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3,056,812

STEROID 21-PYROPHOSPHATE ESTERS

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17 Claims. (Cl. 260—397.45)

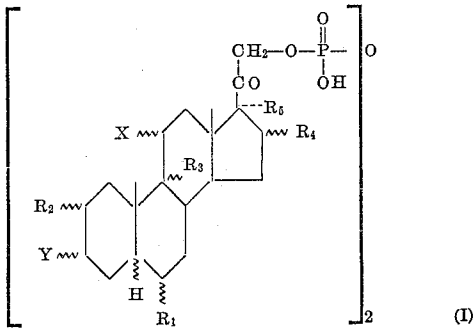
This invention is concerned with new steroid derivatives and their preparation.

Orthophosphoric acid esters of certain adrenocortical and/or anti-inflammatory steroids, wherein the ester grouping is at the 21-position, are known. Such compounds possess the advantage over the corresponding steroid alcohols themselves of improved water solubility particularly in the form of their alkali metal or amine salts and, hence, have peen proposed for use in pharmaceutical formulations wherein water solubility of the steroid derivative is desired.

It has now been found that the pyrophosphoric acid 21-esters of adrenocortical and/or anti-inflammatory steroids, and other physiologically active steriods have marked advantages as compared with the corresponding orthophosphoric acid esters.

In the first place, the pyrophosphoric acid esters (in the form of their water-soluble salts) are in general more stable than the corresponding orthophosphoric acid esters in aqueous solution and remain stable over a greater pH range. Secondly, the 21-pyrophosphate esters of the present invention possess in many cases a significantly higher physiological activity compared with the corresponding orthophosphoric acid esters, particularly on oral administration. Further, the pyrophosphoric acid esters show more prolonged activity in some cases compared with the corresponding orthophosphoric acid esters.

According to the invention, there are provided as new compounds 21-pyrophosphate esters and salts thereof of adrenocortical and/or anti-inflammatory steroids. Representative examples of such compounds as well as useful intermediates for the preparation thereof are compounds of the general formula:



(I)

in which

R_1 is a hydrogen or a fluorine atom or an alkyl group containing 1–6 carbon atoms;

R_2 is a hydrogen atom or an alkyl group containing 1–6 carbon atoms;

R_3 is a hydrogen or a halogen atom, particularly a fluorine or chlorine atom;

R_4 is a hydrogen atom or a hydroxy, acyloxy or alkyl group contining 1–6 carbon atoms.

R_5 is a hydroxy or acyloxy group;

X is a hydroxy group or a ketonic oxygen atom, or (where R_3 is halogen), a halogen atom, particularly a chlorine atom, and

Y is a hydroxy or acyloxy group or a ketonic oxygen atom,

and the corresponding Δ^1, Δ^4, $\Delta^{1,4}$ and $\Delta^{5(6)}$ compounds and salts of all such compounds, especially alkali metal, alkaline earth metal and ammonium salts and salts with organic bases.

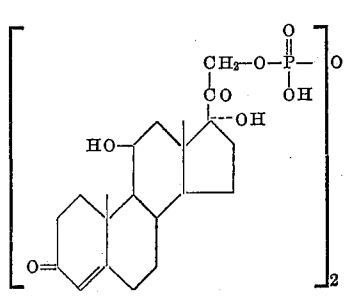
The new compounds according to the general Formula I, as will be seen, include pyrophosphate esters not only of compounds having adrenocortical and/or anti-inflammatory activity but also pyrophosphate esters which can readily be converted to compounds having such activity. Thus, for example, in the production of compounds of the above general formula having adrenocortical and/or anti-inflammatory activity, one may start with a known active 21-hydroxy compound and merely form the 21-pyrophosphate thereof; alternatively, one may start with an intermediate for the desired active 21-hydroxy steroid, e.g. a substance having a saturated ring A, form the pyrophosphate of such intermediate and convert such intermediate pyrophosphate into an active pyrophosphate. The above general formula hence covers the 21-pyrophosphates of compounds which have adrenocortical and/or anti-inflammatory activity or which can be converted into compounds having such activity by known methods.

Particularly valuable compounds according to the invention are adrenocortical steroids, namely those having a double bond at the 4:5-position or double bonds at the 1:2- and 4:5-positions, a keto group at the 3-position, a hydroxy or keto group at the 11-position and a hydroxy group at the 17-position. Such steroids may also have alkyl (α or β) substituents, e.g. methyl or ethyl groups, at the 2 and/or 6-positions and/or 16-position, and/or halogen, e.g. fluorine, chlorine or bromine at the 9-position, and/or fluorine at the 6-position and/or a hydroxy group at the 16-position. Further useful compounds are those having chlorine atoms at the 9- and 11-positions. Such substituents are known to modify the properties of adrenocortical or anti-inflammatory steroids.

The compounds according to the invention are especially valuable as their water-soluble salts, especially the salts of alkali metals, particularly sodium, the water-solubility of such salts being, in general, greater than that of the parent pyrophosphoric acid ester. It may be useful to form water-insoluble salts of the pyrophosphate compounds according to the invention with organic bases, where for example an insoluble compound is required for administration. Such water-insoluble salts are also often of use in the purification of the pyrophosphates.

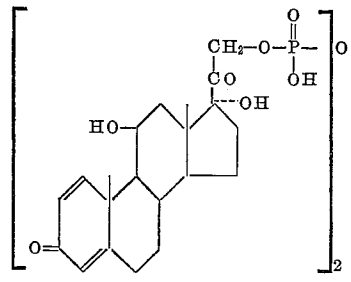
Two compounds of particular interest according to the invention, by reason of their especially favourable adrenocortical properties, are P^1P^2-bishydrocortisone pyrophosphate [i.e. P^1P^2-bis-(11β,17α-dihydroxy-3,20-dioxopregn-4-en-21-yl) pyrophosphate] and P^1P^2-bisprednisolone pyrophosphate [i.e. P^1P^2-bis-(11β,17α-dihydroxy-3,20-dioxopregna-1,4-dien-21-yl) pyrophosphate], together with the salts of these compounds, especially alkali metal, alkaline earth metal and ammonium salts and salts with organic bases. P^1P^2-bisprednisolone pyrophosphate in particular shows an appreciably higher activity than the corresponding orthophosphate.

P^1P^2-bishydrocortisone pyrophosphate has the formula:



(II)

P^1P^2-bisprednisolone pyrophosphate has the formula:



(III)

The pyrophosphates of Formulae II and III are preferably used in therapy in the form of their disodium salts which, in both cases, are conveniently obtained as the tetrahydrate. The disodium salt of the pyrophosphate of Formula II (as the tetrahydrate) has the following characteristics:
M.P. 200–203° C.; $[\alpha]_D$+112.5° (c. 0.74 in H_2O); λ max. (in H_2O): 247 mμ;

$E^{1\%}_{1cm}$ 279

and the disodium salt of the pyrophosphate of Formula III (as the tetrahydrate) has the following characteristics: M.P. 215–217° C.; $[\alpha]_D$+101.3° (c., 0.76 in H_2O); λ max. (in H_2O): 247 mμ;

$E^{1\%}_{1cm}$ 284

It will be appreciated that these characteristics have been obtained using the purest material available to us and may be liable to variation.

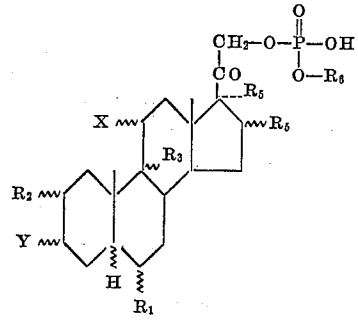
Active pyrophosphates of Formula I above may be administered in any convenient manner. In general, they may be formulated in aqueous solutions, if necessary in the form of salts, either for injection or for topical application, for example as eye or ear drops, or skin lotions. Alternatively, they may be formulated, together with a pharmaceutical carrier, for example as oral preparations, e.g. as tablets, capsules, syrups, elixirs, etc. They may also be formulated as ointments, lotions, suppositories or aerosols.

As a further feature of the invention, therefore, there is provided a pharmaceutical composition comprising one or more active pyrophosphates or their salts (as described above) and a pharmaceutical carrier or diluent.

The pyrophosphates of general Formula I may be prepared by one of the following three methods of which the first method has given the best results.

Method I

The starting material in this method is a steroid 21-aralkyl hydrogen phosphate having the general formula:



(IV)

where R_6 is an aralkyl group, e.g. benzyl or a substituted benzyl group and R_1–R_5, X and Y have the meanings defined above, or a Δ^1, Δ^4, $\Delta^{1,4}$ or $\Delta^{5(6)}$ derivative thereof. This starting material is conveniently obtained by acidification of a corresponding salt thereof, e.g. an alkali metal salt, for example either by direct acidification of an aqueous solution of the alkali metal salt and extraction of the free acid into an organic solvent or by passage of an aqueous alcoholic solution of the alkali metal salt through a column of a cation exchange resin in the H^+ form and isolation of the free acid from the eluate by evaporation or extraction with a solvent. The free acid can be isolated but it is convenient to use, for the extraction, the solvent in which the subsequent reaction is to be performed and to work with the acid in solution throughout.

The steroid 21-aralkyl hydrogen phosphates and their alkali metal salts used as starting materials for this method form the subject of copending application Ser. No. 774,580 filed November 18, 1958 and assigned to the assignee of the present application now Patent No. 2,950,298.

In the first step in the production of the pyrophosphate in this method, two molecules of the steroid 21-aralkyl hydrogen phosphate are condensed to form an intermediate pyrophosphate using a carbodiimide of the general formula:

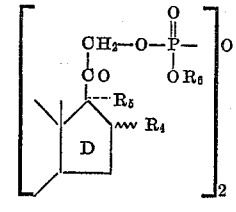
$$R^7N{:}C{:}NR^8$$

where R^7 and R^8 are the same or are different and each represents an alkyl, cycloalkyl, aryl or aralkyl group, preferably in an inert organic solvent, e.g. ethyl acetate. This condensation may be carried out at room temperature. The progress of the reaction can be followed by the change in pH from the acid side towards neutrality. The pH does not necessarily reach 7 but the attainment of a constant pH is an indication of the completion of the reaction. The nature of the solvent used is not very critical although alcoholic solvents may lead to undesirable side products. Dicyclohexylcarbodiimide is the preferred carbodiimide in view of the fact that it forms dicyclohexylurea which can readily be separated from the desired pyrophosphate intermediate by virtue of its sparing solubility.

An alternative step of converting the steroid aralkyl hydrogen phosphate to the desired pyrophosphate intermediate is to heat the phosphate compound with cyanamide or a mono- or di-alkylcyanamide, e.g. dimethylcyanamide, if desired in a solvent medium, e.g. acetonitrile, or in an excess of cyanamide compound itself.

This method is not readily applicable to the treatment of 9,11-dichloro compounds and 9α-chloro-11β-hydroxy compounds since such compounds are liable to degradation under the conditions specified.

The pyrophosphate intermediate formed at this stage has (in the D ring) the structure:



(V)

and to obtain the desired pyrophosphate end product this intermediate must be de-aralkylated. This may be effected by treatment with a salt dissolved in an organic solvent (except with compounds having an unsaturated A-ring and 9,11-dichloro substituents) e.g. with sodium iodide in acetone or lithium chloride in β-ethoxyethanol, or by hydrogenolysis (except when ring A is unsaturated and/or 9,11-dichloro compounds are used).

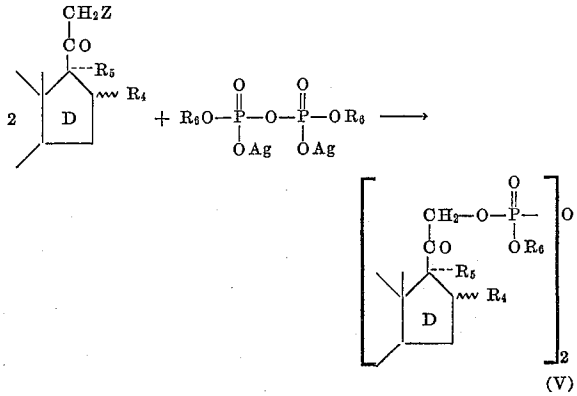
The pyrophosphate may be obtained as a salt e.g. treatment of the pyrophosphate ester intermediate with sodium iodide in boiling acetone for 5 hours leads to the disodium pyrophosphate end product which is filtered off and may be freed of iodine-containing impurities by precipitation from aqueous solution with acetone or by extraction of the impurities with ethanol.

It will be appreciated that the foregoing Method I can be modified in that one may start with an intermediate for the desired end product, form an intermediate aralkyl orthophosphate ester or diaralkyl pyrophosphate ester thereof, convert such ester to an aralkyl orthophosphate ester or di-aralkyl pyrophosphate ester corresponding to the desired pyrophosphate end product which ester is then converted as described to said end product.

Another method for the production of the compounds according to the invention, although not quite so efficient as Method I will now be described.

Method II

This method involves condensation of a 21-halogeno steroid (as the iodide, chloride or bromide) with a P^1P^2 diaralkyl disilver pyrophosphate to form an intermediate pyrophosphate, as follows:



(V)

where Z is iodine, chlorine or bromine and R_4–R_6 have the meanings defined above.

This reaction is preferably carried out in an inert solvetn medium, e.g. dimethylacetamide (except where 9,11-dichloro and 9α-chloro-11β-hydroxy compounds are used). The resultant pyrophosphtae intermediate V is then diaralkylated as described above.

It will be appreciated that the foregoing Method II can be modified in that one can form a diaralkyl pyrophosphate ester of an intermediate of a desired compound, convert such intermediate into a diaralkyl pyrophosphate ester of the desired compound which is then converted to the desired pyrophosphate.

Method III

This method involves condensation of two molecules of the corresponding orthophosphate ester in the presence of a carbodiimide (e.g. dicyclohexyl-carbodiimide) of the general formula:

$$R^7N{:}C{:}NR^8$$

(where R^7 and R^8 have the meanings defined above), or with cyanamide or a mono- or dialkylcyanamide.

When using a carbodiimide it is preferred to carry out the reaction in the presence of a strong tertiary base e.g. a trialkylamine such as tributylamine in a convenient organic solvent, e.g. pyridine, at room temperature. The course of the reaction can conveniently be followed by paper chromatography by observing the disappearance of the orthophosphate spot and the appearance of the pyrophosphate spot.

When using cyanamide or a mono- or dialkylcyanamide, preferably dimethylcyanamide, the reaction may be carried out in the presence of added inert organic solvent although preferably the cyanamide or susbtituted cyanamide also functions as solvent. A strong tertiary base, e.g. tributylamine, may also be present. The reaction takes place by heating for example at a temperature of approximately 100° C.

This process may also be carried out by reacting an orthophosphate ester mono-sodium salt with a carbodiimide in the presence of an organic solvent, preferably dimethylacetamide, but in the absence of a strong base.

Processes of this type are not suitable for the treatment of 9,11-dichloro and 9α-chloro-11β-hydroxy compounds when amines or cyanamides are included in the reaction media as such compounds are liable to degradation under such circumstances.

Salts of the compounds according to the invention with organic bases may be prepared in any convenient way, for example by treating the appropriate alkali metal or ammonium salt with a salt of the appropriate organic base.

In order that the invention may be well understood, the following examples are given by way of illustration only:

EXAMPLE 1

(*a*) *Prednisolone 21-dibenzyl-phosphate.*—11β,17α-dihydroxy-21-iodopregna-1,4-diene-3,20-dione (25 g.) and silver dibenzyl phosphate (25 g.) were boiled under reflux for 2.5 hours in acetonitrile (1000 ml.). The solvent was removed by distillation, finally in vacuo, and the residue boiled twice with ethyl acetate (1500 ml. then 1000 ml.). The insoluble silver salts were removed by filtration through kieselguhr and the filtrate was concentrated to give prednisolone 21-dibenzyl phosphate in three crops, 21.5 g., M.P. 196–197° C. (from 600 ml.), 3.7 g., M.P. 183–184° C. (from 70 ml.) and 1.8 g. M.P. 182–183° C. (from 10 ml.). Total yield 79.7%.

Further recrystallisation from ethyl acetate gave the analytical sample, M.P. 197–199° C. $[\alpha]_D$+86.5° (c., 0.68 in $CHCl_3$). (Found: C, 68.3; H, 6.9; P, 5.3. $C_{35}H_{41}O_8P$ requires C, 67.7; H, 6.7; P, 5.0%.)

(*b*) *Prednisolone 21-benzyl sodium phosphate.*—Prednisolone 21-dibenzyl phosphate (3.0 g.) and sodium iodide (3.0 g.) were boiled under reflux for 6 hours in acetone (300 ml.). The sodium salt (2.49 g.), which began to separate after 20 mins., was filtered from the cooled suspension and washed with acetone.

Recrystallisation of 2.4 g. from aqueous acetone gave the 21-benzyl sodium phosphate (1.9 g., 73.5%) as a monohydrate, M.P. 236–238° C., $[\alpha]_D$+88.1° (c., 0.66 in H_2O)

λ max. (in H_2O): 246.5 mμ; $E^{1\%}_{1\,cm.}$ 277

(Found: C, 58.7; H, 6.5; P, 5.9. $C_{28}H_{34}O_8PNa.H_2O$ requires C, 58.9; H, 6.4; P, 5.4%).

(*c*) *Pednisolone 21-benzyl hydrogen phosphate.*—The sodium salt (1.0 g.) in water (5 ml.) was acidified with 2 N-hydrochloric acid (5 ml.), and the resulting suspension extracted with ethyl acetate (10 ml., then 5×5 ml.) and the extract washed with a little water. The combined extracts were dried for 30 mins. over magnesium sulphate and the drying agent removed by filtration. This solution of prednisolone 21-benzyl hydrogen phosphate was usually used for the next stage, although the acid could be obtained as a solid, M.P. 135–136° C. by removal of solvent and evaporation of a solution of the residue in ether. The solid analysed as a hemihydrate. (Found: C, 62.6; H, 7.15; P, 5.5. $C_{28}H_{35}O_8P.\frac{1}{2}H_2O$ requires C, 62.3; H, 6.7; P, 5.7%.)

(*d*) *P^1P^2-bisprednisolone disodium pyrophosphate.*—A solution of prednisolone benzyl hydrogen phosphate (from 20 g. of the sodium salt) in ethyl acetate (800 ml.) was mixed at room temperature with a solution of dicyclohexylcarbodiimide (8.4 g.) in ethyl acetate (200 ml.). After about 30 mins. the solution was only weakly acidic and acetic acid (10 ml.) was then added to decompose the excess carbodiimide. The solvent was removed in vacuo from the suspension, and the residue extracted with boiling acetone, which left most of the dicyclohexylurea undissolved. On cooling the acetone solution a small amount of the urea was deposited. This

was removed by filtration, and the solution of crude P^1P^2-bisprednisolone dibenzyl pyrophosphate in acetone (1500 ml.) was boiled under reflux for 5 hours with sodium iodide (20 g.). The precipitated sodium salt (13.3 g.) was freed from contaminating iodide by precipitation from water (8 ml.) with acetone (750 ml.) and heating the resultant solid in suspension in ethanol (about 200 ml.). Filtration then gave the disodium pyrophosphate (8.9 g., about 50% overall) as a tetrahydrate, M.P. 215–217° C., $[\alpha]_D$+101.3° (c., 0.76 in H_2O.)

λ max. (in H_2O): 247 mμ; $E^{1\%}_{1cm.}$ 284

(Found: C, 51.9; H, 6.6; P, 6.7; $C_{42}H_{54}O_{15}P_2Na_2.4H_2O$ requires C, 51.5; H, 6.4; P, 6.3%).

EXAMPLE 2

(*a*) *Hydrocortisone 21-benzyl hydrogen phosphate.*—The corresponding sodium salt (0.5 g.) in water (10 ml.) was acidified with 2 N-hydrochloric acid (2 ml.). The initially gummy deposit was filtered after 18 hours at 0° C. and recrystallised from isopropyl ether-acetone by addition of hexane to give the 21-benzyl hydrogen phosphate, M.P. 161–163° C.,

λ max. (in aq. $NaHCO_3$): 248 mμ; $E^{1\%}_{1cm.}$ 313

(Found: C, 63.6; H, 7.0; P, 6.1. $C_{28}H_{37}O_8$ requires C, 63.1; H, 7.2; P, 5.8%.)

(*b*) *P^1P^2-bishydrocortisone dibenzyl pyrophosphate.*—Hydrocortisone 21-benzyl sodium phosphate (4.0 g.) in water (20 ml.) was acidified with 2 N-hydrochloric acid (20 ml.) and the precipitated acid extracted into ethyl acetate (6 x 20 ml.) and the extract washed with a little water. The extract was dried over magnesium sulphate for 30 mins. and the drying agent removed by filtration.

The solution of hydrocortisone benzyl hydrogen phosphate in ethyl acetate (160 ml.) was treated at room temperature with dicyclohexylcarbodiimide (1.6 g.) and after 10 minutes acetic acid (2 ml.) was added to destroy the excess of carbodiimide. After 30 minutes the solvent was removed in vacuo, and the solid residue extracted with ethyl acetate (2 x 20 ml.). The extract was washed with aqueous sodium hydrogen carbonate and water, and the dried solution concentrated to about 10 ml. P^1P^2-bishydrocortisone dibenzyl pyrophosphate slowly separated as an amorphous powder (3.0 g.),

λ max. (in EtOH): 239.5 mμ; $E^{1\%}_{1cm.}$ 294

(Found: C, 64.7; H, 7.4; P, 6.3. $C_{56}H_{72}O_{15}P_2$ requires C, 64.3; H, 6.9; P, 5.9%.)

(*c*) *P^1P^2-bishydrocortisone disodium pyrophosphate.*—P^1P^2-bishydrocortisone dibenzyl pyrophosphate (2.5 g.) and sodium iodide (3.0 g.) were boiled under reflux in acetone (200 ml.) for 5 hours. The precipitated disodium salt was collected by filtration, and after precipitation from water (3 ml.) with acetone (80 ml.) and heating in suspension in ethanol it was obtained as a halogen-free solid (about 50% from hydrocortisone benzyl sodium phosphate).

A sample for analysis showed M.P. 200–203° C., $[\alpha]_D$+112.5° (c., 0.74 in H_2O),

λ max. (H_2O): 247 mμ; $E^{1\%}_{1cm.}$ 279

and analysed as a tetrahydrate. (Found: C, 51.5; H, 7.1; P, 6.0. $C_{42}H_{58}O_{15}P_2Na_2.4H_2O$ requires C, 51.3; H, 6.8; P, 6.3%.)

EXAMPLE 3

Reaction of 11β,17α-dihydroxy-21-iodopregna-1,4-diene-3,20-dione with P^1P^2-dibenzyl disilver pyrophosphate, followed by sodium iodide treatment.—The 21-iodo compound (133 mg.) and the silver salt (100 mg.) were heated to 100° C. for 1 hour in dimethylacetamide (5 ml.). The solvent was removed in vacuo and the residue extracted with chloroform. The chloroform extract was washed with dilute nitric acid, aqueous sodium hydrogen carbonate, and water. Removal of solvent from the dried chloroform solution left a gum (about 200 mg.) which was boiled under reflux for 1 hour with sodium iodide (200 mg.) in acetone (20 ml.). The sodium salt (9 mg.) which separated was identified as P^1P^2-bisprednisolone disodium pyrophosphate by its infra-red spectrum and by its behaviour on a paper chromatogram.

EXAMPLE 4

P^1P^2-bisprednisolone pyrophosphate from prednisolene 21-disodium phosphate using dicyclohexylcarbodiimide.—Prednisolone dihydrogen phosphate was prepared from the disodium salt by passing a solution in methanol through a column of Zeo-karb 225 (H^+ form) and evaporation of the eluate in vacuo. The acid (1.0 g.) and dicyclohexylcarbodiimide (2.35 g.) were dissolved in dry pyridine (50 ml.) and tri-n-butylamine (2 ml.) and kept at room temperature for 28 hours. Paper chromatography of the reaction mixture showed that the conversion of phosphate to pyrophosphate was then virtually complete. Removal of solvent in vacuo left a gum, which was shaken in 50% aqueous ethanol (40 ml.) with Zeo-karb 225 (H^+ form, ca. 40 g.) until the pH of the solution fell to 4. The solution was filtered from resin and precipitated dicyclohexylurea, and the solids washed with aqueous alcohol. The filtrate was passed through a column of Zeo-karb 225 (H^+ form, 25 g.) and elution with aqueous alcohol continued until the eluate was no longer acidic. Titration of the eluate with aqueous sodium hydroxide showed no buffering in the region pH 4–9, indicating the absence of the primary phosphate ester. Paper chromatography of the solution showed a single spot of the correct Rf. value for P^1P^2-bisprednisolone pyrophosphate.

The alcohol was removed from the solution in vacuo, and N,N'-dibenzylethylenediamine diacetate (1.0 g.) was added to the aqueous residue, to precipitate the pyrophosphate as its base salt (1.1 g.), M.P. 120° C. then 172–182° C. After crystallisation from isopropanol P^1P^2-bisprednisolone pyrophosphate N,N'-dibenzylethylenediamine salt had M.P. 182–186° C.

EXAMPLE 5

P^1P^2-bisprednisolone pyrophosphate from prednisolone 21-dihydrogen phosphate, using dimethylcyanamide.—Prednisolone 21-dihydrogen phosphate (1.0 g.) was heated at 100° C. for 3 hours 30 mins. in solution in dimethylcyanamide (10 ml.) and tri-n-butylamine (1 ml.). The volatile components were removed in vacuo and the residue was dissolved in 50% aqueous ethanol and passed through a column of Zeo-karb 225 (H^+ form). Paper chromatography and titration of the eluate with sodium hydroxide indicated that ca. 75% of the starting material had been converted into the required pyrophosphate.

Example 6

P^1P^2-bisprednisolone pyrophosphate from prednisolone 21-sodium hydrogen phosphate with dicyclohexylcarbodiimide.—Prednisolone 21-sodium hydrogen phosphate was prepared by the addition of Zeo-karb 225 (H^+ form) to a solution of the disodium salt in water until the pH of the monosodium salt was reached, followed by evaporation of the filtered solution to dryness in vacuo.

The monosodium salt (1.0 g.) in solution in dimethylacetamide (10 ml.) was added to a solution of dicyclohexylcarbodiimide (2.2 g.) in dimethylacetamide (10 ml.) and the mixture allowed to stand at room temperature for five and a half days. The solvent was removed in vacuo, and the residue in ethanol (20 ml.) and water (10 ml.) was treated with sufficient Zeo-karb 225 (H^+ form) to make it acidic. The suspension was filtered and the filtrate was passed through a column of Zeo-karb 225 (H^+ form) (20 g.). Elution with aqueous alcohol was continued until the eluate was no longer acidic, and the

eluate was titrated with 2 N aqueous sodium hydroxide to pH 6. The solvent was removed in vacuo and acetone was added to the residue to give crude P^1P^2-bisprednisolone disodium pyrophosphate as a solid (0.78 g.), $[\alpha]_D$ +88.5° (c. 1.09 in H_2O). Electrometric titration of the acid obtained from this salt showed the presence of about 10% of the primary 21-disodium phosphate.

Example 7

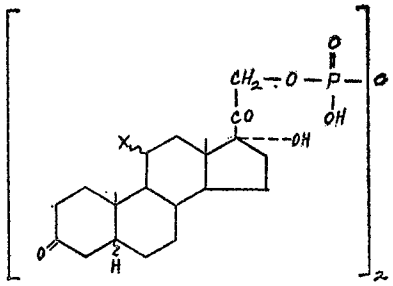
P^1P^2-bisprednisolone N,N'-dibenzylethylenediamine pyrophosphate.—The pyrophosphate disodium salt (220 mg.) in water (1.5 ml.) was treated with a solution of N,N'-dibenzylethylenediamine diacetate (220 mg.) in water (2 ml.) at 0° C. The white crystalline precipitate (230 mg.) of the base salt was filtered off, washed with a little water and dried in vacuo. It had M.P. 186–198° C. (decomp.),

λ max. (ethanol): 241.5 mμ; $E^{1\%}_{1cm.}$ 240

Analysis indicated that the salt was a dihydrate. (Found: C, 61.0; H, 7.4; N, 2.7; P, 5.8. $C_{58}H_{74}O_{15}N_2P_2.2H_2O$ requires C, 61.2; H, 6.9; N, 2.5; P, 5.45%).

I claim:

1. A compound selected from the group consisting of pyrophosphate esters having the general formula:



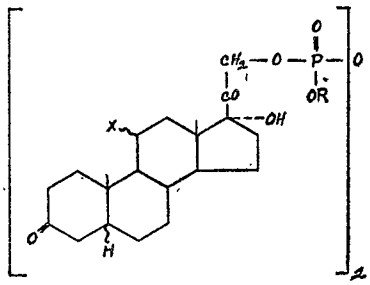
in which X is selected from the group consisting of hydroxy and a ketonic oxygen atom; the corresponding Δ^4 compounds; the corresponding $\Delta^{1,4}$ compounds; and salts of all such compounds said salts being selected from the group consisting of alkali metal and N,N'-dibenzylethylenediamine salts.

2. The compounds of claim 1 which are sodium salts.

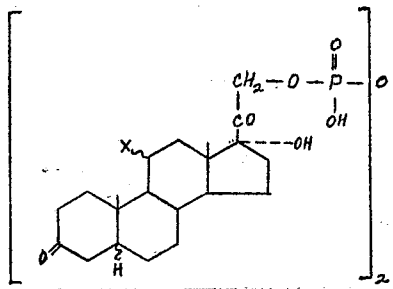
3. The compounds selected from the group consisting of P^1P^2-bishydrocortisone pyrophosphate and salts thereof, said salts being selected from the group consisting of alkali metal and N,N'-dibenzylethylenediamine salts.

4. The compounds selected from the group consisting of P^1P^2-bisprednisolone pyrophosphate and salts thereof, said salts being selected from the group consisting of alkali metal and N,N'-dibenzylethylenediamine salts.

5. A process for the production of alkali metal salts of compounds selected from the group consisting of compounds of the general formula:



in which X is selected from the group consisting of hydroxy and a ketonic oxygen atom; the corresponding Δ^4 compounds; and the corresponding $\Delta^{1,4}$ compounds which comprises the step of reacting with an alkali metal halide in the presence of an inert organic solvent a compound selected from the group consisting of compounds of the formula:



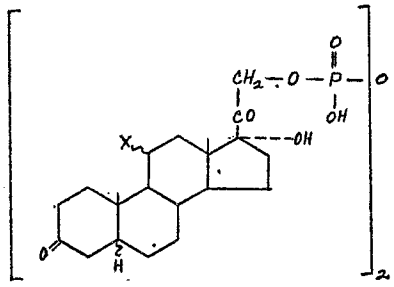
in which R is an aralkyl group; the corresponding Δ^4 compounds; and the corresponding $\Delta^{1,4}$ compounds.

6. A process as defined in claim 5 in which the alkali metal halide is lithium chloride.

7. A process as defined in claim 5 in which R is a benzyl group.

8. A process as defined in claim 5 in which the alkali metal halide is sodium iodide.

9. A process for the production of compounds of the general formula:



in which X is selected from the group consisting of hydroxy and a ketonic oxygen atom; the corresponding Δ^4 compounds; and the corresponding $\Delta^{1,4}$ compounds, which comprises the step of condensing 2 molecules of the corresponding orthophosphate in the presence of a carbodiimide of the general formula:

$$R^7N{:}C{:}NR^8$$

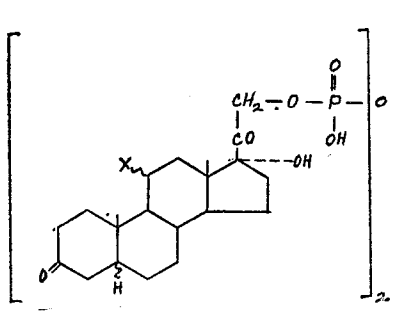
in which R^7 and R^8 are selected from the group consisting of alkyl, cycloalkyl, aryl and aralkyl groups.

10. A process as defined in claim 9 in which the carbodiimide is dicyclohexylcarbodiimide.

11. A process as defined in claim 9 in which the reaction is carried out in the presence of a strong tertiary base.

12. A process as defined in claim 11, in which the strong tertiary base is a trialkylamine.

13. A process for the production of compounds selected from the group consisting of compounds of the general formula:



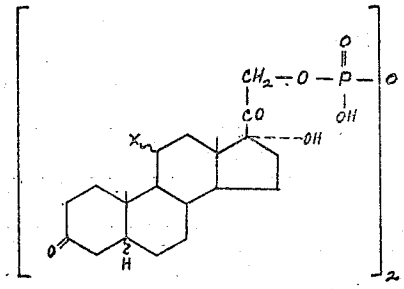
in which X is selected from the group consisting of hydroxy and a ketonic oxygen atom; the corresponding Δ^4 compounds; and the corresponding $\Delta^{1,4}$ compounds in which 2 molecules of the corresponding orthophosphate

are condensed in the presence of a compound selected from the group consisting of cyanamide and mono- and di-alkylcyanamides.

14. A process as defined in claim 13 in which the reaction is carried out in the presence of a strong tertiary base.

15. A process as defined in claim 14 in which the strong tertiary base is a trialkylamine.

16. A process for the production of compounds selected from the group consisting of compounds of the general formula:



in which X is selected from the group consisting of hydroxy and a ketonic oxygen atom; the corresponding Δ^4 compounds and the corresponding $\Delta^{1,4}$ compounds which comprises the step of reacting a mono-sodium salt of the corresponding orthophosphate with a carbodiimide of the general formula:

$$R^7N{:}C{:}NR^8$$

in which R^7 and R^8 are selected from the group consisting of alkyl, cycloalkyl, aryl and aralkyl groups.

17. A process as defined in claim 16 in which the carbodiimide is dicyclohexylcarbodiimide.

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