[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

# Steroidal Sapogenins. LVI. The Preparation of 12-Methyl Sapogenins[2]

BY SAMUEL G. LEVINE AND MONROE E. WALL

RECEIVED NOVEMBER 4, 1959

The reaction of hecogenin acetate with methylmagnesium bromide leads to 12β-hydroxy-12α-methyltigogenin from which the opposite C-12 epimer and various other C-12 substituted steroids were prepared.

During the past few years, interest in the synthesis of methylsubstituted steroidal hormone analogs has increased at a rapid pace; compounds having this type of substitution at various of the nuclear centers have already been prepared.[3] Our interest in steroidal sapogenins as hormone precursors has led us to investigate the conversion of the C-12 ketone hecogenin acetate (I) to 12-methylated products. It will also be seen that the reaction scheme here involved is one which holds promise of concomitantly facilitating the chemical introduction of oxygen at the C-11 methylene group. In the present paper we describe the first phase of our work along these lines.

The reaction of hecogenin acetate (I) with an excess of methylmagnesium bromide led to the loss of the 3-acetate group as well as addition to the 12-ketone function, giving rise to a carbonyl-free, hydroxylic product, $C_{28}H_{46}O_4$, in 86% yield. This substance formed a monoacetate and a monobenzoate under mild esterifying conditions, each ester still exhibiting hydroxyl absorption at 3600 cm.$^{-1}$. These properties are in accord with the expected secondary–tertiary diol structure IIa[4] for the Grignard reaction product. Further experiments here reported confirm this assignment and indicate the C-12 stereochemistry.

Attempted dehydration of the tertiary alcohol function of IIa under acidic (olefin equilibrating) conditions led, in most cases, to amorphous products lacking the infrared absorption pattern characteristic of spiroketal systems.[5] However, treatment of IIa with methanolic hydrogen chloride followed by mild acetylation gave a low yield of crystalline, hydroxyl-free product having an elemental analysis and infrared spectrum in good agreement with the tertiary chloride structure IIIb; a rearranged structure for this substance is, however, not excluded. The major reaction product was, again, intractable.

In marked contrast, treatment of the diol monoacetate IIb with thionyl chloride in pyridine at low temperature caused complete loss of the hydroxyl function with no sign of attendant spiroketal rupture. The reaction product was, however, not uniform but could be partly separated by crystallization into two components: A, m.p. 180° (20%), and B, m.p. 164° (11%). These were found to be isomeric compounds corresponding in empirical formula ($C_{30}H_{46}O_4$) to loss of one molecule of water from the starting alcohol.

If the dehydration reaction had taken place without rearrangement, then one would anticipate the identification of the isomeric products as the simple *exo* (IVb) and *endo* (Vb) olefins. The spectral properties of these compounds are, in fact, in good agreement with these assignments. Thus, olefin A had infrared bands at 3050, 1644 and 887 cm.$^{-1}$ characteristic of a vinylidene group.[6] Olefin B gave rise, instead, to absorption in the 800 cm.$^{-1}$ region as expected for a trisubstituted double bond.[6] The low wave length ultraviolet absorption of these two isomers was consistent with these tentative assignments. The molecular extinction coefficients at 210, 215 and 220 mμ were 485, 123 and 79, respectively, for olefin A. The corresponding values for olefin B were 3740, 1690 and 397; these higher values are in accord[7] with the higher degree of double bond substitution suspected in this compound.

The unrearranged structure of olefin A was put on a firm basis by the following degradation. Treatment of this olefin with osmium tetroxide in benzene solution followed by decomposition of the black osmate with hydrogen sulfide[8] gave a triol monoacetate, $C_{30}H_{48}O_6$ (VIIb). A solution of this substance in ethanolic periodic acid yielded pure hecogenin acetate (I), crystallizing directly from the reaction solution. Olefin A must then be assigned the 12-methylene tigogenin acetate structure IVb.[9]

Mild catalytic hydrogenation of 12-methylenetigogenin acetate (IVb) did not attack the spiroketal system but gave a dihydro-product, $C_{30}H_{48}O_4$. Assuming delivery of hydrogen from the less hindered (α) side of the molecule,[10] this substance must be formulated as 12β-methyltigogenin acetate (VIb). The identical reduction product was obtained (after a longer reaction time) from olefin B.

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted.

(2) Previous paper in this series, Steroidal Sapogenins, LV, Monroe E. Wall, *et al.*, *J. Am. Pharm. Assoc., Sci. Ed.*, in press (1960); presented in part at the 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April 5–14, 1960.

(3) *E.g.*, see W. P. Schneider, F. H. Lincoln, G. B. Spero, H. C. Murray and J. L. Thompson, THIS JOURNAL, **81**, 3167 (1939), and references cited.

(4) Our designations for the various products derived from hecogenin will bear the letter "a" when the 3-alcohol function is present and the letter "b" when a 3-acetate is present.

(5) (a) C. R. Eddy, M. E. Wall and M. K. Scott, *Anal. Chem.*, **25**, 266 (1953); (b) R. N. Jones, E. Katzenellenbogen and K. Dobriner, THIS JOURNAL, **75**, 158 (1953).

(6) (a) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 31; (b) J. L. Beton, T. G. Halsall, E. R. H. Jones and P. C. Phillips, *J. Chem. Soc.*, 753 (1957).

(7) P. Bladon, H. B. Henbest and G. W. Wood, *ibid.*, 2737 (1952).

(8) D. H. R. Barton and D. Elad, *ibid.*, 2085 (1956).

(9) The preparation of 12-methylenetigogenin (IVa) *via* the reaction of hecogenin acetate with triphenyl phosphine-methylene has already been reported (F. Sondheimer and R. Mechoulam, THIS JOURNAL, **79**, 5029 (1957)).

(10) Catalytic hydrogenation of hecogenin acetate takes place from the less hindered side to produce rockogenin acetate, the 12β-hydroxy epimer (G. P. Mueller, L. L. Norton, R. E. Stobaugh, Lin Tsai and R. S. Winniford, *ibid.*, **75**, 4892 (1953)).

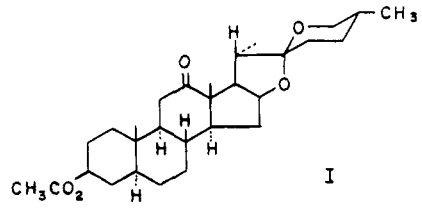

Fig. 1.

It is evident, then, that both olefins have the same carbon skeleton and are formed by simple dehydration of the tertiary alcohol 11b.[11] Olefin B is thus established as 12-methyl-$\Delta^{11}$-tigogenin acetate (Vb).

The two olefins differed sharply in their respective rates of reaction with hydrogen chloride in methanol. Such treatment of 12-methylenetigogenin acetate (IVb) followed by reacetylation produced a wide melting (178–190°), halogenated product mixture completely free of infrared bands characteristic of the starting olefin. The spectrum was, however, very similar to that of the chloro-substitution product IIIb earlier obtained from the 12-carbinol IIa. The *endo*-olefin Vb was recovered substantially unchanged after reaction with methanolic hydrogen chloride and subsequent reacetylation.

At this point, we were interested in two, as yet unanswered, questions: (a) What is the C-12 configuration of the Grignard addition product II? (b) What is the actual composition of the thionyl chloride–pyridine product mixture? These questions are, of course, not unrelated in view of the likely relationship between the stereochemistry of a tertiary alcohol and its course of dehydration.

The C-12 configuration of the Grignard product IIa cannot be confidently assigned from its mode of formation. Such tertiary alcohols have been thought to arise *via* attack by Grignard reagent from the less hindered (here $\alpha$) side of the carbonyl function. The insufficiency of this line of reasoning has, however, been well demonstrated.[12]

Epimeric 1-methylcyclohexanol derivatives have been distinguished[13] by means of their characteristic infrared absorption at 940 cm.$^{-1}$ (equatorial) or 890 cm.$^{-1}$ (axial). In the spectrum of the tertiary alcohol II, however, these regions are obscured by spiroketal absorption.

An approach to the above stereochemical problems was sought, then, through an unequivocal synthesis of the methylcarbinol IIb or of its C-12 epimer.

The previously mentioned reaction of osmium tetroxide with 12-methylenetigogenin acetate (IVb) can be presumed to take place by attack of the reagent from the less hindered[14] $\alpha$-side of the

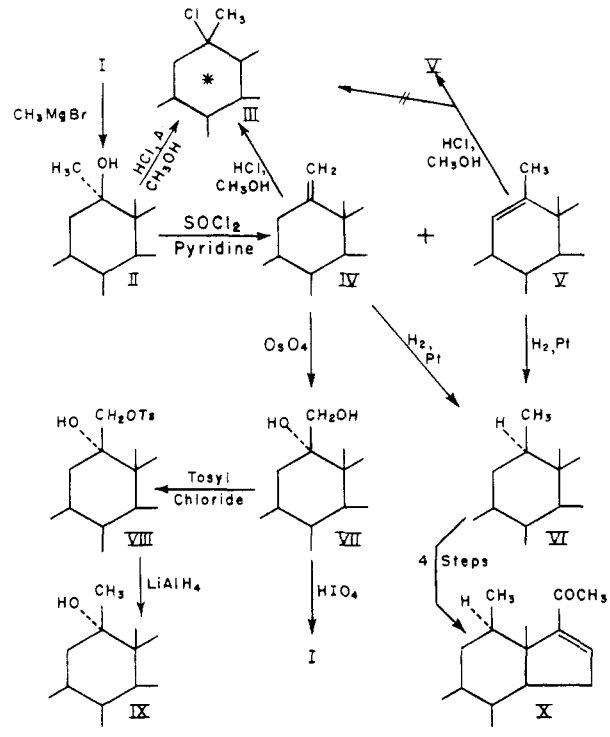


Fig. 2.

unsaturated center leading to the 12$\alpha$-hydroxy-12$\beta$-hydroxymethyl epimer VIIb. Treatment of this triol monoacetate with *p*-toluenesulfonyl chloride in pyridine gave the monotosylate VIIIb. Reduction of this substance by prolonged heating with lithium aluminum hydride in tetrahydrofuran gave a diol which, on reacetylation, produced 12$\alpha$-hydroxy-12$\beta$-methyltigogenin acetate (IXb), m.p. 212.5–213°. The infrared absorption spectrum of this compound, though similar to that of the acetylated Grignard product IIb, m.p. 220°, displayed distinct intensity differences in the regions of 940, 925 and 830 cm.$^{-1}$. The latter compound must, then, possess the opposite C-12 configuration and may be designated as 12$\beta$-hydroxy-12$\alpha$-methyltigogenin acetate (IIb).

It could now be ascertained that the reaction of hecogenin acetate with methylmagnesium bromide did not lead uniformly to the 12$\beta$-hydroxy-12$\alpha$-methyl epimer IIa. The concentrated mother liquors from this preparation afforded additional crystalline but side melting material (9%). The infrared spectrum of this material was different from that of the first crop but was nearly identical with the spectrum of the epimer IXa over the entire frequency range.

With both C-12 epimeric alcohols in hand, it was of particular interest to re-examine the thionyl chloride–pyridine dehydration reaction. Each isomer was accordingly treated with thionyl chloride in pyridine at 0°. No attempt was made to separate pure substances from either reaction mixture but the product composition was, in each case, investigated by halogen determination and infrared analysis. The results are given in Table I.

(11) It is interesting that the cyanohydrin of hecogenin acetate (IIb, 12-CN instead of 12-CH$_3$), on treatment with thionyl chloride in pyridine, is reported to result in dehydration *with carbon skeleton rearrangement* (R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey and N. L. Wendler, THIS JOURNAL, **76**, 4013 (1954)).

(12) L. Ruzicka, N. Wahba, P. Th. Herzig and H. Heusser, *Ber.*, **85**, 491 (1952).

(13) D. H. R. Barton, A. da S. Campos-Neves and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

(14) W. Klyne, "The Chemistry of the Steroids," Methuen, London, 1957, p. 56; see also, T. F. Gallagher and T. H. Kritchevsky, THIS JOURNAL, **72**, 882 (1950).

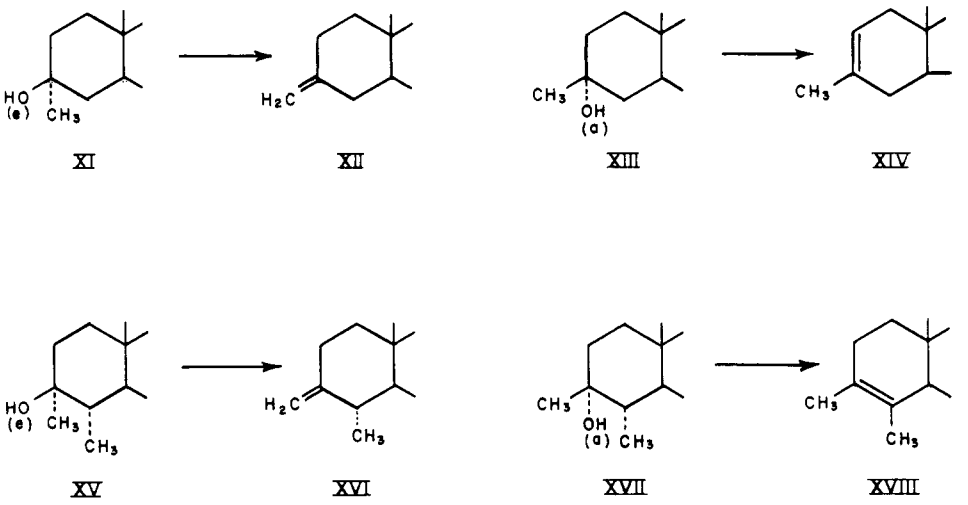


Fig. 3.

Though we regard these figures as approximate only, it is nevertheless clear that the epimeric alcohols yield respective thionyl chloride reaction products of generally similar composition. These results are in marked contrast with those recently reported for the *phosphoryl chloride* dehydration of certain other tertiary alcohols of the 1-methylcyclohexanol type. Thus Barton, *et al.*,[13] have reported that dehydration of 3$\alpha$-methylcholestan-3$\beta$-ol (XI) under these conditions led mostly to 3-methylenecholestane (XII) whereas the epimeric carbinol XIII gave exclusively 3-methylcholest-2-en (XIV). Jones and co-workers,[6b] in studying the similar dehydration of the epimeric 3,4-dimethylcholestanols have likewise found a sharp dependence of olefin structure on alcohol configuration; 3$\alpha$,4$\alpha$-dimethylcholestan-3$\beta$-ol (XV) gave

TABLE I

THIONYL CHLORIDE REACTION PRODUCTS FROM THE EPIMERIC 12-CARBINOLS

| C-12 Epimer | Conformation of hydroxyl | Chloro-[a] product, % | *exo*-[b] Olefin, % | *endo*-[c] Olefin, % |
|---|---|---|---|---|
| 12$\alpha$-Hydroxy-12$\beta$-methyl (IXb) | Axial | 21 | 39 | 40 |
| 12$\beta$-Hydroxy-12$\alpha$-methyl (IIb) | Equatorial | 9 | 35 | 56 |

[a] Calculated as $C_{30}H_{47}O_4Cl$. [b] Obtained by matching the intensity of the 1645 cm.$^{-1}$ (C=$CH_2$) band against known mixtures of olefins IV and V. [c] By difference.

the vinylidene product XVI in contrast to the tetrasubstituted olefin XVIII formed from the opposite C-3 epimer XVII. The preferential production of exocyclic olefins from equatorial alcohols and *endo*-olefins from axial alcohols is thus evident. Similar examples from other series are found in the phosphoryl chloride–pyridine dehydration of the epimeric 17$\alpha$-methyl-17-hydroxy D-homosteroids[15] and in the dehydration of the sesquiterpene maaliol[16] and the diterpene labdanolic acid[17] (as the methyl ester).[18] From results of this kind it has been inferred[18] that the course of phosphoryl chloride dehydration of 1-methylcyclohexanols involves a *trans* and co-planar four-center (hence concerted) reaction requiring the loss of a suitably disposed hydrogen atom.

The lack of stereospecificity in the dehydration of our epimeric tertiary carbinols was consequently unexpected. It is possible that the course of thionyl chloride dehydration is inherently less dependent on alcohol configuration than that of similar reactions with phosphoryl chloride. There is, however, another factor, specific to the ring C alcohols which may oppose a concerted, selective elimination process. Firstly, the concerted, *trans* diaxial dehydration of the axial alcohol IXb to form the endocyclic olefin Vb would require base attack on the highly hindered 11$\beta$-hydrogen atom. Secondly, with either of the epimeric alcohols there may be a strong driving force for *ionization* of the derived chlorosulfonate leading to the tertiary carbonium ion XIX. The formation of this trivalent center at C-12 would be expected[19] to reduce the axial character of the 11$\beta$-hydrogen atom with consequent release of compression energy.[20] Such an intermediate could account for the near random production of olefinic products from the 12-methylcarbinols.

Either the *exo*- or the *endo*-olefin, if obtainable as a major dehydration product, would be a promising starting substance for chemical introduction of oxygen at the C-11 position. It was of interest, then, to determine whether one of these isomers would predominate under olefin-equilibrating con-

(15) H. Heusser, N. Wahba and F. Winternitz, *Helv. Chim. Acta*, **37**, 1052 (1954).

(16) G. Büchi, M. S. v. Wittenau and D. M. White, THIS JOURNAL, **81**, 1968 (1959).

(17) J. D. Cocker and T. G. Halsall, *J. Chem. Soc.*, 4262 (1956).

(18) The conversion of 6-methylcholestane-3$\beta$,6-diol 3-acetate to 6-methylcholesteryl acetate by means of phosphoryl chloride or thionyl chloride in pyridine has been reported, L. F. Fieser and J. Rigaudy, THIS JOURNAL, **73**, 4660 (1951); R. Sneen, *ibid.*, **80**, 3982 (1958). Lack of agreement on the C-6 configuration of the starting alcohol has prevented the inclusion of this reaction among the examples above.

(19) E. J. Corey and R. A. Sneen, *ibid.*, **77**, 2505 (1955).

(20) The relief of non-bonded interactions as a driving force for carbonium ion formation has been proposed by H. C. Brown and M. Nakagawa (*ibid.*, **77**, 3614 (1955)) to account for the high rate of first-order solvolysis of certain aliphatic tertiary halides. However, the much greater complexity of the steroidal carbinol systems precludes any exclusive explanation of our dehydration results.

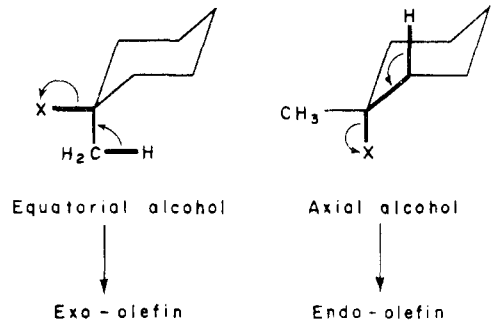


Fig. 4.

ditions. A preponderance of *either* isomer could be predicted depending on whether data from substituted cyclohexane olefins (preference for *endo*)[21] or unsubstituted steroidal olefins (high strain of $\Delta^{11}$-isomer)[22] is invoked. Attempted double bond equilibration of the isomeric olefins was unsuccessful. Depending on the nature and severity of the acidic catalysis, only the starting olefin (in one case, a hydrochloride—see above), spiroketal cleavage products or mixtures of these were obtained. We hope to prepare similar ring C olefins in the pregnane series which will likely be more amenable to equilibration study.

A ring C *saturated* 12-methylpregnane derivative has already been prepared. 12$\beta$-Methyltigogenin acetate (VI) was taken through the degradation sequence earlier described[23] for conversion of steroidal sapogenins to $\Delta^{16}$-pregnen-20-ones. The final product (obtained in low over-all yield) is designated as 3$\beta$-acetoxy-12$\beta$-methyl-5$\alpha$-pregn-16-en-20-one (X) based on its elemental analysis, infrared and ultraviolet spectra and by analogy with many other degradations of this type. The preparation of 12-substituted pregnane derivatives by a different, higher yielding route is currently being investigated.

## Experimental[24]

**12$\beta$-Hydroxy-12$\alpha$-methyltigogenin (IIa).**—A solution of hecogenin acetate (4.0 g.) in benzene (40 ml.) was added over 30 minutes with stirring to 26 ml. of 1.5 *M* ethereal methylmagnesium bromide. After 3 hours further stirring, a solution of ethyl acetate (0.5 ml.) in benzene (5 ml.) was added followed by 10% aqueous ammonium chloride (30 ml.). The organic layer was washed with water, dried, concentrated, and the residue crystallized from heptane. The first crop of secondary-tertiary diol was obtained as plates (3.38 g., 86%), m.p. 185–190°. Four further crystallizations from the same solvent gave the diol IIa (2.69 g.), constant melting at 197–198°, $[\alpha]D$ −46°. This material gave an infrared spectrum identical with that of a sample obtained by evaporation of its mother liquors. All fractions derived from this reaction had a strong hydroxyl band at 3600 cm.$^{-1}$ and were free of carbonyl absorption.

(21) A. C. Cope, D. Ambros, E. Ciganek, C. F. Howell and Z. Jacura, THIS JOURNAL, **81**, 3153 (1959), and references cited.

(22) R. B. Turner, W. R. Meador and R. E. Winkler, *ibid.*, **79**, 4122 (1957).

(23) M. E. Wall, H. E. Kenney and E. S. Rothman, *ibid.*, **77**, 5665 (1955).

(24) Infrared spectra were obtained in carbon disulfide solution, 10.0 g./liter. Optical rotations were measured in chloroform at 23° using a 2-decimeter tube, approximately 12.5 g./liter. We wish to thank Mr. C. T. Leander for infrared data, Mr. S. Serota for optical rotation measurements, and Ruth B. Kelley for elemental analyses. Specification of brand names of materials used does not imply endorsement over other similar commercial products.

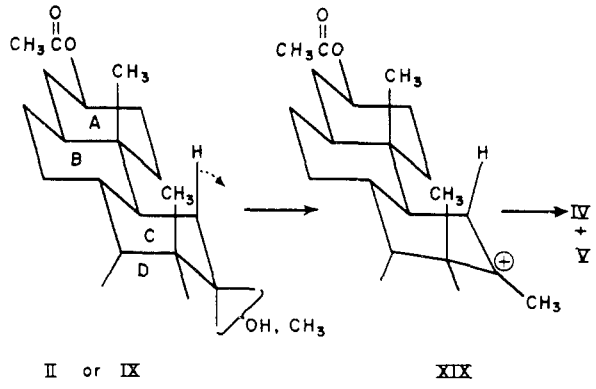


Fig. 5.

*Anal.* Calcd. for $C_{28}H_{46}O_3$: C, 75.29; H, 10.38. Found: C, 75.30; H, 10.58.

The mother liquor material from the first crop was similarly lacking in carbonyl absorption and, on concentration, yielded a further crystalline (but wide melting) fraction (0.34 g., 9%). This substance gave an infrared spectrum which was virtually identical, in the "fingerprint" region with that of 12$\alpha$-hydroxy-12$\beta$-methyltigogenin acetate (IXa, see below).

**12$\beta$-Hydroxy-12$\alpha$-methyltigogenin Acetate (IIb).**—The pure diol IIa (2.69 g., m.p. 197–198°) was treated with acetic anhydride (10 ml.) in pyridine (30 ml.) at room temperature for 16 hours. The monoacetate was obtained as plates from heptane, m.p. 220°, $[\alpha]D$ −47°.

*Anal.* Calcd. for $C_{30}H_{48}O_5$: C, 73.73; H, 9.90. Found: C, 74.06; H, 9.69.

**12$\beta$-Hydroxy-12$\alpha$-methyltigogenin Benzoate.**—A small sample of the diol IIa was treated with benzoyl chloride in pyridine at room temperature. Crystallization of the resulting product from methanol gave the monobenzoate, m.p. 192–194°, $[\alpha]D$ −38°.

*Anal.* Calcd. for $C_{35}H_{50}O_5$: C, 76.32; H, 9.15. Found: C, 76.19; H, 9.42.

**12-Chloro-12-methyltigogenin Acetate (IIIb).**—The diol IIa (2.22 g.) was dissolved in 250 ml. of 1.13 *N* hydrogen chloride in ethanol and heated under reflux for 3 hours. The solution was then cooled, neutralized with solid sodium bicarbonate (approx. 35 g.), and filtered from salts. After dilution with water, 1.11 g. of crystalline product, m.p. 175–183°, was obtained. After three recrystallizations, the resulting material (0.28 g., m.p. 188–195°) was treated at room temperature with acetic anhydride in pyridine. The 3-acetate, probably still a mixture of 12-epimers, was obtained as blades from methanol, m.p. 189–194°, $[\alpha]D$ −40°.

*Anal.* Calcd. for $C_{30}H_{47}O_4Cl$: C, 70.64; H, 9.20 Found: C, 70.68; H, 9.34.

**12-Methylenetigogenin Acetate (IVb) and 12-Methyl-$\Delta^{11}$-tigogenin Acetate (Vb).**—12$\alpha$-Hydroxy-12$\beta$-methyltigogenin acetate (156 g.,[25] m.p. 218–219°) in pyridine (2000 ml.) was stirred at 0° with protection from atmospheric moisture. Thionyl chloride (160 ml.) was added over a period of 20 minutes and stirring at 0° was continued for half an hour. Excess reagent was then destroyed by the cautious addition of *t*-butyl alcohol (160 ml.). The reaction mixture was mixed with 4 liters of ice-cold water and extracted with ether. The organic phase was then washed in turn with cold, dilute sulfuric acid, cold water and saturated brine. The dried ether solution was evaporated and the residue crystallized from 95% ethanol giving 128.4 g. (85%) of mixed olefins, m.p. 140–157°, showing no hydroxyl absorption in the infrared. This material was taken up in boiling methanol containing a small amount of methylene chloride and allowed to cool undisturbed and very slowly. Rapid crystallization of *plates* set in immediately and then subsided by the time the temperature had fallen to 40°. The warm supernatant solution was then decanted off, reheated, and on cooling to room temperature deposited a mass of *prisms*. Similar processing of the concentrated mother liquor yielded further crops of plates and of prisms. The combined plate-

(25) Prepared in three batches by the procedure given above.

crystals, after three recrystallizations from methylene chloride–methanol gave **12-methylenetigogenin acetate**, 29.5 g., 20%, m.p. 178–180°. The analytical sample, obtained by two further recrystallizations from methanol, had m.p. 179.5–189.5°, $[\alpha]_D$ −24.1°; ultraviolet spectrum (end absorption): $\epsilon_{210}$ 485, $\epsilon_{215}$ 123, $\epsilon_{220}$[79]; infrared spectrum: 3050, 1644 and 887 cm.$^{-1}$.

*Anal.* Calcd. for $C_{30}H_{46}O_4$: C, 76.54; H, 9.85. Found: C, 76.47; H, 10.17.

The combined prism fractions, after three recrystallizations from methylene chloride–methanol, gave **12-methyl-$\Delta^{11}$-tigogenin acetate**, 16 g., 11%, m.p. 160–162°. The analytical sample, obtained by three further recrystallizations from methanol, had m.p. 162.5–164.5°, $[\alpha]_D$ −45°; ultraviolet spectrum (end absorption): $\epsilon_{210}$ 3740, $\epsilon_{215}$ 1690, $\epsilon_{220}$ 397; infrared spectrum: 775, 800 and 850 cm.$^{-1}$.

*Anal.* Calcd. for $C_{30}H_{46}O_4$: C, 76.54; H, 9.85. Found: C, 76.38; H, 9.55.

**Treatment of the *exo*- (IVb) and *endo*-(Vb) Olefins with Hydrogen Chloride.**—Hydrogen chloride in methanol (5.0 ml., 3%) was added to a solution of 12-methylenetigogenin acetate (0.200 g.) in methylene chloride (1.0 ml.). After 16 hours, the solution was neutralized with potassium acetate, concentrated to low volume, and distributed between methylene chloride and water. The residue from the dried organic layer was reacetylated (acetic anhydride–pyridine at room temperature) and the product crystallized from methanol, m.p. 178–190°. An infrared spectrum of this substance was very similar to that of the chloro-compound IIIb and was completely lacking in the three bands associated with the starting olefin.

The *endo*-olefin Vb was subjected to a two-step process identical with that above. The product had an infrared spectrum identical with that of the starting olefin.

**12β-Methyltigogenin Acetate (VIb). A. From 12-Methylenetigogenin Acetate.**—The *exo*-olefin IVb (0.500 g.) and platinum oxide (0.200 g., prereduced) in ethyl acetate (19 ml.) and acetic acid (1.0 ml.) were stirred in one atmosphere of hydrogen for 5 hours. The filtered reaction solution was washed with dilute aqueous sodium bicarbonate, dried, and concentrated. The residue was crystallized twice from methanol yielding the reduced product as prisms, 0.31 g., m.p. 178–180°.

B. **From 12-Methyl-$\Delta^{11}$-tigogenin Acetate.**—The *endo*-olefin Vb (0.500 g.) was hydrogenated under similar conditions, but for 24 hours. Three crystallizations of the product from methanol gave prisms, 0.28 g., m.p. 177–179°. A mixture of the two reduced samples had m.p. 178–180°. One further recrystallization of the mixture gave the analytical sample, m.p. 179–181°, $[\alpha]_D$ −66°.

*Anal.* Calcd. for $C_{30}H_{48}O_4$: C, 76.22; H, 10.23. Found: C, 76.23; H, 10.31.

**12α-Hydroxy-12β-hydroxymethyltigogenin Actate (VIIb).**—A solution of 12-methylenetigogenin acetate (0.400 g.) and osmium tetroxide (0.24 g.) in benzene (12.0 ml.) containing pyridine (0.3 ml.) was kept in the dark at room temperature for 48 hours. The reaction mixture was then saturated with hydrogen sulfide, filtered through Celite,[24] washed with water, dried, and concentrated. The residue, on crystallization from hexane, gave the diol VIIb as blades, 0.364 g., 85%, m.p. 225°, $[\alpha]_D$ −47°; infrared spectrum: 3600 cm.$^{-1}$.

*Anal.* Calcd. for $C_{30}H_{48}O_6$: C, 71.40; H, 9.58. Found: C, 71.27; H, 9.38.

**Periodic Acid Oxidation of 12α-Hydroxy-12β-hydroxymethyltigogenin Acetate.**—The diol VIIb (0.330 g.) was dissolved in ethanol (50 ml.) containing periodic acid (0.150 g.) and water (2.0 ml.). After 14 hours at room temperature, the crystalline deposit was collected and washed with cold methanol. Pure hecogenin acetate (0.200 g., 65%) was thus obtained as blades, m.p. 245.0–245.5°, not depressed by admixture with an authentic sample.

**12α-Hydroxy-12β-tosyloxymethyltigogenin Acetate (VIIIb).**—A solution of the diol VIIb (0.854 g.) and *p*-toluenesulfonyl chloride (0.800 g.) in pyridine (3.0 ml.) was kept at 0° for 2 hours and then at room temperature for 16 hours. The reaction mixture was then mixed with ice (approx. 20 g.), extracted with ether, and the extract washed with cold dilute hydrochloric acid followed by saturated sodium chloride. The dried ether solution was concentrated and the residue crystallized from heptane, yielding the tosylate (0.77 g., 69%) as colorless prisms, m.p. 155–160° dec. The analytical sample had m.p. 170° dec., $[\alpha]_D$ −36°; infrared spectrum: 3590, 1732, 1192 and 1189 cm.$^{-1}$.

*Anal.* Calcd. for $C_{37}H_{54}O_8S$: C, 67.45; H, 8.26; S, 4.88. Found: C, 67.65; H, 7.94; S, 4.76.

**12α-Hydroxy-12β-methyltigogenin Acetate (IXb).**—A solution of the tosyl ester VIIIb (0.46 g.) in dry tetrahydrofuran (25 ml.) was treated with lithium aluminum hydride (0.45 g.) by heating under reflux for 18 hours. Excess of reagent was then destroyed by the cautious addition of a few ml. of ethyl acetate to the cooled reaction solution; 10 ml. of saturated brine was added with stirring and the mixture filtered through Celite.[24] The dried ether phase gave a crystalline product after removal of solvent. A portion of this material, presumably 12α-hydroxy-12β-methyltigogenin (IXa), was set aside for infrared analysis (see below) and the remainder acetylated with acetic anhydride in pyridine at room temperature. The diol monoacetate (0.325 g., 95%) was obtained as plates from heptane, m.p. 209–212°. The analytical sample was obtained by three recrystallizations from the same solvent to a constant melting point,[26] 212.5–213°, $[\alpha]_D$ −47°; infrared spectrum: 3602 and 1732 cm.$^{-1}$.

*Anal.* Calcd. for $C_{30}H_{48}O_5$: C, 73.73; H, 9.90. Found: C, 74.06; H, 9.69.

**Infrared Comparison of the C-12 Epimeric Diols IIa and IXa.**—The 12α-hydroxy-12β-methyl epimer IXa, obtained directly from the above hydride reduction reaction followed by one recrystallization, shows a small band at 879 cm.$^{-1}$; the opposite epimer IIa has an absorption minimum at this position. Both compounds have spiroketal bands at 900 and 920 cm.$^{-1}$. The 900 cm.$^{-1}$ bands are equal in intensity but the 920 cm.$^{-1}$ band of the 12β-hydroxy epimer IIa is much stronger than the corresponding band from IXa. A very similar difference in relative intensity of these two bands was also apparent in the spectra of the corresponding 3-acetates.

The Grignard reaction by-product (see under preparation of IIa) is presumed to consist largely of the 12α-hydroxy epimer since its infrared spectrum was virtually identical with that of the diol IXa.

**Thionyl Chloride Dehydration of IIb and IXb as the Pure Isomers. *exo–endo* Product Ratio.**—A cold (0°) solution of each tertiary alcohol—4% in pyridine—was treated with an equal weight of thionyl chloride (10%, in pyridine), added over 20 minutes with stirring. The resulting reaction mixture, after 15 minutes with stirring. The resulting reaction mixture, after 15 minutes at 0°, was mixed with a large excess of ice and the product collected by suction filtration. The solid was washed well with water, dried *in vacuo*, and recrystallized from a small volume of hot methanol.

Infrared spectra of both products—2% in carbon disulfide—were obtained. In each case, bands characteristic of both the *exo*- and *endo*-olefin isomers were present. Of these, only the band at 1644 cm.$^{-1}$ (C—C stretching of C=$CH_2$) is free of interfering near-by absorption and was therefore taken as a measure of the *exo*-olefin concentration. The product obtained from IXb had a band intensity at this position which was duplicated by a solution (2% total concentration) containing 39% IVb and 61% Vb. The product from IXb had a band intensity which was matched by a solution containing 35% IVb and 65% Vb. The product from IIb had 0.68% Cl, the product from IXb had 1.55% Cl; calcd. for $C_{30}H_{47}O_4Cl$, Cl, 7.0.

**3β-Acetoxy-12β-methyl-5α-pregn-16-en-20-one (Xb).**—Employing published procedures,[23] 12β-methyltigogenin acetate (VIb) was treated, in turn, with: (1) pyridine hydrochloride in acetic anhydride under reflux, (2) chromic acid in acetic acid, (3) potassium hydroxide in *t*-butyl alcohol, (4) acetic anhydride in pyridine. The conjugated ketone Xb was obtained as blades from methanol, m.p. 146–147°, $[\alpha]_D$ +44°, $\lambda_{max}^{CH_3OH}$ 237 mμ, log ε 3.9; infrared spectrum 3040, 1731, 1678 and 882 cm.$^{-1}$.

*Anal.* Calcd. for $C_{24}H_{36}O_4$: C, 77.37; H, 9.74. Found: C, 77.37; H, 9.62.

(26) A mixture of this compound and the 220° isomer IIb had m.p. 214–218°.