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2,883,323

WATER-SOLUBLE IONIC ESTERS OF PREGNANOLONES

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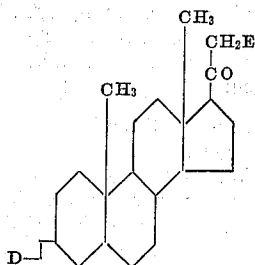
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Serial No. 568,450

8 Claims. (Cl. 167—52)

This invention is concerned with a group of novel ionic esters of steroid compounds which are hormonally inactive and are central nervous system depressants. These materials are related to the water soluble ionic esters of pregnanolones described in U.S. Patent No. 2,708,651, granted May 17, 1955, to G. D. Laubach but they differ in that the added ionic ester portion of the molecule contains one or more nitrogen, oxygen or sulfur atoms. These materials are isomeric with some of those of the above patent which contain nitrogen or oxygen in the ionic ester group, but they are of a different functional type.

The products of the present invention are central nervous system depressants and as such are useful as hypnotics, sedatives, anti-convulsants, analgesics and anesthetics. They possess unexpected advantages over the previous materials in that the presence of the heteroatom or atoms of the functional types disclosed herein in the ester portion of the molecule somehow confers improved pharmacological properties upon them. These advantages include decreased phlebotic action, altered time factors involved in the manifestation of their physiological effects after administration, and their improved adaptability to pharmaceutical compounding.

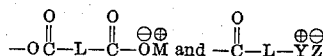
These valuable ionic esters are represented by the following structural formula.



This formula is intended to represent both possible stereoisomeric configurations at C₃ and at C₅. That is, the valuable compounds of this invention are members of both the normal- and the allo-series and the D group, when it is a monovalent group, is in either the α or the β position. In this structural formula the groups D and E may be ionic ester groups, hydroxyl groups, or the lower hydrocarbon carboxylic acid esters of said hydroxyl groups. Said hydrocarbon carboxylic acid groups contain up to about eight carbon atoms in the added unit. By lower hydrocarbon group is meant an alkyl, alkenyl, cycloalkyl, aryl or an aralkyl group containing up to about eight carbon atoms. Examples of such groups are the methyl, propyl, allyl, butyl, cyclohexyl, benzyl and phenyl groups. The carboxylic acids corresponding to these structures are called the lower hydrocarbon carboxylic acids and include acetic, butyric, cyclohexane carboxylic, benzoic and phenylacetic acids. The D group, further, is sometimes a keto group and the group E is sometimes a hydrogen atom.

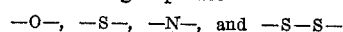
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The term ionic ester groups used above refers to an ester group containing a hydrophilic structural element which confers water solubility on the steroid molecule as a whole. The ionic esters of this invention are represented by the formulas

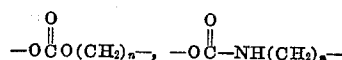


L is a mercaptoalkylene radical, a hydroxyalkylene radical, an aminoalkylene radical, or substituted groups of these types. These latter materials have the sulfur, oxygen, or nitrogen atoms further substituted by lower hydrocarbon groups or lower hydrocarbon carboxylic acid groups. The alkylene radicals from which these L groups are derived are aliphatic groups containing two unoccupied valences which permit them to be further connected as indicated for L in the structural formulas. Such radicals may be straight or branched and contain up to about six atoms in their principal chains, that is in the carbon chain between the two unoccupied valences. The hydroxyalkylene radical, then, contains a hydroxyl group connected to one of the carbon atoms, either of the principal chain or a branch thereof, and the mercapto and aminoalkylene radicals are similarly constituted containing a mercapto or amino group attached to one of the carbon atoms of the alkylene radical. These substituents may be substituted as described above.

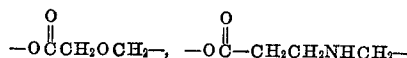
The L group of the ionic ester may also be an azalkylene, an oxalkylene, or a thialkylene radical. Group of this type are in turn related to the alkylene group by the substitution of one of the following hetero groups for a carbon atom of the principal chain of the alkylene group. These hetero groups are



A further limitation on the structures of the azalkylene, oxalkylene, and the thialkylene radicals of the valuable ionic esters of this invention is that at least two of the valence bonds of each hetero group are attached to saturated carbon atoms. Thus the ionic esters of the present invention containing the azalkylene and oxalkylene groups differ from those of the Laubach patent containing the $-\text{O}(\text{CH}_2)_n-$ and $\text{NH}(\text{CH}_2)_n$ groups in that the latter are carbonates or carbamates, e.g.

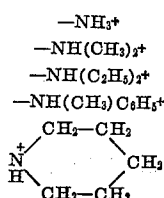


while those of the present invention are all carboxylic esters of the classical type, e.g.



More than one hetero group sometimes appears in the L group, but the compounds are preferred which contain only one hetero group since they are more readily synthesized.

The Y⁺ group is an ammonium function substituted with groups chosen from hydrogen, and lower hydrocarbon groups containing up to 6 carbon atoms in each group. At least one of said substituents is a hydrogen atom in each case. The following illustrate some of the various formulas for Y⁺.

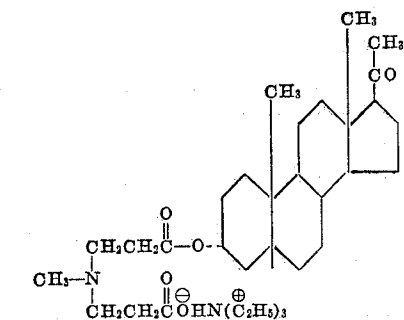
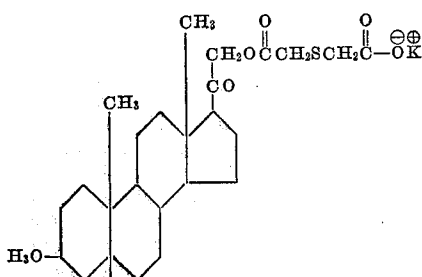
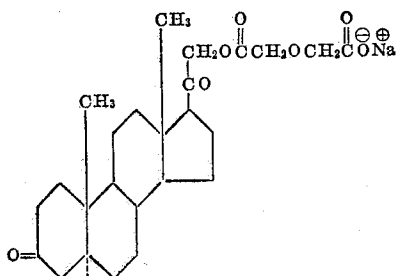
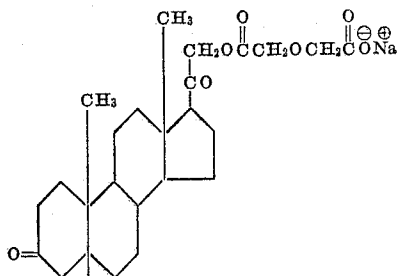


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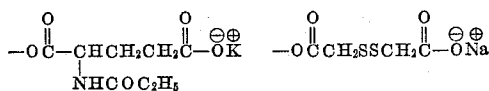
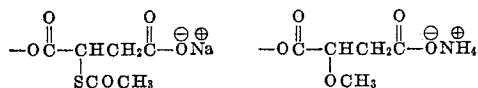
M⁺ is a cation which may be an ammonium ion of the type just described or a sodium or potassium ion.

Z is a pharmacologically acceptable anion. This term has a definite meaning to those skilled in the art. By this is meant the anion of an acid which can be used in physiological preparations to neutralize basic medicinal agents. Such anions may be toxic at certain dosage levels but at the concentrations required with the neutralized medicinal agent, toxic effects due to the anion are absent. Examples of such anions are chloride, bromide, sulfate, methosulfate, phosphate, succinate, and maleate.

In order to further illustrate some structures of the unique compounds of this invention, the following formulas are presented.



Further structures illustrative of the ionic ester groups from which D and E may be selected are as follows.



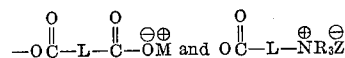
The above description of the structures of the valuable

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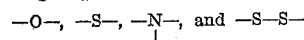
central nervous system depressants of this invention can be summarized as follows:

D is selected from the group consisting of—

(a) Ionic esters having the formula



in which L is selected from the class consisting of the mercaptoalkylene radical, the lower hydrocarbon sulfides and lower hydrocarbon acid thioesters thereof containing up to about eight carbon atoms in the added unit, the hydroxyalkylene radical, the lower hydrocarbon ethers and lower hydrocarbon acid esters thereof containing up to about eight carbon atoms in the added unit, the aminoalkylene radical, the lower hydrocarbon substitutes, and the lower hydrocarbon acid amides thereof containing up to about eight carbon atoms in the added unit, the azalkylene, the oxalkylene, and the thialkylene radicals wherein the hetero groups of said radicals are selected from the group consisting of



and wherein at least two valences of said hetero group are attached to saturated carbon atoms and said L group has up to about six atoms in its principal chain; M⁺ is a cation selected from the group consisting of sodium, potassium and NR₄⁺, each R represents a member of the group consisting of hydrogen and lower hydrocarbon groups wherein at least one of said R groups is a hydrogen atom and each R group contains up to six carbon atoms; Z⁻ is a pharmacologically acceptable ion;

(b) Hydroxyl, the lower hydrocarbon ethers and hydrocarbon carboxylic acid esters thereof containing up to about eight carbon atoms in the added unit;

(c) Keto;

E is selected from the group consisting of—

(a) Ionic ester groups as defined above;

(b) Hydroxyl, and lower hydrocarbon carboxylic acid esters thereof containing up to about eight carbon atoms in the added unit;

(c) Hydrogen;

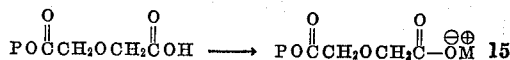
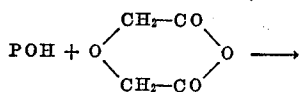
and with at least one of D and E being an ionic ester group as defined above.

The valuable ionic esters of this invention are prepared in a manner similar to that described in the above identified patent for the preparation of the saturated aliphatic type of ionic ester. The length of the principal chain, that is the chain separating the two carboxyl functions, of the ionic ester group determines which of the two synthetic approaches is applicable. The dibasic acids containing two to three atoms in their principal chain form cyclic anhydrides by warming with such dehydrating agents as acetic anhydride or acetyl chloride. For example, diglycolic acid when warmed with acetic anhydride is converted to its anhydride which crystallizes out of the dehydrating medium. This can then be collected, dried, and used for the acylation of a hormonally inactive steroid of the type described above such as pregnane-3,20-dione-21-ol. A hemidiglycolic half acid ester results which is readily converted to a water soluble salt by methods commonly employed for the preparation of salts. The starting steroid for this process, pregnane-3,20-dione-21-ol, is prepared by the catalytic hydrogenation of desoxycorticosterone as described in copending U.S. patent application, Serial No. 484,561, filed January 27, 1955, now abandoned. This process is illustrated in Equation 1 wherein P is intended to signify a steroid

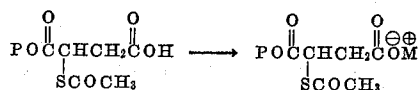
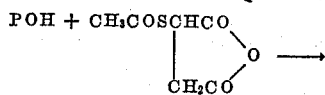
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nucleus conforming to the above generic formula less the free hydroxyl group which is acylated during the process. M⁺ has the same meaning as above. Equation 2 illustrates a similar preparation employing the acetyl derivative of α -mercaptosuccinic anhydride obtained by the treatment of α -mercaptosuccinic acid with acetyl chloride or acetic anhydride as described above.

EQUATION 1



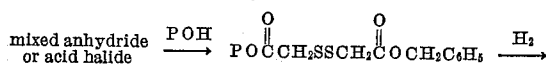
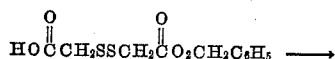
EQUATION 2



For the syntheses of the half esters of the dibasic acids, that do not form cyclic anhydrides, that is those containing less than two and more than about three atoms in their principal chain, resort is had to an alternative method. This involves first protecting one of the carboxyl groups of the dibasic acid with a readily cleaved ester group such as the benzyl, t-butyl, or tetrahydropyranyl esters, general methods for the preparation of which are well known in the art, conversion of the remaining free carboxyl group to an acid halide or a mixed anhydride followed by acylation of the free hydroxyl group of the steroid with it. The original protective ester group is then removed and the carboxylic acid group converted to a water soluble salt.

Convenient processes for the preparation of half esters of the type required in this type of process include partial hydrolysis of the diester, for example with alcoholic potassium hydroxide, or equilibration of equimolar amounts of diester and diacid by heating with a mineral acid to form the monoester. Cleavage of the labile protective ester group involves, for example, hydrogenolysis in the case of the benzyl ester or gentle pyrolysis in the case of the t-butyl or tetrahydropyranyl esters. Useful mixed anhydrides for the acylation reaction are the alkylcarbonic mixed anhydrides or mixed anhydrides with phosphoric or sulfuric acid. This type of process is illustrated in Equation 3 where P has the same meaning as above.

EQUATION 3



The preferred use of the valuable central nervous system depressants of this invention is in anesthesia, although they are also useful as hypnotics, anticonvulsants, and sedatives. They are particularly well suited for use as pre- or basal anesthetics in conjunction with inhalation anesthetics such as nitrous oxide, cyclopropane, and diethyl ether. For this type of use, intravenous administration is preferred since the effect of the drug generally takes place more promptly than by other routes of administration. This is necessary so that the anesthetist will have close control of the degree of central nervous system depression which the patient undergoes. The salts of

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these materials, that is the acid addition, the metal and the amine salts are water soluble and therefore well suited for this purpose since water and water containing small proportions of certain organic solvents such as glycerol or propylene glycol are the only solvents commonly employed in human intravenous therapy. These materials can be prepared for use as sterile solid compositions by blending them with various excipients, carriers, and buffering agents and then sterilizing the solid mixture for example with ethylene oxide, or they can be used alone without solid diluents when sterilized in a similar fashion. The sterile solid is dissolved in sterile water prior to use. Alternatively, the unsterilized solid product can be dissolved in water and the resulting solution sterilized by filtration through a bacteriological filter prior to use. These compounds may be employed in aqueous solutions containing other salts for example enough saline or glucose to make them isotonic. Aqueous buffer solutions in the range of about pH 7 to 9 are also conveniently employed in some instances as solvents. The valuable products of this invention may also be administered by other routes such as orally, rectally, subcutaneously, and intramuscularly. For this purpose, it is useful to compound them into tablets with various tablet forming material such as starch or to prepare elixirs or suspensions with suitable carriers.

The valuable water soluble ionic ester anesthetic agents of this invention were tested in mice by administering them intravenously in sterile aqueous solutions. Varying dosage levels were used with separate groups of mice. From this type of an experiment it was possible to determine at once the approximate toxicity and anesthetic activity of these compounds. For example, dosages of 15, 30, 60, 120 and 240 mg./kg. of the salts were administered to different groups of mice in sterile 5% aqueous solutions. The groups of mice receiving dosages exceeding the toxic limit died. At the lower dosage levels anesthesia resulted. Those that received doses below the anesthetic level were substantially without symptoms. The anesthetic activity was determined by noting the sleeping time and by the duration of the loss of righting reflex experienced by the mice in each group. Based on the data obtained in this test, the materials were administered first to dogs and then to monkeys at dosages calculated to give the anesthetic effect without harm to the animals. Confirmation of the results obtained in the mouse test was obtained although there were, of course, some species differences in sensitivity. These compounds were found to have similar pharmacological activity in human beings.

The following examples are given to further illustrate the methods for synthesizing the valuable products of this invention. However, it is to be understood that these are given for illustrative purposes only and are not to be construed as limiting the invention in any way.

EXAMPLE I

Pregnane-20-one-3 α -ol hemidithiodiacetate

Dithiodiacetic acid, 9.1 g., and 18.1 g. of its dibenzyl ester were dissolved and heated overnight on a steam bath in 50 ml. of dibutyl ether containing 2 ml. of concentrated hydrochloric acid. The mixture was cooled and extracted with successive portions of dilute aqueous sodium bicarbonate until all acidic materials had been removed from the organic layer. The combined aqueous bicarbonate extracts were then acidified, and extracted with ether. Evaporation of the dried ether extracts left a residue which consisted primarily of the monobenzyl ester of dithiodiacetic acid.

The monobenzyl ester was then treated with 10 ml. of thionyl chloride and the mixture warmed on a steam bath for 15 minutes. The excess thionyl chloride was evaporated in vacuo leaving the mono acid chloride mono-

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benzyl ester of dithiodiacetic acid. The acid chloride was dissolved in about 35 ml. of dioxane and added slowly with stirring and external cooling to a solution of 10 g. pregnane-20-one-3 α -ol in 100 ml. of pyridine. The resulting solution was kept at room temperature overnight, poured into a large volume of ice water, and the excess pyridine neutralized with hydrochloric acid. The benzyl ester of pregnane-20-one-3 α -ol hemidithiodiacetate which had precipitated was collected, washed with water, and dried in vacuo.

This unsymmetrical diester was then dissolved in alcohol and hydrogenated at room temperature and a pressure of about three atmospheres using a platinum catalyst supplied as the oxide. After one molar equivalent of hydrogen had been absorbed, the reaction was interrupted. The product was recovered by evaporating the solvent, and purified by dissolving it in cold dilute aqueous sodium carbonate solution and reprecipitating it by acidification with hydrochloric acid. The neutral equivalent of the so-obtained product corresponded to that calculated for the desired hemidithiodiacetate of pregnane-20-one-3 α -21-ol.

EXAMPLE II

Pregnane-20-one-3 α -ol potassium hemidithiodiacetate

One gram of the product of Example I was dissolved in an equivalent quantity of dilute potassium bicarbonate solution. It was necessary to warm the mixture before the acid would dissolve. A small amount of foreign matter was filtered, the clear filtrate frozen, and dried from the frozen state to yield the desired potassium salt.

EXAMPLE III

Pregnane-3,20-dione-21-ol hemidiglycolate

One gram each of diglycolic anhydride and pregnane-3,20-dione-21-ol were dissolved in 10 ml. of dry pyridine and the solution kept at room temperature overnight. The solution was then poured into about 50 ml. of a mixture of ice and water and the excess pyridine neutralized with hydrochloric acid. The product separated, and was collected by filtration, washed and dried.

EXAMPLE IV

Allo-pregnane-3,20-dione-21-ol hemithiodiacetate

One gram of thiodiacetic anhydride was substituted for the diglycolic anhydride in the procedure of Example III. The product resulting from this process proved to be allo-pregnane-3,20-dione-21-ol hemithiodiacetate.

EXAMPLE V

Pregnane-3,20-dione-21-ol sodium hemidiglycolate

The acid of Example III, 1 g., was dissolved by warming with an equivalent quantity of sodium bicarbonate. When all of the acid had dissolved the solution was filtered through a bacteriological filter and the filtrate frozen and dried from the frozen state to yield a sterile sample of pregnane-3,20-dione-21-ol sodium hemidiglycolate.

EXAMPLE VI

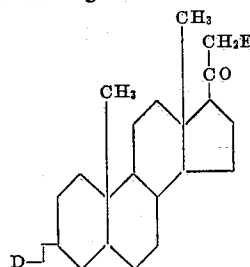
Pregnane-3,20-dione-21-ol hemiacetylminodiacetate

Ten grams of iminodiacetic acid was refluxed overnight with 60 ml. of acetyl chloride. The excess acetyl chloride was then distilled leaving a residue consisting primarily of acetylminodiacetic anhydride. This anhydride was dissolved in pyridine and mixed with a pyridine solution of an equivalent quantity of pregnane-3,20-dione-21-ol in the fashion described above. The product was recovered by pouring the pyridine solution into ice water, neutralizing the excess pyridine, and collecting the material which precipitated.

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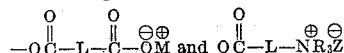
What is claimed is:

1. A compound having the formula

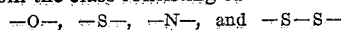


wherein D is selected from the group consisting of:

15 (a) ionic esters having the formula



20 in which L is selected from the class consisting of the mercaptoalkylene radical and the lower hydrocarbon sulfides and lower hydrocarbon acid thioesters thereof containing up to about eight carbon atoms in the added unit; the hydroxyalkylene radical and the lower hydrocarbon ethers and lower hydrocarbon acid esters thereof containing up to about eight carbon atoms in the added unit; the aminoalkylene radical and the lower hydrocarbon substitutes and the lower hydrocarbon acid amides thereof containing up to about eight carbon atoms in the added unit; the azalkylene, the oxalkylene, and the thialkylene radicals wherein the hetero groups of said radicals are selected from the class consisting of



35 and wherein at least two valences of said hetero group are attached to saturated carbon atoms of the alkylene chain, and said L group has up to about six atoms in its principal chain; M⁺ is a cation selected from the group consisting of sodium, potassium and NR₄⁺, each R represents a member of the group consisting of hydrogen and lower hydrocarbon groups wherein at least one of said R groups is a hydrogen atom and each R group contains up to six carbon atoms; Z⁻ is a pharmacologically acceptable anion; (b) hydroxyl, the lower hydrocarbon ethers and hydrocarbon carboxylic acid esters thereof containing up to about eight carbon atoms in the added unit; (c) keto; E is selected from the group consisting of: 40 (a) ionic ester groups as defined above; (b) hydroxyl, and lower hydrocarbon carboxylic acid esters thereof containing up to about eight carbon atoms in the added unit; (c) hydrogen; and with at least one of D and E being an ionic ester group as defined above.

50 2. A pharmaceutical composition which comprises a compound as claimed in claim 1 and a pharmaceutically acceptable carrier.

3. An anesthetic agent comprising a sterile aqueous solution of a compound as claimed in claim 1.

4. Pregnane-3,20-dione-21-ol sodium hemidiglycolate.

5. Allo-pregnane-3,20-dione-21-ol sodium hemidiglycolate.

6. Pregnane-3,20-dione-21-ol sodium hemithiodiacetate.

7. Allo-pregnane-3,20-dione-21-ol sodium hemithiodiacetate.

8. Pregnane-20-one-3 α -ol potassium hemi-3,3'-(methylimino) dipropionate.

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