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SALTS OF STEROIDAL AMINO ACID ESTERS

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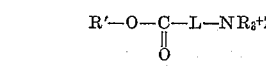
This invention relates to certain novel and useful steroid compounds. In particular it is concerned with salts of certain corticoid amino esters, which are particularly noteworthy because of their high therapeutic activity.

The compound hydrocortisone, several of its derivatives and some esters thereof are well known to have physiological activity as hormones of the cortical type. However, these new corticoid amino ester salts are unexpectedly characterized by enhanced therapeutic value. Furthermore, the compounds of the present invention are generally more water-soluble than hydrocortisone, hence they may be readily adminishered in the form of aqueous solutions.

The hydrocortisone molecule contains a hydroxyl group at the 21-position. As this is the only primary alcohol group in the molecule, it may readily be selectively esterified. Among the particularly valuable compounds of the present invention are salts of amino acid esters of hydrocortisone at this 21-position hydroxyl group. Also included within the concept of hydrocortisone amino acid ester salts are various other compounds which may be considered derivatives of the hydrocortisone nucleus, for instance salts of the amino acid esters of 9-alpha-fluorohydrocortisone and of hydrocortisone having a 14-alpha-hydroxy group in the nucleus.

Another particularly valuable class of compounds of this invention are salts of amino esters of prednisolone, also known as delta-1-dehydro-hydrocortisone. Prednisolone is described and claimed in the copending application Serial No. 483,842 filed January 24, 1955, by Gilbert M. Shull et al. As with hydrocortisone itself, valuable salts of amino acid esters of 9-fluoro prednisolones and 14-hydroxy prednisolones are included within the scope of the present invention. Fourteen-alpha-hydroxy prednisolone is described and claimed in the copending application Serial No. 484,828, now Pat. No. 2,932,606, filed January 28, 1955, by Gilbert M. Shull et al.

The new products are represented by the following formula

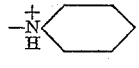


in which R′ is the steroid minus its 21-position hydroxyl group; L is chosen from the group consisting of

$$-(CH_2)_n-$$

$-C_6H_4-$, $-O-(CH_2)_n-$ and $-NH-(CH_2)_n-$, n being a number from 1 to 6; each R represents a member of the group consisting of hydrogen, alkyl, hydroxyalkyl, aminoalkyl, aryl and aralkyl, each such group containing up to ten carbon atoms; and Z^- is a "pharmacologically acceptable anion." The following illustrate some of the various formulas for NR_3^+:

$-N^+H_3$
$-N^+H(CH_3)_2$
$-N^+(C_2H_5)_3$
$-N^+(CH_3)_2CH_2-C_6H_5$
$-N^+(C_2H_5)_2CH_2-CH_2OH$
$-N^+(CH_3)_2CH_2-CH_2-NH_2$



The term "pharmacologically acceptable anion" has a

definite meaning to one skilled in the art. It is defined as a non-toxic anion of any of the simple acids commonly used in pharmacology to neutralize basic medicinal agents when a salt thereof is to be used therapeutically. These acids include, for example, hydrochloric, hydrobromic, hydroiodic, sulfuric, succinic and maleic. The pharmacological activity of the molecule is primarily a function of the cation, the anion serving chiefly to supply electrical neutrality.

As may be seen from inspection of the above formula for the compounds of this invention, they are salts of amino acid esters of the hydrocortisone type steroid, e.g. amino acid ester salts of hydrocortisone per se and its delta-1-dehydro derivative, and their various 14-hydroxylated and 9-fluoro substituted compounds. The new products possess the particular advantage, among others, of being more effective when applied topically. In fact, topical administration, especially for the treatment of skin diseases, is one of the prime values of this new class of compounds. In addition, because of the ionic nature of the bond between the ammonium function NR_3^+ and the anion Z^-, these compounds are water-soluble and therefore may be injected into patients in the desirable form of aqueous solution. This solution form is to be preferred to a crystal-suspension form, because solutions are easier to prepare, and easier to inject since a smaller needle can be used. The time between injection and response is also shorter when solutions are used. This is particularly true in view of the fact that solutions, but not suspensions, may be injected intravenously. Many physicians prefer aqueous solutions to oil solutions since they believe that the oil acts as a foreign body when injected.

Typical dosage forms generally comprise salves, ointments, aqueous solutions and the like containing the new ester salts and pharmaceutically acceptable fillers, carriers, vehicles, etc. and often other therapeutic agents as well. If desired, the new products may be administered alone or in combination with any of a variety of pharmaceutical carriers in a number of dosage forms, the compositions of which will be determined by standard pharmaceutical practices and the chosen route of administration. For example, it is possible to inject these compounds in aqueous solutions made isotonic by the addition of glucose or saline or buffered with non-toxic buffers. Filtration through a Seitz filter is a convenient method of sterilizing solutions to be injected, which, of course, must be sterile. Small amounts of preservatives, such as chlorobutanol, may also be added to maintain sterility.

The methods for preparing these compounds are illustrated in the examples given below. It is to be understood that many of these examples demonstrate a general method of preparation applicable not only to the particular compound being discussed in that example, but also to compounds of a similar chemical nature, for instance compounds differing only in the value of *"n"* in the formula given above.

There are, of course, variations in the effects of the compounds of this invention depending upon the particular substituents. These variations, however, occur only in the group attached to the steroid molecule through its 21-position hydroxyl group. For some surprising reason, changes here are effective to a relatively great degree in enhancing adrenocortical activity.

To summarize, the novel compounds of this invention are amino acid ester salts of hydrocortisone, 14-hydroxy-hydrocortisone, prednisolone, 14-hydroxy prednisolone and the 9-fluoro derivatives of these. They possess great physiological activity of the adrenocortical type, and are useful in the treatment of a wide variety of pathological conditions, especially those calling for anti-inflammatory therapy, for example skin afflictions and rheumatoid arthritis. They have the additional advantages of water-solu-

bility, rapidity of action and rapidity of absorption, and they may be administered in the form of aqueous solutions.

The following examples are given solely for the purpose of illustration and are not to be construed as limitations on this invention, many variations of which are possible without departing from the spirit or scope of the basic discovery here described, namely that of a group of new compounds in which a hydrocortisone-type molecule, made water-soluble by the addition at its 21-position hydroxyl group of a salt of an amino acid ester, has its physiological activity greatly enhanced.

EXAMPLE I

Hydrocortisone dimethylaminoacetate methochloride

To a solution of hydrocortisone in pyridine was added 2 molar equivalents of chloracetyl chloride. After 12 hours the chloracetate was isolated by precipitation with a large volume of dilute, acidified ice water. The filtered and dried chloroacetate was reacted in dimethylformamide solution with slightly more than 1 mole of trimethylamine. Careful dilution of the reaction medium resulted in the precipitation of the desired methochloride, which was characterized by anaylsis. The compound was found to be highly active therapeutically and readily soluble in water.

EXAMPLE II

Hydrocortisone beta-dimethylaminoethyl carbonate

A solution of 1.00 gram of hydrocortisone in 50 ml. of dioxane was added dropwise to a cooled, stirred solution of 0.5 grams of phosgene in 5 ml. of benzene containing 1 ml. of pyridine. The solution was stirred 2 hours at 25° C. and evaporated to dryness in vacuo. The residue was hydrocortisone chloroforate. It was treated with 2 ml. of beta-dimethylaminoethanol and allowed to stand 18 hours. Dilution with aqueous potassium carbonate precipitated the beta-dimethylaminoethyl carbonate, which was extracted with chloroform, and, after evaporation of the chloroform, recrystallized from methanol. The compound readily formed salts and quaternary ammonium compounds. For example, it was converted to the hydrobromide with ethereal hydrogen bromide and to the methiodide with methyl iodide.

EXAMPLE III

Hydrocortisone beta-diethylaminoethyl carbonate

Although the method of making this compound given in Example II is useful, the following method is preferred. One half gram of beta-chloroethyl chloroformate was added to a stirred, cooled solution of one gram of hydrocortisone in 5 ml. of pyridine and the solution allowed to stand 24 hours. It was then stirred into 20 ml. of ice cold 3 N sulfuric acid, and extracted three times with 15 ml. of chloroform. After washing with 1 N sulfuric acid, water, and sodium bicarbonate solution, the chloroform extract was dried over anhydrous sodium sulfate and evaporated to dryness in vacuo. Trituration of the residue with ether yielded the crystalline hydrocortisone beta-chloroethyl carbonate which was converted to the diethylaminoethyl carbonate by refluxing it with an alcoholic solution of diethylamine for 2 hours. The mixture was cooled, treated with saturated aqueous potassium carbonate and extracted with chloroform, which was then evaporated to give the product.

EXAMPLE IV

Hydrocortisone beta-diethylaminoethyl carbamate

One gram of hydrocortisone chloroformate, the preparation of which is shown in the first half of Example II, was treated with 2 ml. of beta-diethylaminoethylamine and allowed to stand for 18 hours. Dilution with aqueous potassium carbonate precipitated the beta-diethylaminoethyl carbamate, which was extracted with chloroform, and after evaporation of the chloroform, recrystallized from methanol. The compound readily formed salts and quaternary ammonium compounds. For example, it was converted to the hydrobromide with ethereal hydrogen bromide and to the methiodide with methyl iodide.

EXAMPLE V

Alternate preparation of hydrocortisone-beta-diethylaminoethyl carbamate

Although the method of Example IV is preferred, another method of making this compound is as follows. One gram of hydrocortisone was dissolved in 5 ml. of dimethylformamide and treated with 0.6 gram of beta-chloroethylisocyanate. After standing 18 hours, the mixture was poured into water, and the precipitated product filtered off and washed with water. The product was hydrocortisone beta-chloroethyl carbamate, which was converted to the diethylaminoethyl carbamate by refluxing it with an alcoholic solution of diethylamine for 2 hours. The mixture was cooled, treated with saturated aqueous potassium carbonate and extracted with chloroform, which was evaporated to give the product.

EXAMPLE VI

Preparation of hydrocortisone N,N-diethylaminoacetate and related compounds

The chloracetate of hydrocortisone (Example I) (5 g.) was dissolved in 450 cc. acetone; 50 cc. diethylamine and 5 cc. of water were added. The mixture was refluxed for one hour and taken to dryness under vacuum on the steam bath. The residue was taken up in chloroform and the chloroform washed with 5% cold aqueous sodium bicarbonate and then with water. The chloroform extract was dried over sodium sulfate and then evaporated under vacuum. The residue was recrystallized from acetone and benzene, M.P. 168–171° C. The yield was 4.9 g. A portion of this amine was dissolved in anhydrous methanol, treated with an excess of ethereal HBr, taken to dryness and recrystallized from methanol-ether, M.P. 232–238° C.

The preparation of the piperidine and morpholine condensation products was carried out in essentially the same manner. The piperidine ester melted at 232–237° C., recrystallized from chloroform-acetone. The morpholine ester melted at 218–221° C. from acetone-benzene.

Piperazine was also used in the condensation with a slight modification; the hydrocortisone chloracetate (.3 g.) and piperazine hexahydrate (.5 g.) were refluxed in 15 cc. acetone. The workup was the same as described above. The product melted at 170–175° C. from benzene-hexane.

EXAMPLE VII

Preparation of prednisolone N,N-diethylaminoacetate and related compounds

To a solution of 30 g. prednisolone and 10.2 ml. pyridine in 99 ml. dimethylformamide, cooled to 0° C. in an ice bath and protected from atmospheric moisture, was added dropwise with stirring 9.6 ml. chloracetyl chloride. Stirring was continued for 1 hour at 0°, then stopped and the reaction allowed to come to room temperature and stand overnight. The following morning the reaction mixture was poured with vigorous stirring into a vessel containing 360 ml. 1 N H_2SO_4, and the product repulped with fresh portions of water until a neutral wash was obtained. The product was thoroughly dried in a vacuum desiccator and recrystallized from isopropyl alcohol, using 200 ml. solvent.

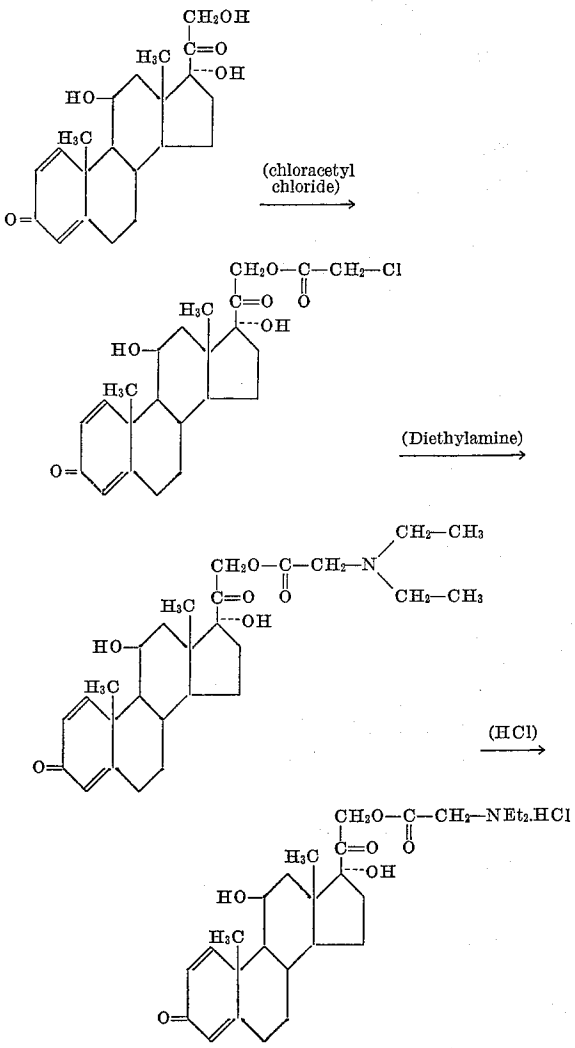
The yield was better than 80%, and the compound had M.P. 240.6–242.8° and $[\alpha]D+114.6$ (dioxane).

Two grams of this prednisolone chloracetate and 40 ml. of colorless, freshly distilled diethylamine were refluxed, with stirring, under nitrogen for one hour. The excess diethylamine was removed in vacuo (water aspirator) at room temperature. The residue was taken up in 100 ml. $CHCl_3$ and a small amount of water; the $CHCl_3$ was

washed with one 50 ml. portion of 5% aqueous sodium bicarbonate and two 50 ml. portions of water, and dried over sodium sulfate. The chloroform was then concentrated to dryness in vacuo. The residue was recrystallized from acetone-hexane: yield 1.67 g., M.P. 175.0–177.2°.

This prednisolone-N,N-diethylaminoacetate (1 g.) was suspended in a mixture of 15 ml. acetone and 15 ml. chloroform. The suspension was cooled to 0° in an ice bath, and with vigorous stirring the ethereal HCl solution was slowly added until the resulting mixture gave an acid reaction to Congo red paper. The product was removed by filtration and recrystallized from ethanol. The yield was approximately 80%, M.P. 237.4–239.8° and [α]D=+120.7 (water). The product was the hydrochloride salt of the prednisolone-N,N-diethylaminoacetate, very active therapeutically and excellently water-soluble.

This reaction is illustrated by the following equation:



EXAMPLE VIII

Following the method of Example II, the beta-dimethylaminoethyl carbonate of prednisolone was prepared, and from it the corresponding hydrobromide and methiodide salts.

EXAMPLE IX

Following the procedure of Example VI, the 21-N,N-diethylaminoacetate of 9-alpha-fluoro-hydrocortisone was prepared, and from it the hydrobromide salt. Similarly, the analogous piperidine, morpholine and piperazine ester salts were obtained.

EXAMPLE X

By the procedure of Example VII the N,N-diethylaminoacetate of 14-alpha-hydroxy prednisolone was prepared, and from this the hydrochloride salt.

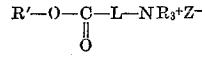
EXAMPLE XI

Fourteen-alpha-hydroxy hydrocortisone in pyridine was treated with 2 molar equivalents of chloracetyl chloride and the resulting chloracetate isolated as described in Example I. Reaction with trimethylamine and careful dilution, also as shown in Example I, precipitated the desired 14-alpha-hydroxy hydrocortisone dimethylaminoacetate methochloride.

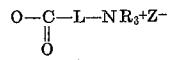
This application is in part a continuation of application Serial No. 486,017, now abandoned, filed February 3, 1955.

What is claimed is:

1. A compound having the formula



in which R′ is chosen from the class consisting of hydrocortisone, 14α-hydroxy-hydrocortisone, and the 9α-fluoro derivatives of these compounds, in each instance minus the 21-position hydroxyl group, L is chosen from the class consisting of $-(CH_2)_n-$, $-O-(CH_2)_n-$ and $-NH-(CH_2)_n-$, n being an integer from one to two, each R represents a member of the class consisting of hydrogen, alkyl, hydroxyalkyl, aminoalkyl, aryl and aralkyl groups containing up to ten carbon atoms in each group, and Z^- is a pharmacologically acceptable anion, said group



being substituted at the 21-position of said steroid molecule.

2. A therapeutic composition comprising a pharmaceutical carrier and a compound as claimed in claim 1.

3. A therapeutic composition comprising a sterile aqueous solution of a compound as claimed in claim 1.

4. A compound according to claim 1 wherein R′ is hydrocortisone, L is $-CH_2-$ and $-NR_3$ is

$$-N^+H(C_2H_5)_2$$

5. The hydrobromide salt of hydrocortisone-N,N-diethylaminoacetate.

6. The hydrobromide salt of 9α-fluorohydrocortisone-N,N-diethylaminoacetate.

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