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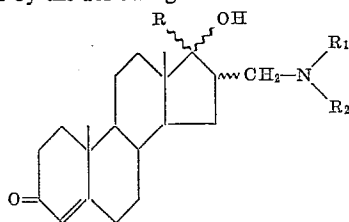
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3,149,132 16-AMINOMETHYL-17-ALKYLTESTOSTERONE DERIVATIVES

Percy L. Julian, Oak Park, and Arthur Magnani, Wilmette, Ill., assignors, by mesne assignments, to Smith Kline & French Laboratories, Philadelphia, Pa., a corporation of Pennsylvania
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This invention relates to novel Mannich derivatives of 17-alkyltestosterones which have unexpectedly been found to have novel pharmacodynamic activity.

More specifically the compounds of this invention are represented by the following formula:



FORMULA 1

in which R is lower alkyl, preferably methyl or ethyl; R₁ and R₂ are lower alkyl of from 1 to 6 carbon atoms inclusive or, when taken together with the nitrogen atom to which they are attached, a standard heterocyclic end group such as pyrrolidinyl, N-lower-alkyl-N-piperazinyl, morpholinyl, piperidinyl, or thiomorpholinyl.

Also included in this invention are the nontoxic pharmaceutically acceptable acid addition and quaternary ammonium salts of the bases of Formula 1 such as salts formed with acids such as hydrochloric, sulfuric, acetic, phosphoric, maleic, ethanedisulfonic etc. acids or quaternaries made with such standard quaternizing agents as methyl iodide, ethyl chloride, methyl sulfate, propyl bromide, ethyl bromide etc. These salts are prepared by standard methods such as reaction of the Mannich base in inert organic solvent such as ether with an excess of the acid or quaternizing agent.

The compounds of this invention as described above have been unexpectedly found to have anti-anabolic or particularly, anti-androgenic activity. In other words these compounds when administered concurrently with testosterone antagonize the well known effects of that drug. Compounds having such activity are variously effective against certain prostate conditions and to treat females exhibiting the Stein-Leventhal syndrome or hirsutism.

The compounds of this invention are prepared using known Mannich derivatives of dehydroisoandrosterone (U.S. Patent No. 2,562,194, U.S. Patent No. 2,890,227 and U.S. Patent No. 2,588,341). It should be noted that the configuration of the 16-aminomethyl moiety of the starting material of these patents is described as a mixture of α and β . While this is not disputed, the major portion of the mixture seems from our data to be α and the compounds described hereafter may be so considered. The configuration at positions 16 and 17 does not seem to have any effect on the utility of the compounds. The Mannich starting materials are reacted with a Grignard agent such as methyl or ethyl magnesium bromide to produce the 16-aminomethyl-17-methyl-5-androsten-3,17-diol which is in turn oxidized usually under Oppenauer conditions to the products of Formula 1.

The Grignard reaction can also result in a mixture of isomers at 17. Both series are included in this invention. Separation of the isomers is detailed in Example 1 but both isomeric compounds have the desired utility.

It will be apparent to one skilled in the art that various well-known modifications of the steroids of Formula 1 can be made, however, the nub of this invention is considered to be the vital 16-aminomethyl moiety coupled with the basic 17-methyltestosterone nucleus. Standard variations such as 19-nor, 4-halo, methyl or hydroxy, 6-halo or methyl, 11 or 12-hydroxy, Δ^1 or other modifications can be made by methods known to the art and are within the purview of this invention. The term "lower alkyl" where used herein means straight or branched alkyl groups of 1 to 6 carbon atoms inclusive but preferably methyl or ethyl.

The following examples will illustrate the synthetic methods necessary for one skilled in the art to practice this invention.

Example 1

210 ml. of a 3-molar ethereal solution of methyl magnesium bromide are added slowly to 210 ml. of tetrahydrofuran. The mixture is stirred and warmed to remove ether, the last traces under vacuo. A solution of 33.5 g. of 16-dimethylaminomethyl-5-androsten-3 β -ol-17-one in 600 ml. of tetrahydrofuran is added. The mixture is stirred for several hours, then allowed to stand overnight. A solution of 67 g. of ammonium chloride in 300 ml. of water is cautiously added with stirring and cooling. The organic layer is separated, washed and evaporated to give a crystalline residue of the 17-methylated compound, M.P. 172–190° C.

The isomeric mixture is separated by fractional crystallization from ethyl acetate to give less soluble plates of 16 α -dimethylaminomethyl-17 α -methyl-5-androsten-3 β ,17 β -diol, M.P. 245–247° C., $[\alpha]_{\text{CHCl}_3}$: –84, and needles of 16 α -dimethylaminomethyl-17 β -methyl-5-androsten-3 β ,17 α -diol, M.P. 189–191° C., $[\alpha]_{\text{CHCl}_3}$: –41. The configuration at 17 is assigned by comparison of the infrared curves.

The 17 α -hydroxy isomer (8 g.) in 500 ml. of toluene and 30 ml. of cyclohexanone at 100° C. with 4 g. of aluminum isopropoxide is heated at reflux for 45 minutes, allowed to cool to 85° C. and diluted with 5 ml. of water. The separated filtrate is steam distilled. The residue is recrystallized from ethyl acetate to give 16 α -dimethylaminomethyl-17 β -methyl-4-androsten-17 α -ol-3-one, M.P. 170–172° C., $[\alpha]_{\text{CHCl}_3}$: +76.

Similarly the 17 β -hydroxy isomer (M.P. 245° C., 6 g.) is oxidized to give crystals from ether of 16 α -dimethylaminomethyl-17 α -methyl-testosterone, M.P. 131–133° C., $[\alpha]_{\text{CHCl}_3}$: +37.

The 17 α -ol (500 mg.) in chloroform is saturated with dry hydrogen chloride gas to separate the hydrochloride salt. Another portion is reacted with ethyl iodide at reflux in chloroform to give the ethiodide quaternary salt.

Example 2

16-Piperidinylmethyldehydroisoandrosterone (11 g.) is reacted with an excess of ethyl magnesium chloride in tetrahydrofuran as in Example 1 to give the isomeric 16-piperidinylmethyl-17-ethyl-5-androsten-3 β ,17-diols which (8 g.) are oxidized with aluminum isopropoxide cyclohexanone to give the 16-piperidinylmethyl-17-ethyltestosterones.

This material with sulfuric acid in chloroform gives the sulfate salt.

Example 3

Substituting 7.5 g. of 16-diethylaminomethyldehydroisoandrosterone in the sequence of Example 1 gives with methyl magnesium bromide in tetrahydrofuran first the separated isomeric 16-diethylaminomethyl-17-methyl-5-androsten-3 β ,17-diols and then the isomeric 16-diethylaminomethyl-17-methyltestosterones.

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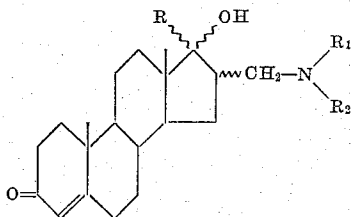
Example 4

Substituting equimolar amounts of 16 α -N-methylpiperazinylmethyldehydroisoandrosterone (prepared by the Julian method, U.S. Patent No. 2,562,194, using N-methylpiperazine, formaldehyde and dehydroisoandrosterone) in Example 1 gives 16 α -N-methylpiperazinylmethyl-17-methyl-5-androsten-3 β ,17-diol then Oppenauer oxidation gives 16-N-methylpiperazinylmethyl-17-methyltestosterone.

Substituting 16 - morpholinylmethyldehydroisoandrosterone, 16-pyrrolidinylmethyldehydroisoandrosterone or 16 - methylaminomethyldehydroisoandrosterone in the process of Example 1 give respectively the 3-ol-5-enes and then the 16-morpholinylmethyl-17-methyltestosterone, 16 - pyrrolidinylmethyl - 17 - methyltestosterones and 16-methylaminomethyl-17-methyltestosterones.

What is claimed is:

1. A compound selected from the group consisting of a free base, its nontoxic pharmaceutically acceptable acid addition salts and its nontoxic pharmaceutically acceptable quaternary ammonium salts, said free base having the formula:

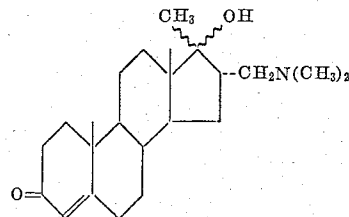


in which R is a member selected from the group consisting of methyl and ethyl; and R₁ and R₂ are members selected from the group consisting of lower alkyl and, when taken together with the nitrogen to which they are

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attached, piperidinyl, morpholinyl, pyrrolidinyl, N-lower alkyl-piperazinyl and thiomorpholinyl.

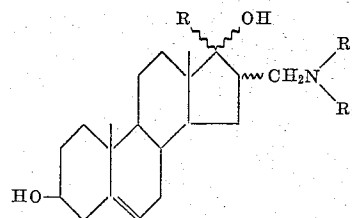
2. A compound of the formula:



3. 16 α - dimethylaminomethyl - 17 β - methyl - 4-androsten-17 α -ol-3-one.

4. 16 α -dimethylaminomethyl-17 α -methyltestosterone.

5. A compound of the structure:



in which R is a member selected from the group consisting of methyl and ethyl; and R₁ and R₂ are members selected from the group consisting of lower alkyl and, when taken together with the nitrogen to which they are attached, piperidinyl, morpholinyl, pyrrolidinyl, N-lower alkyl-piperazinyl and thiomorpholinyl.

6. 16 α - dimethylaminomethyl - 17 β - methyl - 5-androsten-3 β ,17 α -diol.

7. 16 α - dimethylaminomethyl - 17 α - methyl - 5-androsten-3 β ,17 β -diol.

No references cited.