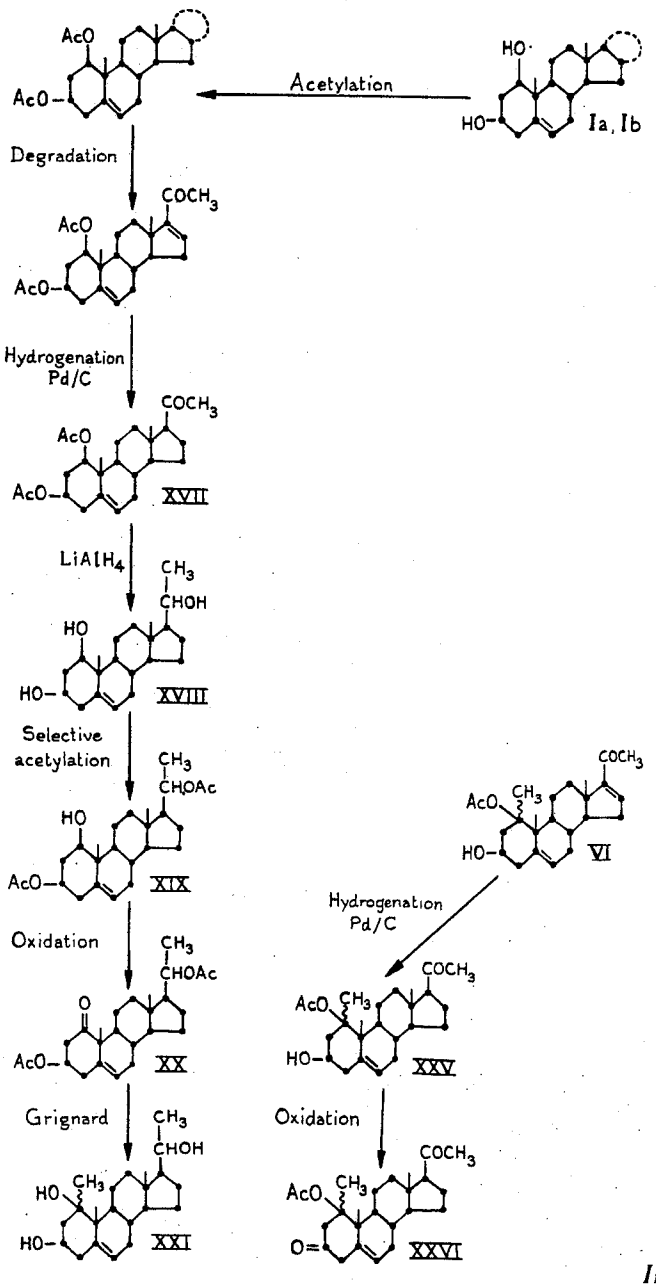
May 26, 1964 B. CAMERINO ETAL 3,134,769

1-METHYL-DIOSGENINS

Filed Aug. 9, 1961 5 Sheets-Sheet 1



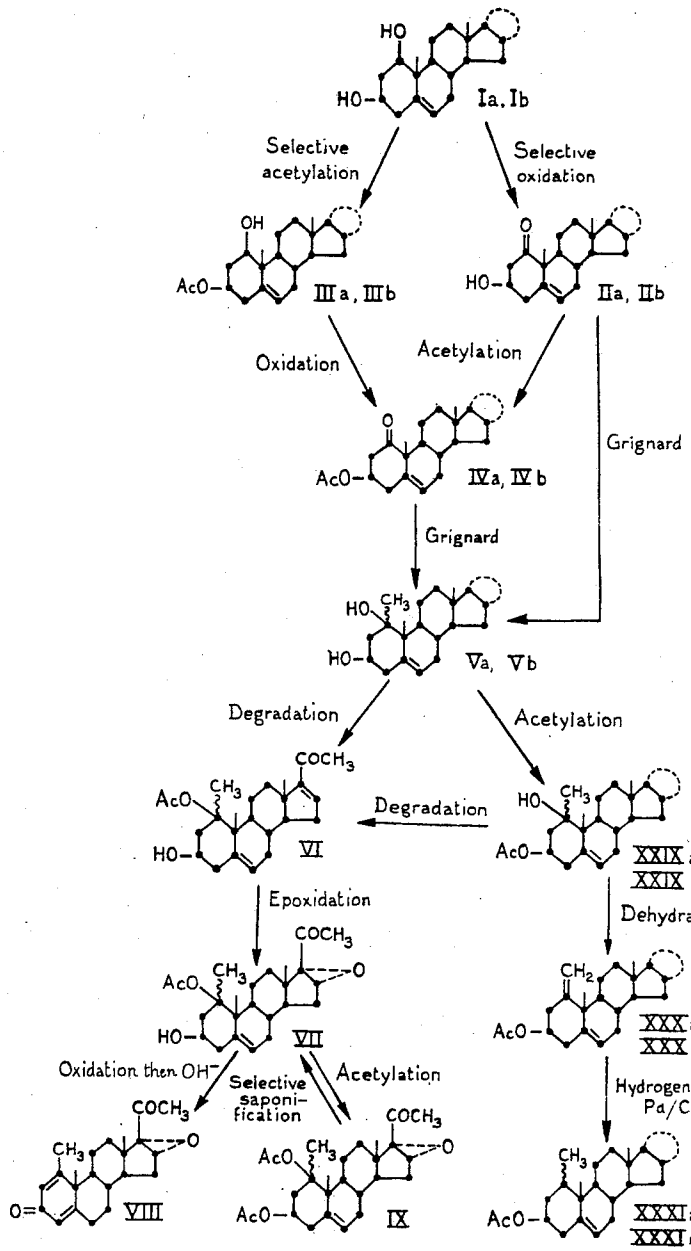
Inventors
Bruno Camerino
Robert Sciaky
Jean Robert

By Sterne, Kessler, Miller & Moaher Attorneys

May 26, 1964 B. CAMERINO ETAL 3,134,769

1-METHYL-DIOSGENINS

Filed Aug. 9, 1961 5 Sheets-Sheet 2



Inventors

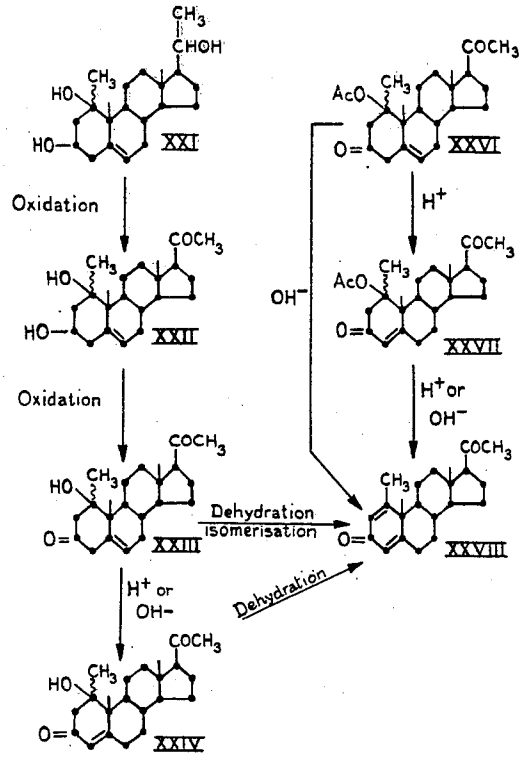
Bruno Camerino
Robert Sciaky
Jean Robert

By Stevens, Davis, Miller & Mosher *Attorneys*

May 26, 1964 B. CAMERINO ETAL 3,134,769

1-METHYL-DIOSGENINS

Filed Aug. 9, 1961 5 Sheets-Sheet 3



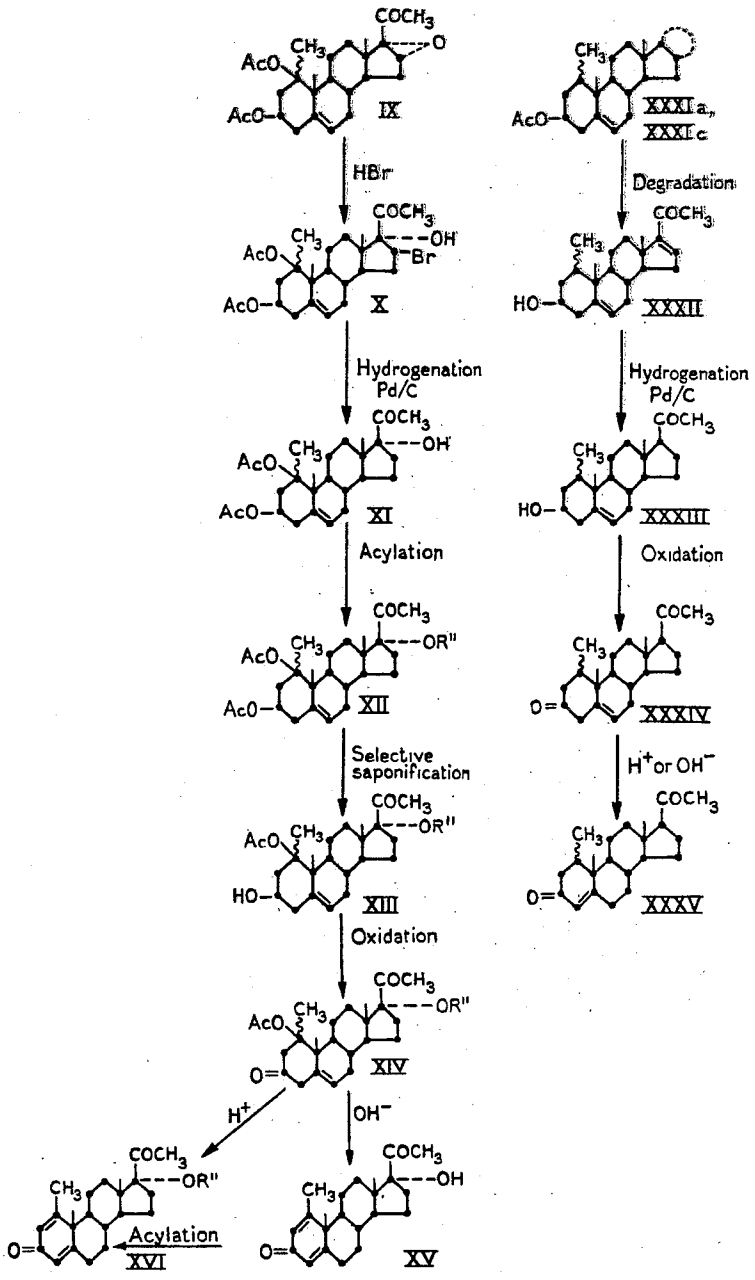
Inventors
Bruno Camerino
Robert Sciaky
Jean Robert

By Strauss, Davis, Miller & Marker Attorneys

May 26, 1964 B. CAMERINO ET AL 3,134,769

1-METHYL-DIOSGENINS

Filed Aug. 9, 1961 5 Sheets-Sheet 4



Inventors
Bruno Camerino
Robert Sciaky
Jean Robert

By Stevens, Davis, Miller & Mosher Attorneys

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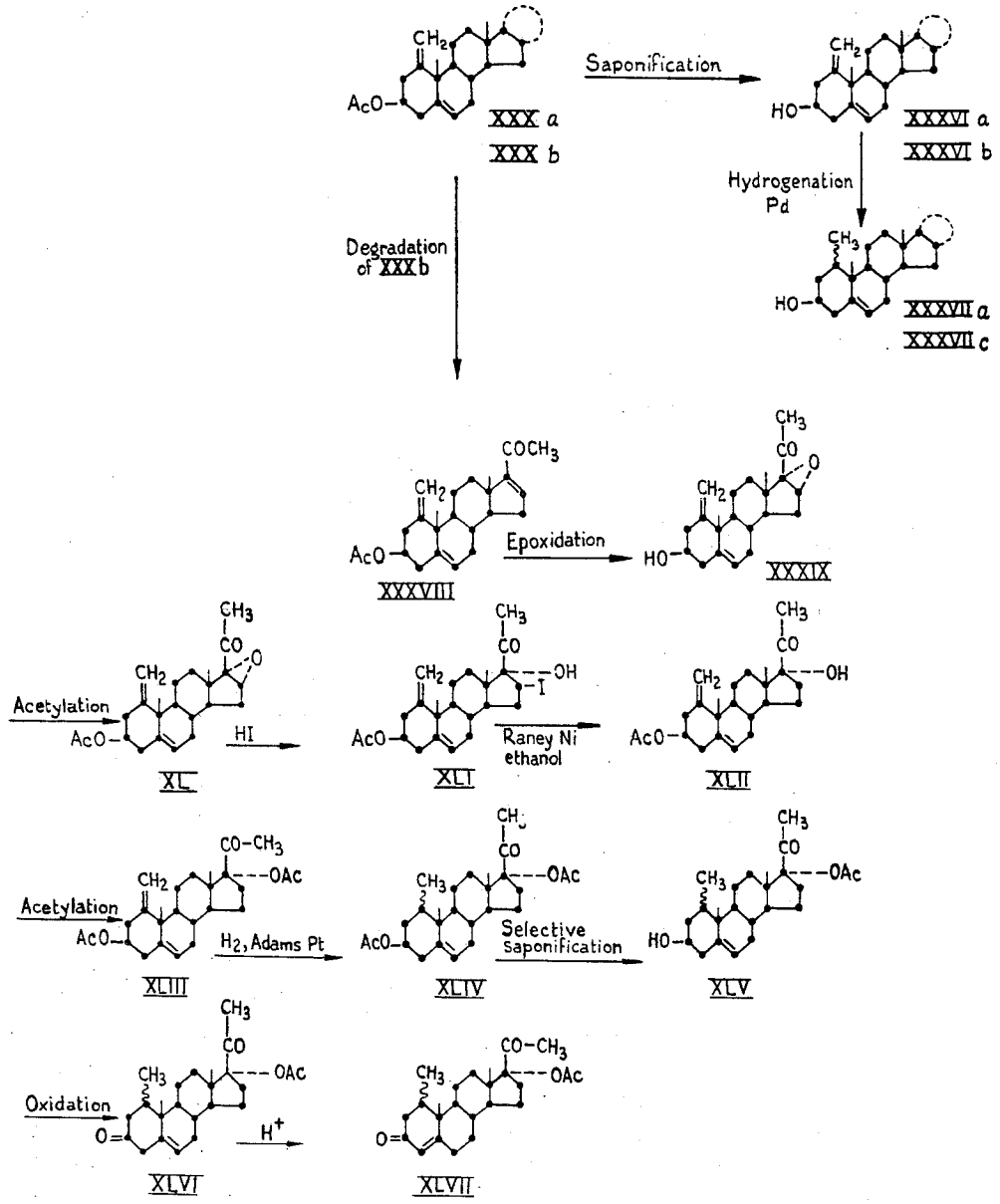
1-METHYL-DIOSGENINS

Filed Aug. 9, 1961 5 Sheets-Sheet 5



XXX a
XXX b
XXXVI a
XXXVI b
XXXVII a
XXXVII c
XXXVIII
XXXIX
XL
XLI
XLII
XLIII
XLIV
XLV
XLVI
XLVII

Inventor
Bruno Camerino
Robert Saiaky
Jean Robert

By Stevens, Davis, Miller & Mosher Attorneys

United States Patent Office

3,134,769

Patented May 26, 1964

1

3,134,769

1-METHYL-DIOSGENINS

Bruno Camerino and Roberto Sciaky, both of Via Turati 18, Milan, Italy, and Jean Robert, 28 Ave. Pasteur, Gentilly, Seine, France

Filed Aug. 9, 1961, Ser. No. 130,358
Claims priority, application Great Britain Oct. 28, 1959
11 Claims. (Cl. 260—239.55)

This invention relates to new steroid compounds, to new processes for the perparation of steroids and to compositions containing the said new compounds. More particularly, it concerns certain new and useful 1-methyl-genins, 1-methylene genins and 1-methyl-pregnane derivatives and a new and advantageous process for the preparation of 1-methyl-genins and 1-methyl-pregnane derivatives in general.

Some 1-methyl steroids are already known, but they either contain an aromatic nucleus (the A or B ring) or are derived from the 19-nor series and their preparation in both cases necessitates the transposition of the methyl group from the 10-to the 1-position; or they possess no double bond in the 4- or 5-position. For instance, the 1-methyl-Δ^6-dehydro-estrogens (described in United States Patent No. 2,671,092) may be prepared by rearrangement of $\Delta^{1,4,6}$-3-keto-dehydrosteroids by treating the latter with a catalyst capable of producing the dienone-phenol rearrangement; 1-methyl-19-nor-testosterone and its derivatives [Ringold et coll., J. Am. Chem. Soc., 78, 2477 (1956)] and 1-methyl-19-nor progesterone and its derivatives [Djerassi et coll., J. Am. Chem. Soc., 78, 2479 (1956)] may be obtained by Birch's reduction of the corresponding 1-methyl $\Delta^{1,3,5}$-3-alkoxy-estratrienes; and 1-methyl-Δ^1-3-keto-dehydrosteroids, may be prepared by the action of diazomethane on Δ^1-3-keto-dehydrosteroids, followed by pyrolysis of the adduct [as described in German Patent Auslegeschrift No. 1,023,764].

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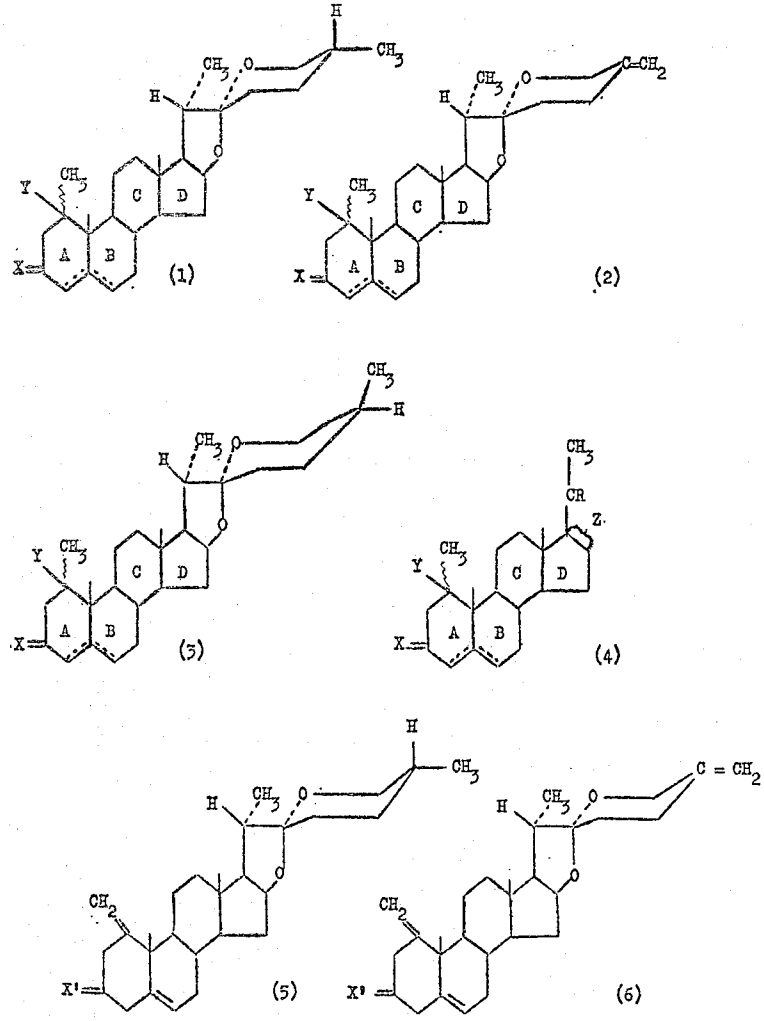
The present invention provides a method of introducing a methyl group into the 1-position of steroids possessing a double bond in the 5-position. The presence of the Δ^5 bond is fundamental, since it can easily be caused to migrate to the 4-position and the majority of physiologically active steroids, such as progestationals, androgens, and anti-inflammatories are Δ^4 compounds.

According to a first feature of the invention, there are provided new 1-methyl-steroids and 1-methylene steroids which are the 1-methyl genins of the following general Formulae 1, 2 and 3, the 1-methyl-pregnane derivatives of the following general Formula 4 and the 1-methylene-genins of the following general Formulae 5 and 6:



wherein the various symbols used have the following meanings:

X= =O or (α-H)β-OH or (α-H)β—$OCOCH_3$
X'=(α-H)β—OH or (α-H)β—$OCOCH_3$
Y= —H or —OH or —$OCOCH_3$ or Δ^1
Z=16α,17α-epoxy or 16β,-Br,17α-OH or 16-H,17α-OH or 16-H,17α-OR'' or 16-H,17α-H or Δ^{16}.

(It will be noted that there is an additional hydrogen atom present in the 16-position, which has not been mentioned in the aforesaid values of Z.)

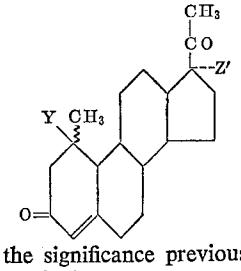
R= =O or (—H)—OH or (—H)—$OCOCH_3$
R''= an acyl group containing up to 9 carbon atoms,

derived from a cyclic or non-cyclic aliphatic carboxylic acid or from an aromatic carboxylic acid. (If R'' is derived from a cyclic aliphatic or aromatic acid, the group —CO— which is included may be attached directly to the nucleus or may occur in a side chain and R'' may represent, for example,

Utilising the nomenclature of M. E. Wall and S. Serota [J. Am. Chem. Soc. 79, 6481 (1957)], the spiroketal chain in general Formulae 1 and 5 has the configuration 20α, 22β, 25D, as in the case of diosgenin, and the spiroketal chain in general Formula 3 has the configuration 20α, 22β, 25L, as in the case of yamogenin. In general Formulae 2 and 6 the ethylenic spiroketal chain is the same as in neoruscogenin [J. Robert, R. Vaupre and G. Poiget, C. R. Acad. Sc. 250, 3187 (1960)]. In the general Formulae 1, 2 and 3 a double bond always exists in the 4,5- or 5,6-position and may exist in the 1,2-position. In general Formula 4 a double bond is always present in the 4,5- or 5,6-position and may exist in the 1,2-position and/or the 16,17-position.

The preferred compounds of the invention are the Δ^4, Δ^5, $\Delta^{5,16}$ and $\Delta^{1,4}$ derivatives, and more especially 1-methyl-1-hydroxy-diosgenin, 1-methyl-1-hydroxy-$\Delta^{25(27)}$-dehydrodiosgenin, 1-methyl-diosgenin, 1-methyl-yamogenin and derivatives of the pregnane series methylated in the 1-position.

The compounds of the foregoing Formulae 1, 2, 3, 5 and 6 are especially useful as intermediates for the preparation of derivatives of 1-methyl pregnanes and in particular those of Formula 4. The compounds of Formulae 1, 2, 3, 5 and 6 can be transformed by the reactions discussed later herein. The compounds of Formula 4, and especially those of the formula:



wherein Y has the significance previously assigned to it and Z' represents a hydrogen atom or a hydroxy or acetoxy group, are physiologically active compounds which exhibit progestative properties and may be employed in the treatment of the following conditions: primary amenorrhea, functional dysmenorrhea, hypo-oligo-menorrhea, sterility, menorrhagia, habitual abortion, threatened abortion and ovulatory disorders. This progestative activity

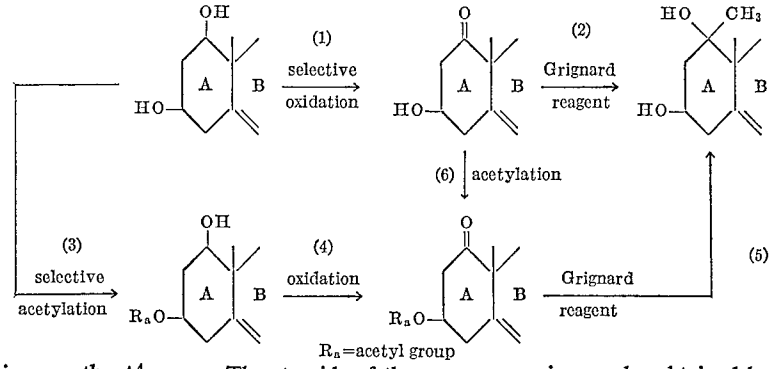
is particularly pronounced in the case of 1-methyl-17α-acetoxy-progesterone.

According to a further feature of the invention there is provided a method for the preparation of a 1-methyl-1-hydroxy-steroid which comprises subjecting a 1,3-dihydroxy-steroid to oxidation in the 1-position, and reacting the resultant 1-keto-steroid with a metallic derivative of methane.

In a specific application of the foregoing general method the formation of 1-methyl-1-hydroxy-genins, such as 1-methyl-1-hydroxy-diosgenin or 1-methyl-1-hydroxy-$\Delta^{25(27)}$-dehydrodiosgenin, is effected by the action of a metallic derivative of methane (also referred to herein as a "Grignard reagent"), such as CH_3MgI, CH_3Mg Br or CH_3Li, in an appropriate solvent, either:

(*a*) On 1-keto-genins having a free hydroxyl group in the 3-position, such as 1-keto-diosgenin or 1-keto-$\Delta^{25(27)}$-dehydrodiosgenin, which are prepared by selective oxidation in the 1-position of 1,3-dihydroxy-genins, such as ruscogenin and neoruscogenin (this is shown as route (1), (2) in the flow-sheet set out below) or

(*b*) On 1-keto-genins having an acetoxy group in the 3-position. The 3-acetoxy-1-keto-genins are obtained by selective acetylation of 1,3-dihydroxy-genins followed by oxidation in the 1-position or by selective oxidation in the 1-position of 1,3-dihydroxy-genins followed by acetylation in the 3-position (these are shown as routes (3), (4), (5) and (1), (6), (5), respectively, in the following flow sheet).



Ra=acetyl group

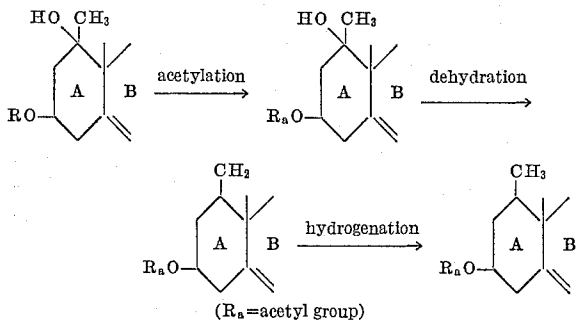
The steroids of the pregnane series can be obtained by similar methods. However, in the case of 20 keto-compounds, before proceeding with either of the above routes (1), (2) or (1), (6), (5) it is necessary to block the 20-keto group, for example by forming a cyclic acetal, so that it does not react with the Grignard reagent. Further, if the route (3), (4), (5) is used, it is preferable to reduce the 20-keto group to a secondary alcohol group and then to effect a selective acetylation in the 3- and 20-positions of the 1,3,20-triol obtained before oxidising in the 1-position. It is to be noted that, in the treatment by the above methods of compounds of the pregnane series, a 1-methyl-1,3-dihydroxy-20-keto-pregnane derivative is obtained by using the routes (1), (2) or (1), (6), (5), while a 1-methyl-1,3,20-trihydroxy-pregnane derivative is obtained by using the route (3), (4), (5). It is possible to convert the latter type of derivative to the corresponding 20-keto derivative.

As starting materials in carrying out the aforesaid process there may be employed ruscogenin and neoruscogenin which are steroidic sapogenins isolated from *Ruscus aculeatus* L. [H. Lapin, C. R. Acad. Sc. 244, 3065 (1957); Ch. Sannie and H. Lapin, Bull. Soc. Chim. 1237 (1957); J. Robert, R. Vaupre and G. Poiget, C. R. Acad. Sc., 250, 3187 (1960)].

According to a further feature of the invention there is provided a method for the preparation of a 1-methyl-steroid free from a hydroxyl group in the 1-position which comprises acetylating in the 3-position a 1-methyl-1,3-dihydroxy-steroid, dehydrating in the 1-position the

resultant 1-methyl-1-hydroxy-3-acetoxy-steroid and hydrogenating the 1 - methylene - 3 - acyloxy - steroid thus obtained.

In a specific application of the above general method for the production of a 1-methyl-steroid free from a hydroxyl group in the 1-position, 1-methyl-genins, such as 1-methyl-diosgenin and 1-methyl-yamogenin, may be prepared by hydrogenation of 1-methylene-genins obtained in a preponderant quantity by dehydration of 1-methyl-1-hydroxy-genins of which the hydroxyl group in the 3-position has been esterified. This may be schematically represented as follows:

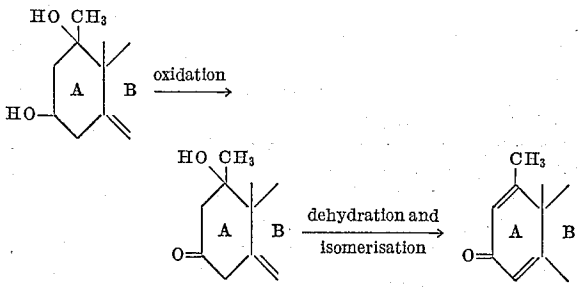


(R_a=acetyl group)

In an alternative route, for the preparation of the corresponding 3-hydroxy compound, the hydrogenation step is preceded by saponification of the 1-methylene-3-acetoxy compound. The same series of reactions can be carried out starting from 1-methyl-1-hydroxy-steroids of the pregnane series to produce 1-methyl-pregnane derivatives.

According to a further feature of the invention there is provided a modification of the method set forth above for the preparation of a 1-methyl-steroid free from a hydroxyl group in the 1-position wherein, for the preparation of 1-methyl-$\Delta^{1,4}$-3-keto-steroids, the said 1-methyl-1,3-dihydroxy-steroid is oxidised in the 3-position and the resultant 3-keto compound is dehydrated.

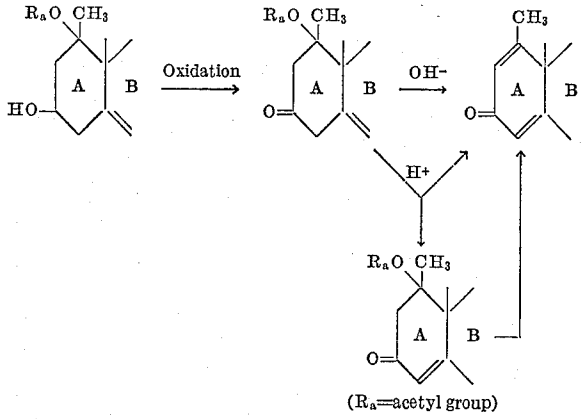
It will be observed that in the above modification, where the hydroxyl group in the 3-position is oxidised, the dehydration step gives, not the 1-methylene derivative, but the 1-methyl-Δ^1 derivative. And, further, since the dehydration is effected in a strongly acid or strongly alkaline medium, a transposition of the double bond from the 5-position to the 4-position occurs, which permits of directly isolating either the 1-methyl-$\Delta^{1,4}$-3-keto-genins or the 1-methyl-$\Delta^{1,4}$-3-keto-pregnane derivatives. As an alternative procedure it is possible to isomerise the said 3-keto compound, by treatment with an acid or alkali, into the corresponding Δ^4 derivative prior to the dehydration step. These procedures are diagrammatically represented as follows:



According to a further feature of the invention there is provided a second modification of the method set forth above for the preparation of a 1-methyl-steroid free from a hydroxyl group in the 1-position wherein, for the preparation of 1-methyl-$\Delta^{1,4}$-3-keto-steroids, a 1-methyl-1-acetoxy-3-hydroxy-steroid is oxidised in the 3-position and the 3-keto compound thus obtained is treated with an alkali or acid whereby the elements of an acetic

acid molecule are eliminated forming a double bond in the 1,2-position.

The series of transformations in the said second modification set forth above is accompanied by a transposition of the double bond in the Δ^5-position to the Δ^4-position and can be diagrammatically represented as follows:



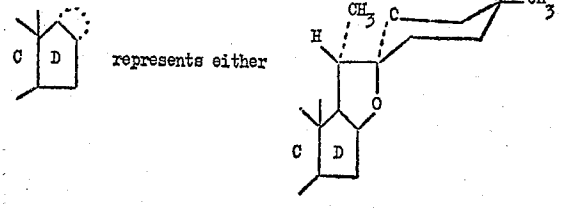
(R_a=acetyl group)

It will be observed that when the 3-keto compound is treated with acid, the product, depending upon the operating conditions, is either a 1-methyl-$\Delta^{1,4}$-3-keto-steroid or a 1-methyl-1-acetoxy-Δ^4-3-keto-steroid. The latter type of compound can be treated with acid or alkali to produce a Δ^1 double bond.

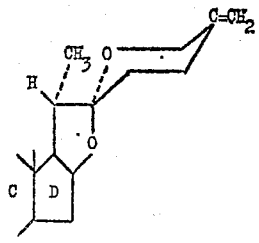
The various processes hereinbefore set forth are illustrated schematically in the accompanying drawings. The five sheets of drawings placed together in the following relative positions:

Sheet 1 Sheet 2
Sheet 5
Sheet 3 Sheet 4

constitute a complete flow-diagram showing the various steps in the processes referred to herein. In these drawings the symbol

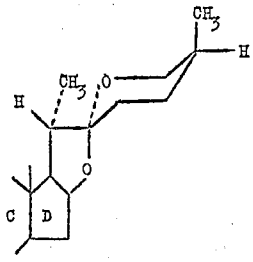


in the case of products having a 20α, 22β, 25D spiroketal chain, and these are represented by the letter "*a*" being placed after the Roman numeral allotted to each compound,



in the case of products having the ethylenic spiroketal chain of neuoruscogenin, and these are represented by

the letter "*b*" being placed after the Roman numeral allotted to each compound,



in the case of products having a 20α,22β,25L spiroketal chain, and these are represented by the letter "*c*" being placed after the Roman numeral allotted to each compound. In the formulae of the drawing, the group R'' has the meaning hereinbefore given, and Ac represents the acetyl group.

Referring now to the accompanying drawing, selective oxidation of ruscogenin (I*a*) or of neoruscogenin (I*b*) to 1-keto-diosgenin (II*a*) or 1-keto-$\Delta^{25(27)}$-dehydrodiosgenin (II*b*) can be carried out by the oxidation with pyridine CrO_3 complex of (I*a*) or (I*b*), dissolved in pyridine, for about 12 to 24 hours at room temperature and with agitation. It is also possible to effect the oxidation of (I*a*) or (I*b*), dissolved in an appropriate solvent such as acetone, with an aqueous solution of a mixture of chromic and sulphuric acids and operating at a temperature between −15° and +20° C.

By reaction of 1-keto-diosgenin (II*a*) or 1-keto-$\Delta^{25(27)}$-dehydrodiosgenin (II*b*) with a Grignard reagent such as methylmagnesium bromide or iodide, in a solvent such as benzene, ether or tetrahydrofuran, or binary mixtures of these solvents, followed by decompostion with acids or aqueous solution of ammonium chloride, there is obtained 1 - methyl - 1 - hydroxy - diosgenin (V*a*) or 1 - methyl-1-hydroxy-$\Delta^{25(27)}$-dehydrodiosgenin (V*b*). The same products (V*a*) and (V*b*) can be prepared by acetylation of (II*a*) or (II*b*), for example by means of acetic anhydride in pyridine to obtain the corresponding acetates (IV*a*) and (IV*b*), which are thereafter reacted with a Grignard reagent. These derivatives (IV*a*) and (IV*b*), can also be obtained from (I*a*) or (I*b*), of which selective acetylation in the 3-position gives the corresponding 3-acetates (III*a*) and (III*b*). The latter two compounds, dissolved in an appropriate solvent such as acetone, are oxidised at a temperature between −15° C. and +20° C. with an aqueous solution of a mixture of sulphuric and chromic acids.

Be degradation of 1-methyl-1-hydroxy-diosgenin (V*a*) or of 1 - methyl-1-hydroxy-$\Delta^{25(27)}$-dehydrodiosgenin (V*b*) there is obtained 1-methyl-$\Delta^{5,16}$-pregnadiene-1,3β-diol-20-one-1-acetate (VI), which can also be obtained by degradation of the products (XXIX*a*) and (XXIX*b*), of which the preparation will hereinafter be described.

The compound (VI), treated with hydrogen peroxide and alkali in methanolic solution, yields the 16α,17α-epoxy derivative (VII), which by acetylation with pyridine and acetic anhydride may be transformed into the 1,3-diacetate (IX). This product (IX) can be converted back to compound (VII) by saponification. 1-methyl-16α,17α-epoxy-$\Delta^{1,4}$-pregnadiene-3,20-dione (VIII) is synthesised from the 1,3-dihydroxy-1-acetate derivative (VII) which is oxidised, in an appropriate solvent such as acetone, with an aqueous solution of a mixture of chromic and sulphuric acids at −15° to +20° C. and treated with alcoholic alkali in order to obtain the Δ^1 double bond.

1 - methyl-16α,17α-epoxy-Δ^5-pregnen-1,3β-diol-20-one-diacetate (IX) reacts with hydrobromic acid to yield the bromohydrin (X), in which the bromine is replaced by hydrogen by hydrogenation of (X), in the presence of palladium on charcoal and in the presence of an alkaline reagent, such as triethylamine, ammonium acetate or calcium carbonate, to product (XI).

The product (XI) is acylated in the 17-position in the presence of toluene-p-sulphonic acid to give triacyl compound (XII) which is selectively saponified in the 3-position, for example with $KHCO_3$, to obtain (XIII) which, dissolved in an appropriate solvent such as acetone, is oxidised at a temperature between −15° and +20° C. with an aqueous solution of a mixture of chromic and sulphuric acids, to give (XIV). Alkali treatment of (XIV) causes the displacement of the double bond from position 5 to position 4, the elimination of the acetoxy group in position 1 with formation of a double bond in position 1 and, at the same time, the saponification of the acyloxy group in the 17-position, to yield 1-methyl-17α-hydroxy-1,2-dehydroprogesterone (XV).

The acid treatment of (XIV) eliminates the 1-acetoxy group with formation of a double bond in the 1-position, and also causes migration of the double bond in the 5-position to the 4-position. There is thus obtained 1-methyl - 17α - acyloxy-1,2-dehydroprogesterone (XVI). The product (XVI) can also be obtained by esterification of the hydroxyl group in the 17α-position of (XV), for example by treating it with a derivative of an acid R''OH, such as an anhydride or a chloride, in the presence of toluene-p-sulphonic acid.

Selective acetylation, with acetic anhydride and acetic acid under suitable conditions, is effected on Δ^5-pregnen-1β,3β,20β-triol (XVIII), prepared by reduction of Δ^5-pregnen - 1β,3β - diol-20-one-1,3 - diacetate (XVII) with $LiAlH_4$ in a suitable solvent such as tetrahydrofuran or ether, to obtain the 3,20-diacetate (XIX). The product (XVII) [which is prepared from ruscogenin (1*a*) or from neoruscogenin (I*b*) by acetylation of the hydroxyl groups situated in 1- and 3-positions, degradation of the diacetate and hydrogenation with palladium on charcoal] is known [H. Lapin Bull. Soc. Chim. 1501 (1957)].

The compound (XIX), dissolved in an appropriate solvent such as acetone, is oxidised at a temperature between −15° and +20° C. with an aqueous solution of a mixture of chromic and sulphuric acids to obtain Δ^5-pregnen-3β,20β-diol-1-one-3,20-diacetate (XX) which is treated with a Grignard reagent, such as CH_3MgI or CH_3MgBr, in a suitable solvent and subsequently decomposed, with an acid or a solution of NH_4Cl, to yield 1-methyl-Δ^5-pregnen-1,3β,20β-triol (XXI). By selective oxidation in the 20-position of (XXI), dissolved in an appropriate solvent such as acetone, with an aqueous solution of a mixture of chromic and sulphuric acids and at a temperature between −15° and +20° C., there may be obtained 1-methyl-Δ^5-pregnen-1,3β-diol-20-one (XXII) which is further oxidised in the 3-position under the same conditions to give 1-methyl-Δ^5-pregnen-1-ol-3,20-dione (XXIII), which may be prepared in a single step by oxidation of (XXI) under the above conditions. The product (XXIII) is rearranged to give 1-methyl-1-hydroxy-progesterone (XXIV).

On hydrogenation of the 1-monoacetate of 1-methyl-$\Delta^{5,16}$-pregnadiene-1,3β-diol-20-one (VI) in the presence of a catalyst such as palladium on charcoal, there is obtained the corresponding pregnene (XXV) which, dissolved in a suitable solvent such as acetone, is oxidised between −15° and +20° C. by an aqueous solution of a mixture of sulphuric acid and chromic acid to give 1-methyl-1-acetoxy-3,20-dioxo-pregn-5-ene (XXVI).

Treatment in acid medium of (XXVI) produces the migration of the double bond from the 5-position to the 4 - position to give 1-methyl-1-acetoxy-progesterone (XXVII).

Treatment in alkaline medium of (XXVI) produces the migration of the double bond from the 5-position to the 4-position and the elimination of the acetoxy group in the 1-position with formation of the double bond in

the 1-position to give 1-methyl-1,2-dehydro-progesterone (XXVIII), which can also be prepared from (XXIII) or (XXIV) or (XXVII).

1-methyl-1-hydroxy-diosgenin (V*a*) and 1-methyl-1-hydroxy-$\Delta^{25(27)}$-dehydrodiosgenin (V*b*) can be selectively acetylated in the 3-position to give the corresponding acetates (XXIX*a* and XXIX*b* respectively). Dehydration, for example by means of thionyl chloride, of the acetates gives essentially the 3-acetate of 1-methylene-diosgenin (XXX*a*) and the 3-acetate of 1-methylene-$\Delta^{25(27)}$-dehydrodiosgenin (XXX*b*) which, on catalytic hydrogenation, such as with palladium on charcoal, give the corresponding 1-methyl derivatives (XXXI*a* and XXXI*c*). By degradation of these latter compounds, there is obtained 1-methyl-3β-hydroxy-$\Delta^{5,16}$-pregnadien-20-one (XXXII), of which the double bond in the 16-position is selectively hydrogenated in the presence of a suitable catalyst such as palladium on charcoal. There is thus obtained 1-methyl-3β-hydroxy-Δ^5-pregnen-20-one (XXXIII), which, dissolved in an appropriate solvent such as acetone, is oxidised at a temperature between $-15°$ and $+20°$ C. with an aqueous solution of a mixture of chromic and sulphuric acids, to give 1-methyl-Δ^5-pregnen-3,20-dione (XXXIV). 1-methyl-progesterone (XXXV) is prepared from (XXXIV) by causing migration of the double bond from the 5-position to the 4-position by means of an acid or alkaline medium.

Saponification of (XXX*a*) and (XXX*b*) gives the corresponding 3-hydroxy derivatives (XXXVI*a*, XXXVI*b*) which, on hydrogenation in the presence of a catalyst such as palladium, gives 1-methyl-diosgenin (XXXVII*a*) and 1-methyl-yamogenin (XXXVII*c*), respectively.

The preparation of 1-methyl-17α-acetoxy-progesterone (XLVII) from the 3-acetate of 1-methylene-$\Delta^{25(27)}$-dehydrodiosgenin (XXX*b*) may be effected as follows. Degradation of (XXX*b*) gives 1-methylene-3β-acetoxy-$\Delta^{5,16}$-pregnadien-20-one (XXXVIII) which is dissolved in a suitable solvent such as methanol and epoxidised in the 16, 17-position, by treatment with hydrogen peroxide under strongly alkaline conditions, to give 1-methylene-3β-acetoxy-16α,17α-epoxy-Δ^5-pregnen-20-one (XXXIX). Acetylation of (XXXIX) forms the corresponding 3β-acetoxy compound (XL) and treatment of the latter in solution in peroxide-free dioxan with an iodine-free solution of hydriodic acid under oxygen-free conditions causes rupture of the epoxy ring giving 1-methylene-3β-acetoxy-16β-iodo-17α-hydroxy-Δ^5-pregnen-20-one (XLI). Reduction of (XLI) with Raney nickel and ethanol eliminates the 16β-iodine atom to give 1-methylene-3β-acetoxy-17α-hydroxy-Δ^5-pregnen-20-one (XLII) and acetylation of this compound gives the corresponding 17α-acetoxy compound (XLIII). Hydrogenation of (XLIII) in the presence of Adams' platinum saturates the 1-methylene group to give 1-methyl-3β,17α-diacetoxy-Δ^5-pregnen-20-one (XLIV) and by selective saponification of the latter in the 3-position with HCl and methanol there is obtained 1-methyl-3β-hydroxy-17α-acetoxy-Δ^5-pregnen-20-one (XLV). Oxidation of (XLV) with a solution prepared as described in procedure A(ii) which follows gives 1-methyl-17α-acetoxy-Δ^5-pregnen-3,20-dione (XLVI) and heating this in acid medium effects transposition of the Δ^5 double bond tto the 4-position thus giving 1-methyl-17α-acetoxy-progesterone (XLVII).

The examples set forth below will serve to illustrate the production of compounds according to the invention. The temperatures are given in degrees centigrade. The following procedures are illustrative of the production of intermediate compounds:

(A) 1-KETO-DIOSGENIN (II*a*) FROM RUSCOGENIN (I*a*)

(i) 40 grams of ruscogenin dissolved in 400 ml. of pyridine are added to a suspension of CrO_3-pyridine complex in pyridine (prepared from 40 g. of CrO_3 and 400 ml. of pyridine) with stirring and at room temperature. After 20 hours of stirring the mixture is poured into 3.2 l. of water. The product is extracted with benzene, the organic extracts are washed with water, dried and evaporated to dryness under vacuum. The residue is crystallised from ethyl acetate. Yield: 12.75 g. of 1-keto-diosgenin (II*a*) melting at 220–222°.

(ii) 14 millilitres of an oxidising solution (prepared from 266 g. of CrO_3, 230 ml. of conc. H_2SO_4, 400 ml. of water and the resulting solution diluted with water to 1 litre) are added to a solution of 20 g. of ruscogenin in 2400 ml. of acetone with stirring at $-15°$. After 1.5 minutes, 20 ml. of a 30% aqueous solution of $NaHSO_3$ are added and after 10 minutes stirring a solution of sodium acetate 3H_2O and 30 ml. of water) is introduced. The mixture is concentrated to 400 ml. under vacuum and slowly poured into 2 l. of water. The prepiciptate is filtered, washed with water, dried and crystallised from acetone. Yield: 10.16 g. of (II*a*) melting at 218°–224°.

(B) RUSCOGENIN-3-ACETATE (III*a*) FROM RUSCOGENIN (I*a*)

A mixture of 140 g. of ruscogenin, 3360 ml. of acetic acid and 560 g. of acetic anhydride is heated for 18 hours at 60°. The solution is evaporated to dryness in vacuo. The crystalline residue is washed with 1 litre of ether, in which the 3-acetate of ruscogenin is scarcely soluble. After filtration, washing with ether and drying of the insoluble matter, there are obtained 49 g. of the first fraction, melting point 228–231°.

The residue obtained by evaporation of the washing ether of the first fraction is agitated for 1 hour with 460 ml. of boiling di-isopropyl ether. The suspension is filtered while hot and the insoluble matter is washed with 100 ml. of di-isopropyl ether.

After drying, there are recovered 17.5 g. of the second fraction, instantaneous melting point 229–231°.

Saponification with alcoholic potassium hydroxide of the residue of evaporation of the diisopropyl ether which has been employed to purify the second fraction permits of recovering 67 g. of ruscogenin, melting point 198–202°.

(C) NEORUSCOGENIN-3-ACETATE (III*b*) FROM NEORUSCOGENIN (I*b*)

By proceeding as in the case of ruscogenin, 140 g. of neoruscogenin give:

Neoruscogenin-3-acetate, first fraction: 57 g., melting point 240–245°.

Neoruscogenin-3-acetate, second fraction, recrystallised from isopropanol: 11.4 g., melting point 240–245°.

Saponification by means of alcoholic potassium hydroxide of the residue of evaporation of the mother liquors of the second fraction permits of recovering 75 g. of neoruscogenin, melting point 192–200°.

(D) 1-KETO-DIOSGENIN-3-ACETATE (IV*a*) FROM (II*a*)

A mixture of 12.75 g. of (II*a*), 51 ml. of pyridine and 19 ml. of acetic anhydride is shaken over-night at room temperature. The solution is then warmed on a water-bath for 15 minutes and poured into 500 ml. of water. The precipitate is filtered, washed with water and dried. Yield: 14 g. of the acetate (IV*a*) melting at 192–194°.

(E) 1-KETO-DIOSGENIN-3-ACETATE (IV*a*) FROM (III*a*)

34 g. of ruscogenin-3-acetate dissolved in 4590 ml. of acetone are treated with 20.4 ml. of the oxidising solution prepared in procedure A(ii) at 13–15° with agitation in a nitrogen atmosphere. The solution is agitated

for 4 minutes, whereafter 4590 ml. of water are added thereto. After agitation for 1 hour at 0°, the precipitate is filtered, washed with 50% acetone and dried. There are obtained 32.2 g. of 1-keto-diosgenin-3-acetate melting at 192–194°.

(F) 1-KETO-$\Delta^{25(27)}$-DEHYDRODIOSGENIN-3 ACETATE (IV*b*) FROM (III*b*)

25 g. of neoruscogenin-3-acetate dissolved in 3375 ml. of acetone are treated with 15 ml. of the oxidising solution prepared in procedure A(ii) at 15° with agitation in a nitrogen atmosphere. The solution is agitated for 4 minutes, whereafter 3375 ml. of water are added thereto. After agitation for a quarter of an hour, the precipitate is filtered, washed with 50% acetone and dried. There are obtained 22.3 g. of 1-keto-$\Delta^{25(27)}$-dehydrodiosgenin-3-acetate, M.P. 228–232°.

Example 1

1-METHYL-1-HYDROXY-DIOSGENIN (V*a*) FROM (II*a*)

16.96 grams of 1-keto-diosgenin dissolved in 400 ml. of anhydrous benzene are added to a solution of methylmagnesium iodide in ether (prepared from 40 g. of Mg, 130 g. of CH_3I and 760 ml. of anhydrous ether). The suspension is warmed at 4547° for 7 days and then slowly poured into an aqueous solution of NH_4Cl in water (360 g. of NH_4Cl in 1900 ml. of iced water). The organic layer is separated and the aqueous solution is extracted with ether again. The combined organic extracts are washed with water, dried and evaporated to dryness. The residue is dissolved in 150 ml. of benzene and chromatographed on 400 g. of Florisil. 1-methyl-1-hydroxy-diosgenin is eluted with a benzene-ether mixture (1:1). 13.4 grams of (V*a*) melting at 200° are obtained.

Example 2

1-METHYL-1-HYDROXY-DIOSGENIN (V*a*) FROM (IV*a*)

To a solution of CH_3MgI (prepared from 2.9 g. of Mg and 17 g. of CH_3I) in 255 ml. of anhydrous ether is slowly added with gentle boiling a solution of 9.5 g. of (IV*a*) in 500 ml. of tetrahydrofuran. This addition takes about 1 hour. Ether is distilled off and, during the distillation, tetrahydrofuran is added until the internal temperature rises to 63°. At this point the distillation is interrupted and the mixture is boiled for 15 hours. The suspension is treated with 400 ml. of a 25% aqueous solution of NH_4Cl and, by operating in the usual manner, 5.1 g. of crude 1-methyl-1-hydroxy-diosgenin melting at 195–205° is obtained. After crystallisation from aqueous methanol there is obtained 4.35 g. of pure 1-methyl-1-hydroxy-diosgenin (V*a*) melting at 215–216°.

Example 3

1-METHYL-1-HYDROXY-$\Delta^{25(27)}$-DEHYDRODIOSGENIN (V*b*) FROM (IV*b*)

To a solution of methylmagnesium iodide (prepared from 3.86 g. of magnesium and 24.85 g. of methyl iodide in 266 ml. of anhydrous ether) there is added slowly a solution of 10 g. of 1-keto-$\Delta^{25(27)}$-dehydrodiosgenin-3-acetate (IV*b*) in 350 ml. of anhydrous benzene. The mixture is refluxed for 3 hours, shaken for a further 15 hours at room temperature and then treated with 500 ml. of a 25% aqueous solution of ammonium chloride.

After the usual treatment, the crude product dissolved in benzene is chromatographed on 95 g. of Woelm neutral alumina (activity:1). A small ketone fraction is eluted by 380 ml. of benzene and then the column is eluted by 950 ml. of ethanol. The alcoholic eluate is evaporated to dryness under vacuum and the residue is recrystallised from a 10% solution of methanol in di-isopropyl ether. There is obtained 3.55 g. of 1-methyl-1-hydroxy-$\Delta^{25(27)}$-dehydrodiosgenin (V*b*), melting at 168–176°. The pure product, obtained by crystallisation from ethyl acetate, melts at 192–194°.

Example 4

1-METHYL-1-HYDROXY-DIOSGENIN-3-ACETATE (XXIX*a*) FROM (V*a*)

A solution of 4.1 g. of (V*a*) in 8 ml. of pyridine and 4 ml. of acetic anhydride is heated for 1 hour on a water bath. After cooling, the solution is poured into 120 ml. of iced water. The precipitate is filtered, washed with water and dried.

4.25 grams of (XXIX*a*), M.P. 185–190°, are obtained. After recrystallisation from ethanol, the product melts at 197–198°.

Example 5

1-METHYL-1-HYDROXY-$\Delta^{25(27)}$-DEHYDRODIOSGENIN-3-ACETATE (XXIX*b*) FROM (V*b*)

A solution of 4 g. of (V*b*) in 36 ml. of pyridine and 25 ml. of acetic anhydride is heated for 1 hour on a water bath. After cooling, the solution is poured into 300 ml. of iced water. The precipitate is filtered, washed with water and dried. After recrystallisation from ethanol, 2.85 g. of (XXIX*b*) are obtained, M.P. 222–226°.

Example 6

1-METHYLENE-DIOSGENIN-3-ACETATE (XXX*a*) FROM (XXIX*a*)

6 millilitres of thionyl chloride are poured drop-by-drop into a solution of 10 g. of (XXIX*a*) in 170 ml. of pyridine maintained at 0°. The solution is then agitated for 15 minutes at 0° and then poured into 900 ml. of iced water. The precipitate is filtered, washed with water, dried and recrystallised from ethanol and then from isopropanol. 4.37 g. of (XXX*a*) are obtained, M.P. 156°.

Example 7

1-METHYL-DIOSGENIN-3-ACETATE (XXXI*a*) FROM (XXX*a*)

2 grams of 1-methylene-diosgenin-3-acetate (XXX*a*) are hydrogenated in 225 ml. of ethanol in the presence of 1.5 g. of 5% palladium on charcoal at room temperature and atmospheric pressure. After fixation of 1 mole equivalent of hydrogen, the hydrogenation is stopped. The catalyst is filtered and the alcoholic liquor distilled to dryness in vacuo.

After repeated recrystallisations of the residue from ethanol, 0.4 g. of (XXXI*a*) are obtained, M.P. 146–148°, $[\alpha]_D^{22}$ (c.=1, $CHCl_3$)=−90°.

Example 8

1-METHYLENE-$\Delta^{25(27)}$-DEHYDRODIOSGENIN-3-ACETATE (XXX*b*) FROM (XXIX*b*)

6.9 millilitres of thionyl chloride are poured drop-by-drop into a solution of 11.5 g. of (XXIX*b*) in 195 ml. of pyridine maintained at 0°. The solution is thereafter agitated for 15 minutes at 0° and then poured into 1 litre of ice water. The precipitate is filtered, washed with water, dried and recrystallised from ethanol. 9.6 grams of (XXX*b*) are obtained, M.P. 145–155°. The pure product obtained by repeated crystallisations from ethanol melts at 185–187°.

Example 9

1-METHYL-YAMOGENIN-3-ACETATE (XXXI*c*) FROM (XXX*b*)

5.7 grams of 1-methylene-$\Delta^{25(27)}$-dehydrodiosgenin-3-acetate (XXX*b*) are hydrogenated in 635 cc. of ethanol in the presence of 5.7 g. of 5% palladium on charcoal under atmospheric pressure and at ambient temperature. After fixation of 2 mole equivalents of hydrogen, the hydrogenation is stopped. The catalyst is filtered and the alcoholic liquor is evaporated to dryness in vacuo.

After crystallisation of the residue from isopropanol, 2.81 g. of (XXXI*c*) are obtained, M.P.=181–183°, $[\alpha]_D^{22}$ (c.=1, $CHCl_3$)=−90°.

Example 10

1-METHYLENE-DIOSGENIN (XXXVI*a*) FROM (XXX*a*)

8.17 grams of 1 - methylene - diosgenin - 3 - acetate (XXX*a*), prepared as described in Example 6 are added to a solution of 8.17 g. of potassium hydroxide pellets in 817 cc. of methanol; the mixture is heated to reflux for one hour under nitrogen and with agitation. After cooling the solution 8.17 cc. of acetic acid are added thereto and the mixture is evaporated to dryness under vacuum; the crystalline residue is taken up in 250 cc. of water, the solution filtered and the residue washed with water and then dried over night under vacuum in the presence of concentrated sulphuric acid.

The crude produce is dissolved in 134 cc. of benzene and then chromatographed on a column of silica gel (134 g.). Elution of the column with a benzene ethyl acetate mixture (95:5) leads to the isolation of 5.09 g. of 1-methylene-diosgenin, M.P. 148°–149°, $[\alpha]_D^{20}$ $=-91°\pm5°$ (c.=1, chloro-form).

Example 11

1-METHYLENE-$\Delta^{25(27)}$-DEHYDRODIOSGENIN (XXXVI*b*) FROM (XXX*b*)

Following the procedure described in Example 10, but starting with 13.3 g. of 1-methylene-$\Delta^{25(27)}$-dehydrodiosgenin-3-acetate (XXX*b*) (M.P. 145–155°) prepared as described in Example 8, there is obtained 5.73 g. of 1-methylene-$\Delta^{25(27)}$-dehydrodiosgenin, M.P. 171–173°.

Example 12

1-METHYL-DIOSGENIN (XXXVII*a*) FROM (XXXVI*a*)

1.33 grams of 1-methylene-diosgenin (XXXVI*a*) dissolved in 66 cc. of ethanol are hydrogenated in the presence of 2.66 g. of 3% palladium on charcoal under atmospheric pressure and at room temperature. The hydrogenation is stopped after the absorption of 1.4 mole equivalents of hydrogen; the catalyst is then filtered off and the ethanolic solution evaporated to dryness under vacuum.

The crude product is dissolved in 50 cc. of benzene and then chromatographed on a column of silica gel (25 g.). Elution of the column with a benzene-ethyl acetate mixture (9:1) gives 0.63 g. of 1-methyl-diosgenin, M.P. 125–130°.

Example 13

1-METHYL-YAMOGENIN (XXXVII*c*) FROM (XXXVI*b*)

2 grams of 1 - methylene - $\Delta^{25(27)}$ - dehydrodiosgenin (XXXVI*b*) dissolved in 100 cc. of ethyl acetate are hydrogenated in the presence of 1.6 g. of 10% palladium on barium sulphate under atmospheric pressure and at room temperature. The hydrogenation is stopped after the absorption of 2.3 mole equivalents of hydrogen; the catalyst is then filtered off and the filtrate evaporated to dryness under vacuum.

The crude product is purified by two crystallisations from ethanol and there is obtained 0.32 g. of 1-methyl-yamogenin, M.P. 177°–178°.

Example 14

1-METHYL-DIOSGENIN ACETATE (XXXI*a*) FROM (XXX*a*)

6.9 grams of 1-methylene-diosgenin acetate (XXX*a*) are hydrogenated in a mixture of 414 cc. ethyl acetate and 13.8 cc. acetic acid in the presence of 0.69 g. of Adams' platinum at ordinary pressure and temperature; the absorption of hydrogen is very rapid and when it falls to about 2 cc. of hydrogen per minute the hydrogenation is stopped, the volume of hydrogen absorbed then corresponding to about 1.1 molecular equivalents. The duration of the hydrogenation is 45 minutes.

The catalyst is filtered off and the filtrate evaporated to dryness under vacuum. After recrystallisation of the residue from 63 cc. of ethanol there is obtained 4.49 g. of (XXXI*a*), melting point 147°–149°, $[\alpha]_D^{26}=-92°\pm2°$ (c.=1, chloroform).

This application is a continuation-in-part of application Serial No. 64,462, filed October 24, 1960, now abandoned.

We claim:

1. 1-methylene-diosgenin.
2. 1-methylene-diosgenin-3-acetate.
3. 1-methylene-$\Delta^{25(27)}$-dehydrodiosgenin.
4. 1-methylene-$\Delta^{25(27)}$-dehydrodiosgenin-3-acetate.
5. A process for the preparation of a compound selected from the class consisting of 1-methyl-1-hydroxy-diosgenin and 1-methyl-1-hydroxy - $\Delta^{25(27)}$ - dehydrodiosgenin which comprises oxidising in the 1-position a compound selected from the class consisting of ruscogenin and neoruscogenin with a reagent selected from the class consisting of a sulphuric acid-chromic acid mixture and a pyridine-chromic anhydride complex, reacting the 1-keto derivative thus obtained with a methyl magnesium halide and hydrolysing the resultant magnesium complex.
6. A process for the preparation of a compound selected from the class consisting of 1-methyl-1-hydroxy-diosgenin and 1-methyl-1-hydroxy - $\Delta^{25(27)}$ - dehydrodiosgenin which comprises acetylating in the 3-position a compound selected from the class consisting of ruscogenin and neoruscogenin with acetic anhydride, oxidising the acetyl derivative obtained with an agent selected from the class consisting of a sulphuric acid-chromic acid mixture and a pyridine-chromic anhydride complex, whereby the 1-hydroxy group is converted to a 1-oxo group, reacting the keto derivative obtained with a methyl magnesium halide and hydrolysing the resultant magnesium complex.
7. A process for the preparation of a compound selected from the class consisting of 1-methylene-diosgenin and 1-methylene-$\Delta^{25(27)}$-dehydrodiosgenin which comprises acetylating in the 3-position a compound selected from the class consisting of 1-methyl-1-hydroxy-diosgenin and 1-methyl-1-hydroxy - $\Delta^{25(27)}$ - dehydrodiosgenin with acetic anhydride, reacting the acetyl derivative thus obtained with thionyl chloride and de-acetylating the resultant product by reacting it with an alkali metal hydroxide.
8. A process for the preparation of a compound selected from the class consisting of 1-methyl-diosgenin and 1-methyl-yamogenin which comprises hydrogenating a compound selected from the class consisting of 1-methylene-diosgenin and 1-methylene-$\Delta^{25(27)}$-dehydrodiosgenin with hydrogen in the presence of palladium.
9. A process for the preparation of a compound selected from the class consisting of 1-methyl-diosgenin-3-acetate and 1-methyl-yamogenin-3-acetate which comprises hydrogenating a compound selected from the class consisting of 1-methylene-diosgenin-3-acetate and 1-methylene - $\Delta^{25(27)}$ - dehydrodiosgenin - 3 - acetate in an ethyl acetate-acetic acid medium and in the presence of a reagent selected from the class consisting of palladium and Adams' platinum.
10. 1-methyl - 1 - hydroxy - $\Delta^{25(27)}$ - dehydrodiosgenin which has melting point 192–194° C.
11. 1-methyl - 1 - hydroxy - $\Delta^{25(27)}$ - dehydrodiosgenin 3-acetate which has melting point 222–226° C.

References Cited in the file of this patent

Fieser et al.: Steroids (1959), Reinhold Publishing Company, pages 549 and 831 relied on.