen to react with the antibody in serum A was prepared by removing *N. muris* worms from the gut of the infested rats, centrifuging the homogenate and collecting the supernatant liquor. This liquor was diluted with water to give a protein content of 1 mg./ml. and is known as serum B.

Sprague-Dawley rats in the body weight range 100 to 130 gms. were sensitised by intra dermal injection of 0.1 mls. of serum A into the right flank. Sensitivity was allowed to develop for 24 hours and the rats were then injected intravenously with 1 ml./100 gms. body weight of a mixture of serum B (0.25 mls.), Evans Blue dye solution (0.25 mls.) and the solution of the compound under test (0.5 mls. varying percentages of active

matter). Insoluble compounds were administered as a separate intraperitoneal injection 5 minutes before intravenous administration of serum B and Evans Blue dye. For each percentage level of active matter in the solution under test five rats were injected. Five rats were used as controls in each test. The dosages of the compound under test were selected so as to give a range of inhibition values.

Thirty minutes after injection of serum B the rats were killed and the skins removed and reversed. The intensity of the anaphylactic reaction was assessed by comparing the size of the characteristic blue weal produced by spread of the Evans Blue dye from the sensitisation site, with the size of the weal in the control animals. The size of the weal was rated as 0 (no weal detected, i.e. 100% inhibition) to 4 (no difference in size of weal, i.e. no inhibition) and the percentage inhibition for each dose level calculated as:—

$$\% \text{ inhibition} = \frac{(\text{Control group score} - \text{treated group score}) \times 100}{\text{Control group score}}$$

The percentage inhibitions for the various dose levels were plotted graphically for each compound. From these graphs the dosage required to achieve a 50% inhibition of the

anaphylactic reaction (ID_{50}) may be determined. These results are tabulated in Table II.

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b: 5,4-

- di(2-
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ethoxy-
b') di-

ethoxy-
b') di-

0 - di-
5,4-

ethoxy-
benzo

ethoxy-
b: 5,4-

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b: 5,4-

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TABLE II

Name of Compound	LD ₅₀ mg/kg	ID ₅₀ values in mg/Kg of the salt
4,10-Dioxo-2,8-dicarboxy-5-methoxy-4H,10H-benzo (1,2-b:3,4-b') dipyrans disodium salt	>1000	0.73
4,6-Dioxo-2,8-dicarboxy-4H,6H-benzo (1,2-b:5,4-b') dipyrans disodium salt	>1000	0.18
4,10-Dioxo-2,8-dicarboxy-4H,10H-benzo (1,2-b:3,4-b') dipyrans disodium salt	>1000	7.6
4,10-Dioxo-2,8-dicarboxy-5-benzoyloxy-4H,10H-benzo (1,2-b:3,4-b') dipyrans disodium salt	500	0.36
4,10-Dioxo-2,8-dicarboxy-5-methyl-4H,10H-benzo (1,2-b:3,4-b') dipyrans disodium salt	circa 1000	9.5
4,6-Dioxo-2,8-dicarboxy-5-methoxy-4H,6H-benzo (1,2-b:5,4-b') dipyrans disodium salt	—	0.32
4,10-Dioxo-2,8-dicarboxy-6-ethyl-4H,10H-benzo (1,2-b:3,4-b') dipyrans disodium salt	>200	10
4,6-Dioxo-2,8-dicarboxy-10-methyl-4H,6H-benzo (1,2-b:5,4-b') dipyrans disodium salt	1000	0.25
4,10-Dioxo-2,8-dicarboxy-5-hydroxy-4H,10H-benzo (1,2-b:3,4-b') dipyrans disodium salt	>250	5
4,6-Dioxo-2,8-dicarboxy-10-ethyl-4H,6H-benzo (1,2-b:5,4-b') dipyrans disodium salt	>250	0.1
4,6-Dioxo-2,8-dicarboxy-10-nitro-4H,6H-benzo (1,2-b:5,4-b') dipyrans disodium salt	>500	1.6
6,10-Dicarboxy-4-methyl-2,8,12-trioxo-2H,8H,12H-benzo (1,2-b:3,4-b':5,6-b'') tripyran disodium salt.	>500	4.25

EXAMPLE 16

To confirm the results obtained by the animal tests set out in Example 15, one compound [4,10 - dioxo - 2,8 - dicarboxy - 5-methoxy - 4H,10H - benzo (1,2 - b:3,4 - b') dipyrans disodium salt] was selected at random and its effectiveness in relieving allergic asthma in man determined. In this test, the ability of the compound to reduce airway constriction

or obstruction following the administration of an antigen was assessed by means of a spirometer.

In carrying out the tests a human subject was given one dose of antigen at each visit, since a partial, variable, temporary desensitisation occurs after each dose of antigen. The dose of antigen was administered by aerosol at a rate of 8 litres of air per minute

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which :

using a Wright nebuliser for 120 seconds. The visits occurred at intervals of at least three days and, where possible, were made at constant intervals. The concentration of the antigen given to each subject was adjusted so that the maximum reduction in the forced exhalation volume in one second (F.E.V.) observed within 30 minutes of antigen administration was about 40%. Having determined the approximate dose of antigen required to achieve a satisfactory reduction in F.E.V., the subject was then tested for the effect of the compound under test. This was done by administering the determined amount of anti-

gen 1 hour after a measured amount of the compound under test.

Administration of the compound was achieved by inhalation of an aerosol of a 5% solution of the sodium salt of the compound under test using a Wright nebuliser. Inhalation was carried out over a period of 20 minutes at a rate of 0.2 ml. of solution per minute.

The F.E.V. of the subject was then measured at intervals after the antigen had been administered and the degree of protection afforded calculated from the following formula:

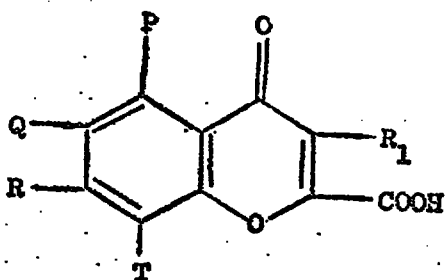
$$100 \times \frac{\text{Max F.E.V. fall in control visits} - \text{Max. F.E.V. in test visits}}{\text{Max. F.E.V. in control visits}}$$

The average protection of the compound tested is given below:—

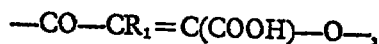
Interval after antigen administration	2 hours	4 hours	6 hours	8 hours
Percentage Inhibition	49.5	46	30.5	20.5

WHAT WE CLAIM IS:—

1. A compound of formula I,



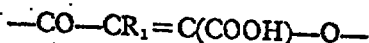
wherein an adjacent pair of P, Q, R and T form the chain



the remainder of P, Q, R and T are the same or different and each is hydrogen or a substituent other than hydrogen,

each R₁ may be the same or different, and is hydrogen, an alkyl group containing from 1 to 10 carbon atoms, an alkoxy group containing from 1 to 10 carbon atoms, an aryl group, a substituted alkyl or alkoxy group containing from 1 to 10 carbon atoms, or a substituted aryl group, and pharmaceutically acceptable derivatives thereof.

2. A compound according to Claim 1, wherein one or more adjacent pairs of P, Q, R and T, together form the chain



which may be bonded to the benzene ring

in either sense; the remainder of P, Q, R and T are the same or different and each is hydrogen; alkyl containing from 1 to 10 carbon atoms, alkyl containing from 1 to 10 carbon atoms and carrying a

halo, hydroxy, lower alkoxy, acetoxy; carboxy; amino; lower alkylamino; lower dialkylamino; or a hydroxylamino substituent group; unsaturated alkyl containing from 1 to 10 carbon atoms; phenylalkyl, halophenylalkyl or alkylphenylalkyl wherein the alkyl groups contain from 1 to 10 carbon atoms; phenyl; naphthyl; or phenyl and naphthyl carrying a halo; lower alkyl; nitro, carboxy or hydroxy substituent group;

pyridyl; furyl; pyrrolyl; cycloalkyl containing from 4—6 carbon atoms; cycloalkyl containing from 4 to 6 carbon atoms and carrying a

hydroxyl, lower alkoxy or carboxy substituent group;

nitrile; nitro; nitroso; hydroxy; alkoxy containing 1 to 10 carbon atoms; alkoxy containing from 1 to 10 carbon atoms and carrying a

hydroxy, lower alkoxy, carboxy, halo, amino, lower alkylamino, or lower dialkylamino substituent group;

alkenyloxy or alkynyloxy containing from 1 to 10 carbon atoms; benzyloxy; phenyloxy; naphthyloxy; pyridyloxy; cyclohexyloxy; cyclopentyloxy; epoxyloweralkoxy; amino; lower alkylamino; lower dialkylamino; cycloalkylamino containing from 4 to 6 carbon atoms; phenylamino; naphthylamino; diphenylamino; haloloweralkylamino; lower alkenylamino; aminoloweralkylamino; hyd-

and is understood in the art that the compound of formula I may be administered in man determined. In this test, the ability of the compound to reduce airway constriction

using a Wright nebuliser for 120 seconds. The visits occurred at intervals of at least three days and, where possible, were made at constant intervals. The concentration of the antigen given to each subject was adjusted so that the maximum reduction in the forced exhalation volume in one second (F.E.V.) observed within 30 minutes of antigen administration was about 40%. Having determined the approximate dose of antigen required to achieve a satisfactory reduction in F.E.V., the subject was then tested for the effect of the compound under test. This was done by administering the determined amount of anti-

gen 1 hour after a measured amount of the compound under test.

Administration of the compound was achieved by inhalation of an aerosol of a 5% solution of the sodium salt of the compound under test using a Wright nebuliser. Inhalation was carried out over a period of 20 minutes at a rate of 0.2 ml. of solution per minute.

The F.E.V. of the subject was then measured at intervals after the antigen had been administered and the degree of protection afforded calculated from the following formula:

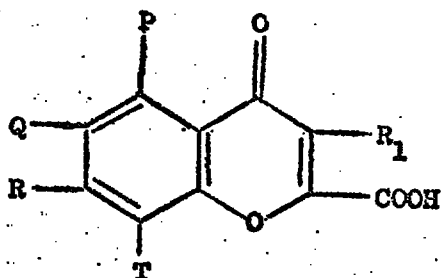
$$100 \times \frac{\text{Max F.E.V. fall in control visits} - \text{Max. F.E.V. in test visits}}{\text{Max. F.E.V. in control visits}}$$

30 The average protection of the compound tested is given below:—

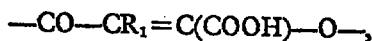
Interval after antigen administration	2 hours	4 hours	6 hours	8 hours
Percentage Inhibition	49.5	46	30.5	20.5

WHAT WE CLAIM IS:—

1. A compound of formula I,



35 wherein an adjacent pair of P, Q, R and T form the chain

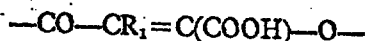


the remainder of P, Q, R and T are the same or different and each is hydrogen or a substituent other than hydrogen,

40 each R₁ may be the same or different, and is hydrogen, an alkyl group containing from 1 to 10 carbon atoms, an alkoxy group containing from 1 to 10 carbon atoms, an aryl group, a substituted alkyl or alkoxy group containing from 1 to 10 carbon atoms, or a substituted aryl group,

and pharmaceutically acceptable derivatives thereof.

50 2. A compound according to Claim 1, wherein one or more adjacent pairs of P, Q, R and T, together form the chain



which may be bonded to the benzene ring

in either sense; the remainder of P, Q, R and T are the same or different and each is hydrogen; alkyl containing from 1 to 10 carbon atoms, alkyl containing from 1 to 10 carbon atoms and carrying a

halo, hydroxy, lower alkoxy, acetoxy; carboxy; amino; lower alkylamino; lower dialkylamino; or a hydroxylamino substituent group;

unsaturated alkyl containing from 1 to 10 carbon atoms; phenylalkyl, halophenylalkyl or alkylphenylalkyl wherein the alkyl groups contain from 1 to 10 carbon atoms; phenyl; naphthyl; or phenyl and naphthyl carrying a halo; lower alkyl; nitro, carboxy or hydroxy substituent group;

pyridyl; furyl; pyrrolyl; cycloalkyl containing from 4—6 carbon atoms; cycloalkyl containing from 4 to 6 carbon atoms and carrying a

hydroxyl, lower alkoxy or carboxy substituent group;

nitrile; nitro; nitroso; hydroxy; alkoxy containing 1 to 10 carbon atoms; alkoxy containing from 1 to 10 carbon atoms and carrying a

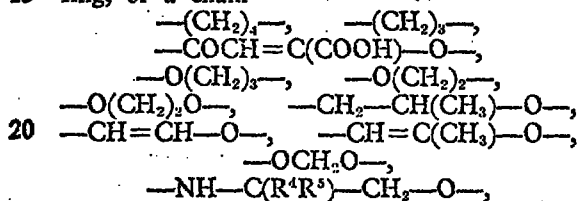
hydroxy, lower alkoxy, carboxy, halo, amino, lower alkylamino, or lower dialkylamino substituent group;

alkenyloxy or alkynyloxy containing from 1 to 10 carbon atoms; benzyloxy; phenyloxy; naphthyloxy; pyridyloxy; cyclohexyloxy; cyclopentyloxy; epoxyloweralkoxy; amino; lower alkylamino; lower dialkylamino; cycloalkylamino containing from 4 to 6 carbon atoms; phenylamino; naphthylamino; diphenylamino; haloloweralkylamino; lower alkenylamino; aminoloweralkylamino; hyd-



roxyamino; ureyl; thioureyl; guanidino; thiol; lower alkyl thiol; phenyl thiol; sulphonic acid; halogen or

- 5 one or more of P, Q, R and T may be a group OY wherein Y is an alkyl or phenyl-alkyl group the alkyl portion of which contains from 1 to 10 carbon atoms and in which one or more of the CH₂ groups has been replaced by oxygen, sulphur or carbonyl, which alkyl or phenyl lower alkyl may carry one or more hydroxyl or carboxyl substituent groups; or an adjacent pair of P, Q, R and T (together with the adjacent carbon atoms in the benzene ring) together form a benzene ring, or a chain



- wherein R⁴ is hydrogen or lower alkyl or lower alkoxy and R⁵ is hydrogen, or R⁴ and R⁵ together form a =O group),

- 25 and each R_i may be the same or different and is hydrogen, alkyl containing from 1—10 carbon atoms, alkoxy containing from 1—10 carbon atoms or phenyl,

- 30 and pharmaceutically acceptable derivatives thereof.

3. A compound according to either one of Claims 1 or 2, wherein those of P, Q, R and T not forming a

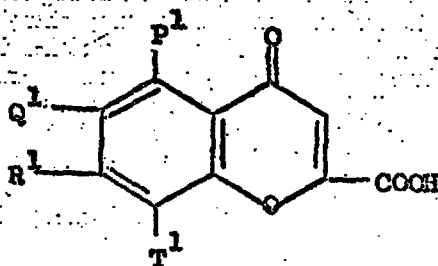
- 35 chain are hydrogen or halogen, hydroxy, nitro, lower alkyl, lower alkenyl, benzyl, phenyl, lower alkoxy, lower alkenyloxy, phenyloxy, benzyloxy or the fused ring substituents specified in Claim 2 or such groups carrying a halogen, hydroxy or lower alkoxy substituent.

4. A compound according to either one of Claims 1 or 2, wherein those of P, Q, R and T not forming a



- chain are hydrogen, chlorine, bromine, nitro or lower alkyl or alkoxy groups containing from 1 to 6 carbon atoms, which may carry a hydroxy, lower alkoxy or phenyl substituent.

5. A compound of formula,



wherein an adjacent pair of P¹, Q¹, R¹ and T¹ together forms the chain



which may be bonded to the benzene ring in either sense; and the other two of P¹, Q¹, R¹ and T¹ may be the same or different and each is hydrogen, halogen, nitro, lower alkyl, lower alkoxy, or a lower alkyl or alkoxy group carrying a hydroxy, lower alkoxy or phenyl substituent, and pharmaceutically acceptable derivatives thereof.

6. A compound according to either one of Claims 1 or 2 in which those of P, Q, R and T which do not form a chain



are selected from the group consisting of hydrogen, hydroxy, nitro, halogen, lower alkyl, lower alkoxy or lower alkenyloxy groups (which groups may carry a hydroxy or lower alkoxy substituent), a benzyl oxy group or an adjacent pair of P, Q, R and T may, together with the carbon atoms on the benzene ring form a fused oxygen containing 5 membered ring, and

each R_i is selected from the group consisting of hydrogen, alkyl containing from 1 to 10 carbon atoms, alkoxy containing from 1 to 10 carbon atoms and phenyl.

7. A compound according to either one of Claims 1 or 2 in which those of P, Q, R and T which do not form a



chain are selected from methoxy, hydroxy, nitro, methyl, bromo, benzyloxy, ethyl, chloro, allyloxy, butyl, propyl and pentyl.

8. A compound according to any of the preceding claims, wherein each R_i is hydrogen.

9. 4,10 - Dioxo - 5 - methoxy - 2,8 - dicarboxy - 4H,10H benzo (1,2 - b: 3,4 - b') dipyrans.

10. 4,10 - Dioxo - 2,8 - dicarboxy - 5-hydroxy - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.

11. 4,10 - Dioxo - 5 - methyl - 2,8 - dicarboxy - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.

12. 2,8 - Diethoxycarbonyl - 4,10 - dioxo - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.

13. 2,8 - Dicarboxy - 4,6 - dioxo - 10-nitro - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.

14. 2,8 - Dicarboxy - 4,6 - dioxo - 10-methyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.

15. 6 - Bromo - 2,8 - dicarboxy - 4,10-dioxo - 5 - hydroxy - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.

16. 4,6 - Dioxo - 2,8 - dicarboxy - 4H,6H-benzo (1,2 - b: 5,4 - b') dipyrans.



17. 5 - Benzyloxy - 4,10 - dioxo - 2,8-dicarboxy - 4H,10H - benzo (1,2 - b; 3,4 - b') dipyrans.
18. 5 - Methoxy - 4,6 - dioxo - 2,8 - dicarboxy-4H,6H-benzo (1,2b: -5,4-b') dipyrans.
19. 4,10 - Dioxo - 6 - ethyl - 2,8 - dicarboxy - 4H,10H - benzo (1,2 - b. 3,4 - b') dipyrans.
20. 4,6 - Dioxo - 2,8 - dicarboxy - 10-ethyl - 4H,6H - benzo (1,2 - b. 5,4 - b') dipyrans.
21. 6,10 - Dicarboxy - 4 - methyl - 2,8,12-trioxo - 2H,8H,12H - benzo (1,2 - b: 3,4 - b'): 5,6 - b'') tripyrans.
22. 4,10 - Dioxo - 6 - chloro - 2,8 - dicarboxy - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
23. 4,10 - Dioxo - 2,8 - dicarboxy - 5-allyloxy - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
24. 4,10 - Dioxo - 2,8 - dicarboxy - 5,6-dimethyl - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
25. 4,10 - Dioxo - 2,8 - dicarboxy - 5,6-dipentyl - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
26. 4,10 - Dioxo - 2,8 - dicarboxy - 5,6-di(phenylpropoxy) - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
27. 4,10 - Dioxo - 2,8 - dicarboxy - 5,6-diethoxy - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
28. 4,10 - Dioxo - 2,8 - dicarboxy - 5-pentyloxy - 3,9 - dimethyl - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
29. 4,10 - Dioxo - 2,8 - dicarboxy - 6-butyl - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
30. 4,10 - Dioxo - 2,8 - dicarboxy - 5,6-di(ethoxyethoxy) - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
31. 4,10 - Dioxo - 2,8 - dicarboxy - 6-nitro - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
32. 4,10 - Dioxo - 2,8 - dicarboxy - 6-butyl - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
33. 4,10 - Dioxo - 2,8 - dicarboxy - 5,6-di(2 - hydroxyethoxy) - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
34. 4,10 - Dioxo - 2,8 - dicarboxy - 5,6-di(2 - chloroethoxy) - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
35. 4,10 - Dioxo - 2,8 - dicarboxy - 5-methoxy - 6 - bromo - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
36. 4,10 - Dioxo - 2,8 - dicarboxy - 5-methoxy - 6 - ethyl - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
37. 4,10 - Dioxo - 2,8 - dicarboxy - 6-amino - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
38. 4,10 - Dioxo - 2,8 - dicarboxy - 6-acetylamino - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
39. 4,10 - Dioxo - 2,8 - dicarboxy - 5-methoxy - 6 - allyl - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
40. 4,10 - Dioxo - 2,8 - dicarboxy - 5-methoxy - 6 - diethylaminomethyl - 4H,10H-benzo (1,2 - b: 3,4 - b') dipyrans.
41. 4,10 - Dioxo - 2,8 - dicarboxy - 5-(2 - hydroxypropoxy) - 4H,10H - benzo (1,2 - b: 3,4 - b') dipyrans.
42. 4,6 - Dioxo - 2,8 - dicarboxy - 5-methyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
43. 4,6 - Dioxo - 2,8 - dicarboxy - 5-methyl - 3,7 - dimethyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
44. 4,6 - Dioxo - 2,8 - dicarboxy - 10-amino - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
45. 4,6 - Dioxo - 2,8 - dicarboxy - 10-acetylamino - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
46. 4,6 - Dioxo - 2,8 - dicarboxy - 5-methyl - 10 - ethyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
47. 4,6 - Dioxo - 2,8 - dicarboxy - 10-methoxy - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
48. 4,6 - Dioxo - 2,8 - dicarboxy - 10-hydroxy - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
49. 4,6 - Dioxo - 2,8 - dicarboxy - 10-bromo - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
50. 4,6 - Dioxo - 2,8 - dicarboxy - 5-methyl - 10 - ethoxyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
51. 4,6 - Dioxo - 2,8 - dicarboxy - 5-hydroxy - 10 - ethyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
52. 4,6 - Dioxo - 2,8 - dicarboxy - 5,10-diethyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
53. 4,6 - Dioxo - 2,8 - dicarboxy - 10-butyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
54. 4,6 - Dioxo - 2,8 - dicarboxy - 5,10-dipentyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
55. 4,6 - Dioxo - 2,8 - dicarboxy - 5,10-diethoxy - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
56. 4,6 - Dioxo - 2,8 - dicarboxy - 5-butoxybutoxy - 10 - methyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
57. 4,6 - Dioxo - 2,8 - dicarboxy - 5-phenylethoxy - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
58. 4,6 - Dioxo - 2,8 - dicarboxy - 5,10-di(2 - hydroxyethoxy) - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
59. 4,6 - Dioxo - 2,8 - dicarboxy - 3,7-dimethyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.
60. 4,6 - Dioxo - 2,8 - dicarboxy - 3,7-diethoxy - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyrans.





b') dipyran.

61. 4,6 - Dioxo - 2,8 - dicarboxy - 5,10-dibromo - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyran.

5 62. 4,6 - Dioxo - 2,8 - dicarboxy - 5-methoxy - 10 - (1 - hydroxyethyl) - 4H,6H-benzo (1,2 - b: 5,4 - b') dipyran.

63. 4,6 - Dioxo - 2,8 - dicarboxy - 10-ethoxymethyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyran.

10 64. 4,6 - Dioxo - 2,8 - dicarboxy - 10-hydroxymethyl - 4H,6H - benzo (1,2 - b: 5,4 - b') dipyran.

65. 4,6 - Dioxo - 2,8 - dicarboxy - 5-(2 - hydroxypropoxy) - 10 - ethyl - 4H,6H-benzo (1,2 - b: 5,4 - b') dipyran.

15 66. A compound according to any of the preceding claims in the form of a pharmaceutically acceptable salt, ester or amide thereof.

20 67. A compound according to Claim 66, wherein the compound is in the form of a pharmaceutically acceptable salt thereof.

68. A compound according to claim 67 wherein the salt is a sodium salt.

25 69. A compound according to Claim 1 and substantially as hereinbefore described.

70. A pharmaceutical composition comprising, as active ingredient, a compound according to any one of the preceding claims in combination with a pharmaceutically acceptable diluent or carrier.

30 71. A composition according to Claim 70, wherein the active ingredient is in water soluble form.

35 72. A composition according to Claim 70 or Claim 71, wherein the compound is in a form suitable for administration by inhalation.

40 73. A composition according to any one of Claims 70 to 72 and comprising a solution or suspension of the active ingredient in a liquified propellant medium.

45 74. A composition according to any one of Claims 70 to 73 comprising a bronchodilator.

50 75. A composition according to Claim 74, wherein the bronchodilator comprises isoprenaline, adrenaline, orciprenaline, isoetharine or a salt thereof.

76. A composition according to Claim 75, wherein the bronchodilator is isoprenaline sulphate.

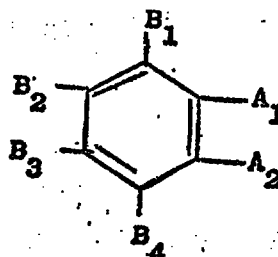
55 77. A composition according to any one of Claims 74 to 76, wherein the bronchodilator is present as a minor proportion of the active ingredient.

78. A pharmaceutical composition substantially as hereinbefore described.

60 79. A pharmaceutical composition substantially as hereinbefore described in Example 16.

80. A process for the production of a compound of formula I, as defined in Claim 1, or a pharmaceutically acceptable derivative

thereof, which comprises cyclisation of a compound of formula,



wherein B₁, B₂, B₃ and B₄ have the same significances as P, Q, R and T in Claim 1, save that one or more adjacent pairs of B₁, B₂, B₃ and B₄ represent the pair of groups A₁ and A₂,

A₁ and A₂ are the pairs of groups

1) —COCHR, COCOR¹¹ and —OM, or

11) —H and —O—C(COOH)=CR, COOH

M is hydrogen, an alkali metal or an alkyl group,

R₁ is as defined in Claim 1, and

R¹¹ is an —OH group, or a group which may be hydrolysed to an —OH group,

and if desired or necessary converting the compound of formula I to a pharmaceutically acceptable derivative thereof.

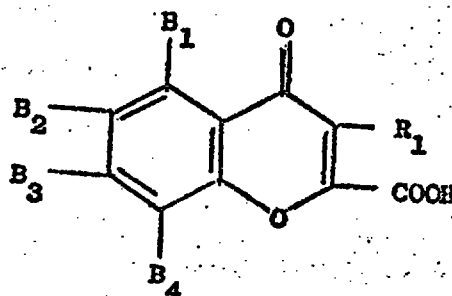
81. A process according to part 1) of the Claim 80, wherein the cyclisation is carried out under acidic conditions.

82. A process according to part II) of the Claim 80, wherein the cyclisation is carried out in the presence of a dehydrating agent and under anhydrous conditions.

83. A process according to part II) of the Claim 80, wherein the cyclisation is effected by converting the carboxy groups to acyl chloride groups and subjecting the resulting acyl chloride to an intramolecular Friedel Crafts reaction.

84. A process according to any one of the Claims 80 to 83, wherein all the pairs of groups A₁ to A₂ are the same.

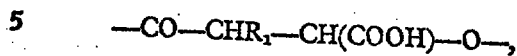
85. A process for the production of a compound of formula I, as defined in Claim 16, or a pharmaceutically acceptable derivative thereof, which comprises dehydrogenating a compound of formula XII,



XII

wherein B₁, B₂, B₃ and B₄ have the same

significances as P, Q, R and T in Claim 1, save that,
one or more adjacent pairs of B₁, B₂, B₃ and B₄ represent the chain



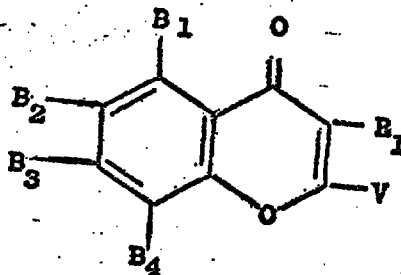
and

R₁ is as defined in Claim 1,
and if desired or necessary converting the compound of formula I to a pharmaceutically acceptable derivative thereof.

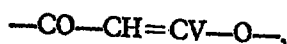
86. A process according to Claim 85, wherein the dehydrogenation is carried out using as dehydrogenation agent selenium dioxide, palladium black or chloranil, or by bromination followed by dehydrobromination of the compound of formula II.

87. A process for the production of a compound of formula I, as defined in Claim 1, or a pharmaceutically acceptable derivative thereof, which comprises oxidising or hydrolysing a compound of formula VII,

VII



wherein B₁, B₂, B₃ and B₄ have the same significances as P, Q, R and T in Claim 1 save that,
one or more adjacent pairs of B₁, B₂, B₃ and B₄ represent the chain



and

V represents a group oxidisable or hydrolysable to a $-\text{COOH}$ group,
and if desired converting the compound of formula I to a pharmaceutically acceptable derivative thereof.

88. A process according to Claim 87, wherein the group $-\text{V}$ is an amide, nitrile, ester, substituted or unsubstituted alkyl, acyl, alkenyl or arylalkenyl group.

89. A process according to either of Claims 87 or 88, wherein the group $-\text{V}$ is an ester group.

90. A process according to Claim 88, wherein the group $-\text{V}$ is a methyl or a styryl group.

91. A process for the production of a pharmaceutically acceptable salt of a compound of formula I, as defined in Claim 1, which comprises converting a compound of formula I, a different salt thereof or an ester thereof to the desired salt.

92. A process according to Claim 91, which comprises reacting a compound of formula I, or an ester thereof, with an appropriate base.

93. A process according to either of Claims 91 or 92, wherein the pharmaceutically acceptable salt is an alkali-metal or an alkaline earth metal salt.

94. A process according to Claim 93, wherein the salt is a sodium salt.

95. Processes for the production of a compound of formula I, as defined in Claim 1, and pharmaceutically acceptable derivatives thereof, substantially as hereinbefore described.

96. Processes for the production of a compound of formula I, as defined in Claim 1, and pharmaceutically acceptable derivatives thereof, substantially as hereinbefore described in any one of Examples 1 to 13.

97. A compound of formula I, as defined in Claim 1, or a pharmaceutically acceptable derivative thereof, whenever produced by a process according to any one of Claims 80 to 96.

F. MURPHY,
Agent for the Applicants,
Fisons Limited,
Harvest House,
Felixstowe,
Suffolk.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1971.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

