United States Patent Office 2,878,246 Patented Mar. 17, 1959

2,878,246

PREPARATION OF 6-METHYL STEROIDS OF THE PREGNANE SERIES FROM DIOSGENIN

Luis E. Miramontes, Miguel A. Romero, and Fortunato Ahuad Farjat, Mexico City, Mexico, assignors to G. D. Searle & Co., Chicago, Ill., a corporation of Delaware

No Drawing. Application September 27, 1957 Serial No. 686,562

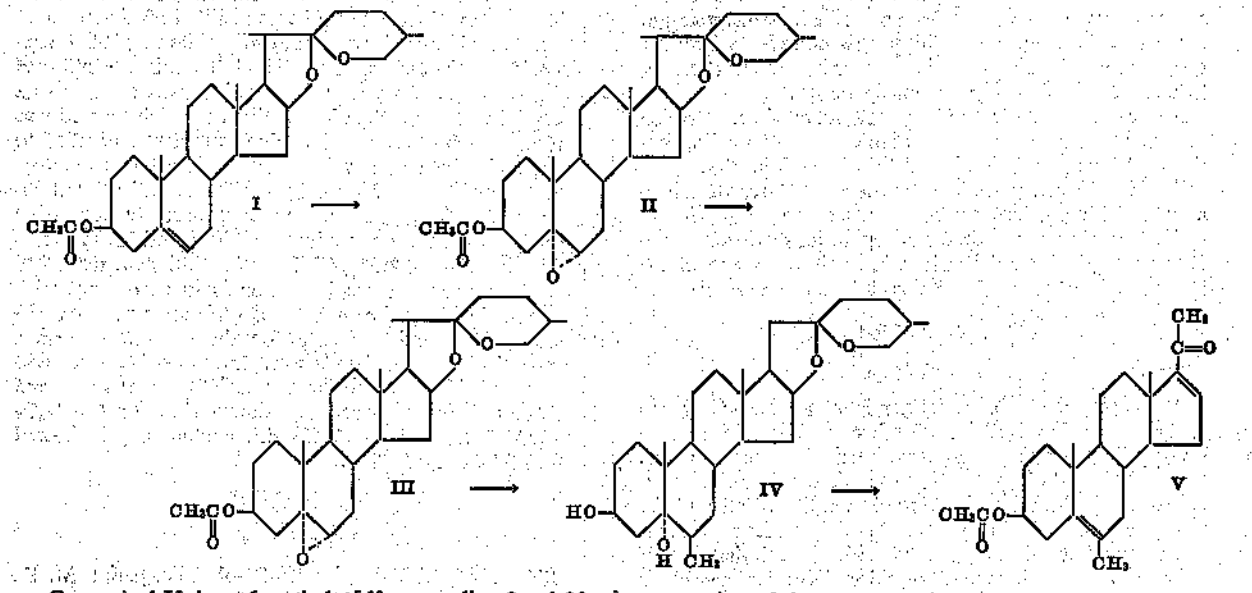
12 Claims. (Cl. 260—239.55)

The present invention relates to a novel method for the preparation of 6-methyl steroids from diosgenin, and to the novel intermediates resulting from the method.

The C–6 methylated steroids have recently been demonstrated to be potent chemotherapeutic agents, e. g., Spero et al., J. A. C. S. 79, p. 1515 (1957). However, for widespread utilization of C–6 methylated compounds such as 6α-methyl, 11β,17α-dihydroxy-21-acetoxy-4-pregnene-3,20-dione or 6α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione it is necessary to assure their availability in large, preferably unlimited, quantities.

Since diosgenin, and its acetate, can be prepared inexpensively from plant materials in unlimited quantities, synthesis from diosgenin would make the C–6 methylated steroids commercially available to the medical profession. The instant invention provides a method for converting diosgenin into novel C–6 methyl steroids, which in turn can be converted into the compounds described by the Spero et al. article.

The following equations illustrate preparation of 6-methyl-5,16 pregnadien 3β-ol 20-one acetate.



Compound V, i. e., 6-methyl $\Delta^{5,16}$-pregnadien 3β-ol 20-one acetate is a direct 6-methylated homologue of the well-known intermediate for corticoids, androgens, estrogens and progestional hormones: $\Delta^{5,16}$-pregnadien 3-β-ol-20-one acetate (16-dehydropregnenolone acetate). As such it is convertible, for example, into the 6α methyl Δ^4-pregnene-11β,17α-21-triol-3,20-dione described by the Spero et al, article or the 6-methyl progesterone disclosed by Ringold et al. (J. Org. Chem., January 1957, pp. 99, 100). It may also, of course, be converted into such other C–6 methyl compounds as may be required in the future by the medical profession.

Thus, for example, compound V may be converted into 6α-methyl-17α-hydroxyprogesterone by following the procedure outlined in Fritsche et al. application S. N. 686,564 filed simultaneously herewith. As disclosed in Loken application S. N. 686,563 filed simultaneously herewith, 6α-methyl-17α-hydroxy progesterone and its 17 esters exhibit progestational activity.

Briefly, the process is as follows:

Diosgenin acetate (I) is treated with an organic peracid to form the corresponding oxide, (II) which as expected is obtained as a mixture of the α and β-oxides. The α-oxide (III) is isolated by fractional crystallization and treated with methyl magnesium bromide to obtain 5α-hydroxy-6β-methyl tigogenin (IV) which, under the conditions employed for degradation to the pregnane series, undergoes a dehydration at C–5 to form, predominantly, 6-methyl-5,16-pregnadien-3β-ol-20-one acetate (V); confirmation of the 5-6 location of the double bond is obtained by the difference of molecular rotation calculated from the data reported by L. F. Fieser and J. Rigaudy for the cholesterol series [J. A. C. S. col. 73, p. 4660 (1957)].

The instant process contains several novel features apparently uniquely applicable to the diosgenin series, which are specifically desirable expedients in the synthesis of the C–6 methyl derivatives. These expedients will be detailed in the description of the overall process which follows.

The epoxidation can be accomplished employing conventional reagents, for example, per acetic acid, perphthalic acid or perbenzoic acid under conventional epoxidizing conditions. In each instance the oxide product is a mixture of the α, β epimeric oxides of diosgenin (II).

Inasmuch as only the reaction of the α oxide with the Grignard reagent results in the desired 6-methylation, a separation of the α and β oxides and employment only of the α oxide will prevent wastage of valuable reagents by production of undesired side products from the β oxide. Moreover, separation of the α and β oxides allows, for example, recycling the β oxide via formation of the 5,6 glycol then its methyl sulfonate and back to an oxirane ring having the α configuration. According to the practice of the instant invention the α and β oxide separation can be effected by fractional crystallization from heptane as set forth in the examples. The differential solubility of the epimeric oxides in the solvent allows crystallization to proceed fractionally. Similarly the corresponding