307. *Compounds Related to the Steroid Hormones. Part IX.*[1] *Oxygenation of Steroid Ketones in Strongly Basic Medium: a New Method of Preparation of 17α-Hydroxypregnan-20-ones.**

By (Miss) E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton.

20-Oxo-steroids, in presence of a t-alkoxide in the corresponding alcohol, react with oxygen to give the 17α-hydroperoxy-20-ketone in fair yield; reduction, best with zinc and acetic acid, then gives the 17α-hydroxy-20-ketone. The speed of hydroperoxidation is notably affected by the nature of the substituents at $C_{(16)}$ and in ring c. In the same way, a 6-oxo-5α-steroid is converted, *via* the 5α-hydroperoxy-derivative, into the 5α-hydroxy-6-ketone. 3-Oxo-5α- and 12-oxo-steroids, on the other hand, are oxidised to the 2,3- and 11,12-dioxo-compounds respectively.

Ketones react rather sluggishly with oxygen, and the products are usually those resulting from cleavage of the carbon chain adjacent to the carbonyl group;[2] the α-hydroperoxy-ketone has been postulated as an intermediate, and such a compound has been isolated, along with its decomposition products, from the oxidation of di-isopropyl ketone at 100°.[3] However, when a ketone forms a stable enol, the latter (but not the ketonic form), in solution in ether, light petroleum, or benzene, reacts readily with oxygen at ordinary temperature to give the α-hydroperoxy-ketone, which, under these mild conditions, is easily isolated;[4,5] even secondary α-hydroperoxy-ketones have been prepared in this way, in spite of the ease with which they are dehydrated to α-diketones.[6]

Most simple ketones exist to a negligible extent in their enolic forms under neutral conditions, but enolisation is favoured by basic or acidic conditions. However, although several workers have shown that, in strongly basic medium, ketones will take up oxygen rapidly at ordinary temperature, they have, again, usually isolated cleavage products; this is readily explained by the initial formation of the α-hydroperoxy-ketone, for such compounds are known to be cleaved by base.[7] That autoxidation of ketones can proceed without cleavage of the carbon chain is indicated by the conversion of αβ-unsaturated ketones of the cyperone series into their γ-hydroxy-derivatives by oxygenation in presence of aqueous base[8] and by the recent observation that certain rotenone derivatives give α-ketols under similar conditions.[9] It seems probable that the hydroperoxy-ketones are intermediates in such oxidations, since there are analogies for the " reduction " of such compounds to the ketols by dilute alkali.[4b,c]

More important, for the present purpose, was the observation that, even under strongly basic conditions, the reaction can leave the carbon chain intact. Thus, cyclic ketones of type (I), in the limonin series, react with oxygen in presence of potassium t-butoxide in

* A preliminary account of part of this work was published in *Proc. Chem. Soc.*, 1960, 214.

[1] Part VIII, *J.*, 1962, preceding paper.

[2] (*a*) Sharp, Whitcomb, Patton, and Moorhead, *J. Amer. Chem. Soc.*, 1952, **74**, 1802; (*b*) Pritzkow, *Chem. Ber.*, 1954, **87**, 1668.

[3] Sharp, Patton, and Whitcomb, *J. Amer. Chem. Soc.*, 1951, **73**, 5600; cf. ref. 2*b*.

[4] (*a*) Kohler, *Amer. Chem. J.*, 1906, **36**, 177; 1907, **37**, 369; (*b*) 1906, **36**, 529; (*c*) Kohler, Westheimer, and Tishler, *J. Amer. Chem. Soc.*, 1936, **58**, 264; (*d*) Fuson, McKusick, and Spangler, *ibid.*, 1945, **67**, 597; (*e*) Attenburrow, Connett, Graham, Oughton, Ritchie, and Wilkinson, *J.*, 1961, 4547.

[5] Cf. Julian and his co-workers, *J. Amer. Chem. Soc.*, 1934, **56**, 2174; 1935, **57**, 1607; 1945, **67**, 1721; Rigaudy, *Compt. rend.*, 1948, **226**, 1911; Dufraisse, Etienne, and Rigaudy, *Bull. Soc. chim. France*, 1948, **15**, 804.

[6] Kohler, Tishler, and Potter, *J. Amer. Chem. Soc.*, 1935, **57**, 2517; Kohler and Thompson, *ibid.*, 1937, **59**, 887; Fuson, Maynert, and Shenk, *ibid.*, 1945, **67**, 1939; Fuson and Jackson, *ibid.*, 1950, **72**, 1637; Fuson and Tzi-Lieh Tan, *ibid.*, 1948, **70**, 602.

[7] (*a*) Doering and Haines, *J. Amer. Chem. Soc.*, 1954, **76**, 482; (*b*) Elkik, *Bull. Soc. chim. France*, 1959, 933.

[8] Cardwell and McQuillin, *J.*, 1955, 525; Howe and McQuillin, *J.*, 1958, 1513.

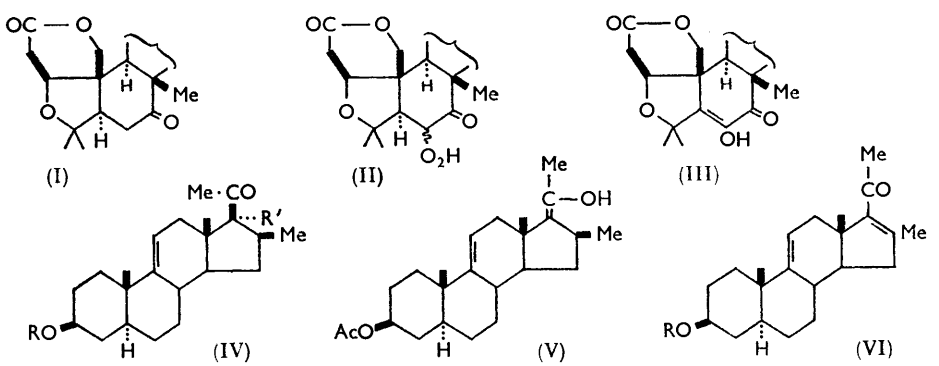
[9] Crombie and Godin, *J.*, 1961, 2861.

t-butyl alcohol to give the enolised α-diketone (III), presumably by way of the hydroperoxide (II).[10] The utility of the method for introducing an oxygen function α- to an existing carbonyl group was strikingly demonstrated by the direct conversion of the fully conjugated carotenoid diketone, canthaxanthin, into the corresponding bisdiosphenol astacene.[11]

We have now applied the reaction to a number of steroid ketones and have found that, here again, the carbon skeleton can be preserved and useful products obtained.

In the 20-oxo-series, we have studied most extensively the oxidation of 3β-hydroxy-16β-methyl-5α-pregn-9-en-20-one (IV; R = R′ = H) and its acetate; the corresponding 17α-hydroxy-compound (IV; R = H, R′ = OH) is an intermediate in the preparation of the highly active cortisone analogue, 9α-fluoro-16β-methylprednisolone, and its synthesis by established methods presents certain difficulties.[4e,12]

The acetate (IV; R = Ac, R′ = H),[4e] dissolved in t-butyl alcohol containing the sodium or potassium alkoxide, or in t-pentyl alcohol containing sodium t-pentoxide, absorbed 1 mol. of oxygen rapidly. Reaction was fastest (3—5 min.) and gave the best results with a large excess of the alkoxide (8—16 equiv.) in nearly saturated solution. Partial hydrolysis of the acetate group usually occurred during the oxygenation, and the reaction time was prolonged (to 10—20 min.) to allow this to go to completion. By such reactions, 17-hydroperoxy-3β-hydroxy-16β-methyl-5α-pregn-9-en-20-one (IV; R = H,



R′ = O_2H) was obtained as stable crystals in up to 59% yield. In some runs with sodium t-butoxide, hydrolysis of the ester group was much slower, and it was possible to isolate a modest yield of the corresponding 3-acetate (IV; R = Ac, R′ = O_2H), a compound whose preparation by autoxidation of the enol (V) in neutral solution has been described earlier.[4e] The variation in rate of hydrolysis of the ester group was almost certainly the result of fortuitous minor variations in water content of the sodium-dried t-butyl alcohol used; independent experiments showed that a 0·43N-solution of sodium t-butoxide in t-butyl alcohol caused complete hydrolysis of the 3β-acetoxy-group of (IV; R = Ac, R′ = H) in 10 min. at room temperature when the solvent contained 0·14% of water, but that hydrolysis was <20% complete in this time when the solvent contained 0·04% of water.

The hydroperoxide (IV; R = H, R′ = O_2H) slowly decomposed under the basic conditions of its formation, as shown by a drop in rotation, and it seemed desirable to avoid the extra reaction-time involved in completing the hydrolysis of the acetoxy-group. Since hydrolysis of the acetoxy-group in (IV: R = Ac, R′ = H) under either basic or acidic conditions is accompanied by epimerisation at $C_{(17)}$ (see below), the 3-hydroxy-compound (IV; R = R′ = H) was prepared from the 16-methyl-$\Delta^{9,16}$-20-ketone (VI; R = Ac)[4e] by hydrolysis of the acetoxy-group and subsequent hydrogenation of the

[10] Arigoni, Barton, Corey, and Jeger, *Experientia*, 1960, **16**, 41; Barton, Pradhan, Sternhell, and Templeton, *J.*, 1961, 255.

[11] Davis and Weedon, *Proc. Chem. Soc.*, 1960, 182.

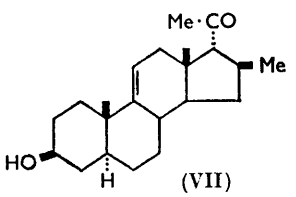
[12] Carrington, Eardley, Elks, Green, Gregory, Long, and Sly, *J.*, 1961, 4560.

16,17-double bond. Unfortunately, the yield of hydroperoxide (IV; R = H, R′ = O_2H) was no better from the 3β-hydroxy-compound (IV; R = R′ = H) than from its acetate, in spite of the short reaction time needed.

In the absence of oxygen, compound (IV; R = R′ = H) is slowly epimerised at $C_{(17)}$ under the basic conditions. (A 16β-methyl-group is known to reverse the usual order of stability of the 17α- and 17β-acetyl side-chain.[4e,13]) Further, the epimer (VII) takes up oxygen extremely slowly under the usual reaction conditions and gives an ill-defined, non-peroxidic product. (The difference in behaviour between the two epimers must be the consequence of less ready enolisation of the 17α-epimer; Dr. J. F. Oughton, of these laboratories, has observed a similar difference of reactivity under enol acetylating conditions.) The 17α-compound (VII) might, then, be expected as a by-product of the hydroperoxidation of ketone (IV; R = R′ = H); it was in fact found in the products of some early reactions, but could not be detected by paper chromatography when our optimal conditions were used.

Among several reagents investigated for reduction of the 17α-hydroperoxide, zinc dust in acetic acid proved best and gave 3β,17-dihydroxy-16β-methyl-5α-pregn-9-en-20-one (IV; R = H, R′ = OH) in very high yield. Catalytic reduction in presence of palladium gave the same product in lower yield and paper chromatography indicated the same as true of potassium iodide–acetic acid and sodium sulphite. Use of sodium hydrogen sulphite or of chromous chloride, on the other hand, gave complex mixtures.

The oxygenation conditions described above were applied to 3β-hydroxy-5α- (VIII; R = R′ = H, X = H_2) and 3α-hydroxy-5β-pregnan-20-one (IX; R = R′ = H, X = H_2), and the corresponding 11,20-diketones (VIII and IX; R = R′ = H, X = O), to 3β-



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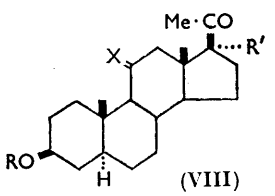

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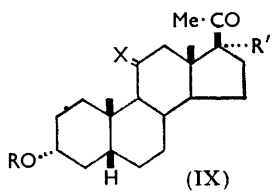

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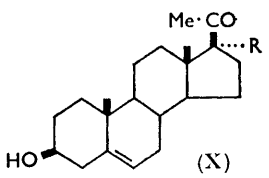

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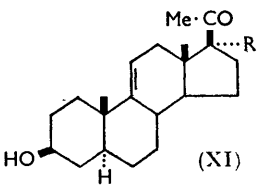

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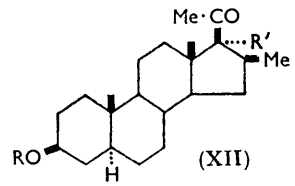


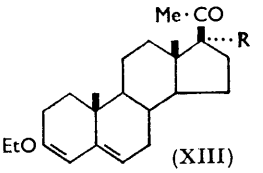
(XII)

hydroxypregn-5-en-20-one (X; R = H), to 3β-hydroxy-5α-pregn-9-en-20-one (XI; R = H) and to 3β-hydroxy-16β-methyl-5α-pregnan-20-one (XII; R = R′ = H) (or, in some instances, the corresponding 3-acetates). There was no evidence of interference by the 11-oxo-group in the 11,20-diketones; in agreement with this, 11-oxotigogenin was unaffected under our usual conditions. In each instance the 17α-hydroperoxy-20-ketone was obtained, usually in 40—60% yield, and was reduced to the 17α-hydroxy-20-ketone with zinc dust in acetic acid. Although there was no difference in the outcome of these reactions, significant differences in the rate of oxygenation were observed; the slowest were with the compounds (VIII; R = R′ = H; X = H_2), (IX; R = R′ = H, X = H_2), (X; R = H), and (XIII; R = H) (see below) saturated and unsubstituted in ring c and unsubstituted at $C_{(16)}$. Structural features that brought about increased reactivity were, in increasing order of effectiveness, a 9,11-double bond, an 11-oxo-group, and a 16β-methyl group; the effects of the 16β-methyl group and the 9,11-double bond were cumulative, the rate of oxygenation of (IV; R = R′ = H) being the highest of all we studied.

[13] Wettstein, *Helv. Chim. Acta*, 1944, **27**, 1803; Romo, Lepe, and Romero, *Bol. Inst. Qúim., Univ. nac. auton. México*, 1952, **4**, 125.

Unexpectedly, 3β-hydroxy-16α-methyl-5α-pregn-9-en-20-one absorbed oxygen exceedingly slowly under the usual conditions, and no hydroperoxide could be isolated.

The preparation of 17α-hydroperoxyprogesterone (XIV) was undertaken in the hope that it might have interesting biological properties. Reaction of progesterone with ethyl orthoformate and sulphuric acid in dioxan at room temperature gave the 3-monoenol ethyl ether (XIII; R = H) in 55% yield. Oxygenation in the usual way gave the 17α-hydroperoxide (XIII; R = O_2H) in rather poor yield, and this in turn was treated with acetic acid in methanol to regenerate the 3-oxo-Δ^4-grouping of 17α-hydroperoxyprogesterone (XIV) without attack on the hydroperoxide. Compound (XIV) showed no progestational activity in the McPhail test, when administered subcutaneously to rabbits in a 3 mg. dose.



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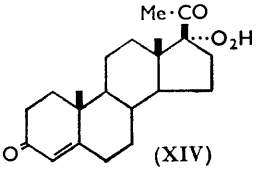
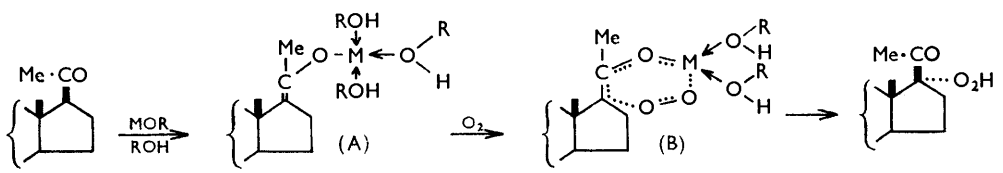


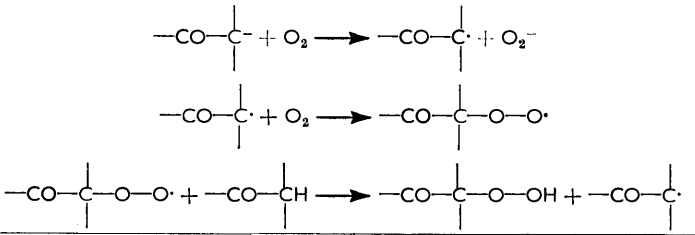
(XIV)

Possibly pertinent to the mechanism of hydroperoxidation are some experiments in which primary and secondary alkoxides were used in place of t-butoxide (cf. ref. 7*b*). Thus, attempts to oxygenate either 3β-hydroxy-16β-methyl-5α-pregn-9-en-20-one (IV; R = R′ = H) or 3α-hydroxy-5β-pregnane-11,20-dione (IX; R = R′ = H, X = O) in presence of methanolic sodium methoxide were unsuccessful, even with considerably higher concentrations of base than were necessary with t-butoxide. That this was not due simply to failure of the weaker base to allow enolisation was indicated by the fact that the 16β-methyl compound (IV; R = R′ = H) underwent extensive epimerisation at $C_{(17)}$. Sodium isopropoxide in propan-2-ol behaved similarly to the primary alkoxide. Since, in the absence of oxygen, the rates of epimerisation of the 16β-methyl-20-ketone (IV; R = R′ = H) were closely similar with primary, secondary, and tertiary alkoxide, it seems likely that there is a specific solvent effect in the oxygenation step. A possible mechanism, which would account for this, involves a cyclic transition state, akin to one suggested in the alkylation of cyclic β-diketones.[14]



The step A ⟶ B, involving displacement of one of the solvent molecules by oxygen, would be less easy with the primary and secondary alcohols, which show a greater tendency than t-butyl alcohol to form co-ordinate compounds.

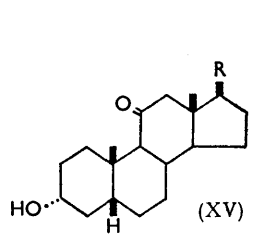
However, Russell[15] has recently provided evidence that autoxidation of anions may proceed by a chain process, represented for ketones as follows:



[14] Brändström, *Arkiv Kemi*, 1953, **6**, 155 cf. Toromanoff, *Bull. Soc. chim. France*, 1961, 799.
[15] Russell, Abs. 17th Nat. Org. Chem. Symposium, Amer. Chem. Soc., 1961, p. 71.

The apparently favourable effects of t-alkoxides could be the result of inhibition of the chain-reaction by primary and secondary alcohols or alkoxides.

21-Acetoxy-3α-hydroxy-5β-pregnane-11,20-dione (XV; R = $CO{\cdot}CH_2{\cdot}OAc$) absorbed oxygen rapidly under our usual conditions. The product contained little peroxidic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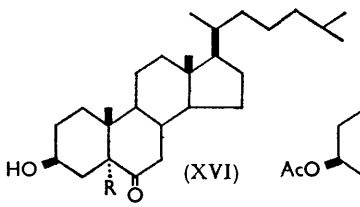
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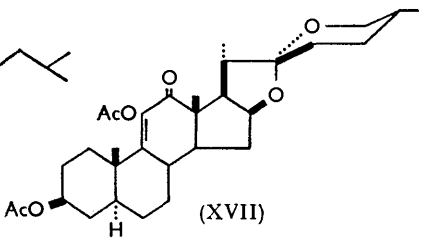
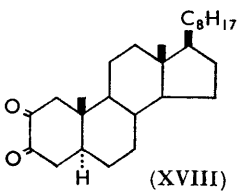

(XVII)

material; not unexpectedly, the only compound isolated was the 17β-carboxylic acid (XV; R = CO_2H). An authentic specimen was prepared by oxidation of the ketol (XV; R = $CO{\cdot}CH_2{\cdot}OH$) with sodium bismuthate.

3β-Hydroxy-5α-cholestan-6-one (XVI; R = H) reacted with oxygen in a similar way to the 20-ketones, giving a rather poor yield of the 5α-hydroperoxide (XVI; R = O_2H), which was reduced by zinc dust to 3β,5-dihydroxy-5α-cholestan-6-one (XVI; R = OH). Attack at $C_{(5)}$ is in accord with the known enolisation of 5α-6-ketones towards $C_{(5)}$ under the conditions of base-catalysed methylation.[16]

Hecogenin was slow to take up oxygen and the product was virtually free from peroxide. After acetylation, 3β,11-diacetoxy-5α,25D-spirost-9-en-12-one (XVII) was isolated with some difficulty; this is analogous to the limonin example mentioned above and presumably involved the secondary 11-hydroperoxy-12-ketone, which was dehydrated spontaneously to the 11,12-diketone, in equilibrium with its enol.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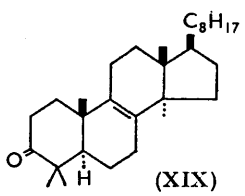
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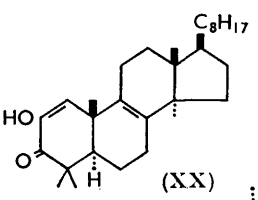
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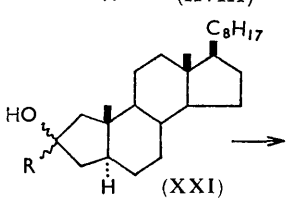
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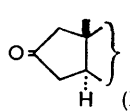
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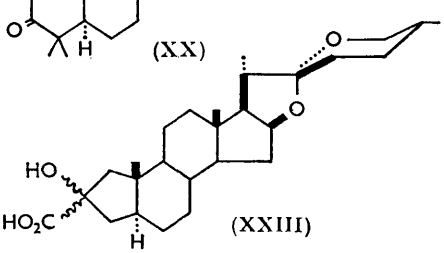
(XXIII)

In the same way, smooth conversions into diosphenol were observed in the potassium t-butoxide-induced oxygenation of cholestanone and lanost-8-en-3-one (XIX), the products being, respectively, the mixed enols of cholestane-2,3-dione (XVIII) [17] and the diosphenol (XX).[18]

Oxygenation of cholestanone in presence of triphenylmethylsodium in tetrahydrofuran proceeded readily to furnish 2ξ-hydroxy-A-nor-5α-cholestane-2ξ-carboxylic acid (XXI; R = CO_2H), characterised as its methyl ester and by reduction with lithium aluminium

[16] Fried, Arth, and Sarett, *J. Amer. Chem. Soc.*, 1960, **82**, 1684; Fried, Nutile, and Arth, *ibid.*, p. 5704.

[17] Stiller and Rosenheim, *J.*, 1938, 353.

[18] Cf. Chaudhry, Halsall, and Jones, *J.*, 1961, 2725; Hirschmann, Bailey, Walker, and Chemerda, *J. Amer. Chem. Soc.*, 1959, **81**, 2822.

hydride to the diol (XXI; R = CH_2·OH). The constitution of the hydroxy-acid (XXI; R = CO_2H) was proved by oxidation to A-nor-5α-cholestan-2-one (XXII) [19] by chromic acid. The hydroxy-acid (XXI; R = CO_2H) is no doubt formed by benzilic acid-type rearrangement of the dione (XVIII) generated at an earlier stage.[18]

Some recent papers [20] have shown that alkoxides are stronger bases in aprotic than in proton-containing solvents. Use of potassium t-butoxide in benzene in the reaction of 20-oxo-steroids with oxygen led to rapid reaction, which did not, however, stop after absorption of 1 mol. of the gas and gave mixtures from which no pure product could be isolated. One of the complications was found to involve oxidation of a 3-hydroxyl group (which is unaffected under our usual conditions), for cholestanol itself was slowly oxidised to give, as the only isolated product, the A-nor-hydroxy-acid (XXI; R = CO_2H); tigogenin, under similar conditions, gave a compound formulated, on the basis of its analysis and infrared spectrum, as the analogous compound (XXIII). These conversions presumably involve oxidation of the 3β-ol to 3-ketone as first step (cf. refs. 15 and 21) and then the series of reactions outlined above.

Professor G. Ourisson (University of Strasbourg) has kindly informed us (October, 1961) of his experiments (to be published by R. Hanna and G. Ourisson in *Bull. Soc. chim. France*) on the use of the potassium t-butoxide–oxygen reaction to synthesise triterpenoid 2,3-diketones and of other interesting results that he has observed, using this reaction. Where comparison is appropriate, Professor Ourisson's results are in good agreement with those reported in the present paper.

Experimental

M. p.s were measured on a Kofler block. Infrared spectra were recorded on a Perkin–Elmer model 21 spectrophotometer with rock-salt optics.

The oxygenations were carried out as follows: oxygen was stored over water in the graduated vessel of a " hydrogenator " and was conducted to the reaction vessel through a drying tube packed with calcium chloride or magnesium perchlorate. The alkoxide solution was shaken in oxygen until there was no further uptake of the gas. A solution of the steroid in the same alcohol was then added and shaking was continued for the times stated. Uptake of oxygen usually became very slow after about 1 mol. of the gas had been absorbed. In some instances the reaction time was prolonged to allow complete hydrolysis of an ester grouping.

3β-*Hydroxy*-16-*methyl*-5α-*pregna*-9,16-*dien*-20-*one* (VI; R = H).—3β-Acetoxy-16-methyl-5α-pregna-9,16-dien-20-one [4e] (10 g.) in methylene chloride (60 ml.) was added to methanol (700 ml.) containing aqueous 60% w/w perchloric acid (20 ml.). The solution was left overnight at room temperature, then poured into water, and the white solid was filtered off and dried. Crystallisation from methanol gave 3β-*hydroxy*-16-*methyl*-5α-*pregna*-9,16-*dien*-20-*one* in three crops (7·5 g., 85%), m. p. 192—194°, $[\alpha]_D$ +59° (*c* 1·0 in $CHCl_3$). A purified sample had m. p. 198—199°, $[\alpha]_D$ +59° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ (in Nujol) 3600 (OH), 1650 and 1600 (CO·C=C) and 822 cm.$^{-1}$ (CH=CR) (Found: C, 80·4; H, 9·7. $C_{22}H_{32}O_2$ requires C, 80·4; H, 9·8%).

3β-*Hydroxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* (IV; R = R′ = H).—3β-Hydroxy-16-methyl-5α-pregna-9,16-dien-20-one (5 g.) in tetrahydrofuran (100 ml.) containing triethylamine (10 ml.) was hydrogenated at room temperature and pressure in presence of 10% palladium–charcoal (0·75 g.); 1·07 mols. of hydrogen were taken up in 15 min. The catalyst was filtered off through kieselguhr, the filtrate was poured into water, and the product was isolated with ethyl acetate. Crystallisation of the residue from methanol gave 3β-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* (3·6 g., 72%), m. p. 165—168°, $[\alpha]_D$ +38° (*c* 1·0 in chloroform), $\nu_{max.}$ (in CS_2) 3620 and 1035 (OH), 1710 (C=O), 1350 (COMe), and 820 cm.$^{-1}$ (CH=CR) (Found: C, 79·95; H, 10·4. $C_{22}H_{34}O_2$ requires C, 79·95; H, 10·4%).

[19] (*a*) Windaus and Dalmer, *Ber.*, 1919, **52**, 162; (*b*) Evans, de Paulet, Shoppee, and Winternitz, *J.*, 1957, 1451.

[20] Cram, Rickborn, and Knox, *J. Amer. Chem. Soc.*, 1960, **82**, 6412; cf. Parker, *J.*, 1961, 1328; Zaugg, Dunnigan, Michaels, Swett, Wang, Sommers, and DeNet, *J. Org. Chem.*, 1961, **26**, 644.

[21] Le Berre, *Bull. Soc. chim. France*, 1961, 1198.

17-*Hydroperoxy*-3β-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* (IV; R = H, R′ = O_2H).—(i) *From* 3β-*acetoxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one*. (*a*) With sodium t-butoxide. 3β-Acetoxy-16β-methyl-5α-pregn-9-en-20-one [4e] (5 g.) in t-butyl alcohol (40 ml.) was added, under oxygen, to a solution of sodium t-butoxide prepared from sodium (5 g.) and t-butyl alcohol (500 ml.), and the solution was shaken with oxygen for 10 min. (absorption of 1 mol. was complete after 4 min.). Acetic acid (40 ml.) and water (100 ml.) were added and the alcohol was distilled off at 40° under reduced pressure. Water (200 ml.) was added and the solution was left at 0° overnight. The white solid was filtered off, washed with water, and dried *in vacuo* at 60° to give crude 17-*hydroperoxy*-3β-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* (4·9 g.), m. p. 154—158° (decomp.), $[\alpha]_D$ +44° (*c* 1·0 in MeOH). Crystallisation from ethyl acetate gave the pure hydroperoxide (2·9 g., 59%), m. p. 162—165° (decomp.), $[\alpha]_D$ +67° (*c* 1·0 in MeOH), $\nu_{max.}$ (in Nujol) 3480 (bonded 3-OH), 3200 (bonded 17-O_2H), 1705 (C=O) and 852 cm.$^{-1}$ (O–O) (Found: C, 72·7; H, 9·5. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·45%).

(*b*) With potassium t-butoxide. Potassium (1·5 g.) was dissolved in t-butyl alcohol (40 ml.) and to the solution, under oxygen, was added the steroid (2 g.) in the same alcohol (10 ml.); the solution was shaken with oxygen for 20 min., slightly less than 1 mol. being absorbed. Isolation as in (*a*) gave the crude hydroperoxide (1·7 g.), m. p. 159—162° (decomp.), $[\alpha]_D$ +56° (*c* 1·0 in MeOH). Crystallisation from aqueous methanol gave the pure product (1·06 g., 55%), m. p. 161·5—163° (decomp.), $[\alpha]_D$ +67° (*c* 1·0 in MeOH).

(*c*) With sodium t-pentoxide. Sodium (2 g.) was dissolved in t-pentyl alcohol (240 ml.), the steroid (2 g.) was added, and the solution was shaken with oxygen for 10 min. (absorption was complete after 7 min.). Acetic acid (20 ml.) was added and the alcohol was distilled off at 50° under reduced pressure. Water (100 ml.) was added and the product was isolated with chloroform to give a yellow hydroperoxide (crude 1·6 g.; pure 0·95 g., 49%), m. p. 162·5—165° (decomp.), $[\alpha]_D$ +67° (*c* 1·0 in MeOH).

(ii) *From* 3β-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one*. This ketone (0·5 g.) in t-butyl alcohol (5 ml.) was added to a solution of potassium t-butoxide (1·5 g. of potassium in 45 ml. of the alcohol), and the solution was shaken with oxygen for 4 min., during which 1 mol. of gas was absorbed. Isolation as in (*a*) above gave the crude hydroperoxide (0·47 g.); crystallisation from aqueous methanol gave the pure product (50%), m. p. 161—163° (decomp.), $[\alpha]_D$ +67° (*c* 1·0 in MeOH).

3β-*Acetoxy*-17-*hydroperoxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* (IV; R = Ac, R′ = O_2H).—3β-Acetoxy-16β-methyl-5α-pregn-9-en-20-one (250 mg.) was oxidised as in experiment (*a*) above, and the product was isolated in the same way. The infrared spectrum of the crude product (230 mg.; m. p. 123—127°) indicated that little or no hydrolysis of the 3β-acetate had occurred. Crystallisation of this material (190 mg.) from aqueous methanol gave 3β-acetoxy-17-hydroperoxy-16β-methyl-5α-pregn-9-en-20-one (80 mg., 36%), m. p. 156—158°, $[\alpha]_D$ +57° (*c* 1·0 in MeOH). This material was identified, by infrared spectrum and mixed melting point determination, with a specimen prepared by oxygenation, under neutral conditions, of 3β-acetoxy-16β-methyl-5α-pregna-9,17-dien-20-ol.[4e] The difference between the outcome of this experiment and that of (*a*) is attributed to differences in the amount of water present (see p. 1579).

3β,17-*Dihydroxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* (IV; R = H, R′ = OH).—*By reduction of the* 17-*hydroperoxide* (IV; R = H, R′ = O_2H). (*a*) With zinc and acetic acid. 17-Hydroperoxy-3β-hydroxy-16β-methyl-5α-pregn-9-en-20-one (926 mg.) in acetic acid (80 ml.) was shaken with zinc dust (2·5 g.; acid-washed) for 4¼ hr. at room temperature. The excess of zinc was filtered off and washed with ethyl acetate; water (200 ml.) was added to the filtrate, and the combined filtrate and washings were extracted with ethyl acetate. The extract was washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated to dryness, giving a semi-crystalline product (870 mg.), m. p. 194—203°, $[\alpha]_D^{23}$ +39° (*c* 1·0 in dioxan). Crystallisation from aqueous methanol gave 3β,17-*dihydroxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* (690 mg., 78%), m. p. 199—204°, $[\alpha]_D^{23}$ +39° (*c* 1·0 in dioxan), $\nu_{max.}$ (in $CHBr_3$) 3620 and 3450 (OH), and 1706 and 1680 cm.$^{-1}$ (17α-hydroxy-20-ketone) (Found, after drying at 150°/0·1 mm. for 4 hr.: C, 76·1; H, 9·85. $C_{22}H_{34}O_3$ requires C, 76·3; H, 9·9%). The compound crystallised from ethanol in a second crystalline form, m. p. 218—221°. The two forms had identical infrared spectra in bromoform solution. In Nujol, the spectra of both forms showed ketone absorption at 1695 cm.$^{-1}$, but differed in the finger-print region; in particular the low-melting form had a strong characteristic band at 1305 cm.$^{-1}$, which was absent from the other.

(*b*) With zinc in ethanol–acetic acid. The steroid (250 mg.) was dissolved in ethanol (5 ml.) and acetic acid (5 ml.), and zinc (0·75 g.) was added. The reduction was carried out as in the preceding paragraph and gave material (225 mg.), m. p. 190—195°, $[\alpha]_D$ +38° (*c* 1·0 in dioxan).

(*c*) With hydrogen in presence of palladised charcoal. 17-Hydroperoxy-3β-hydroxy-16β-methyl-5α-pregn-9-en-20-one (1 g.) in ethanol (50 ml.) was hydrogenated at room temperature and pressure in presence of 10% palladised charcoal (300 mg.), 1 mol. being absorbed in 25 min. The catalyst was filtered off through kieselguhr, water was added, and the ethanol was distilled off under reduced pressure. The solution was stored at 0° for 2 hr. and the white solid was filtered off and dried, to give crude 3β,17-dihydroxy-16β-methyl-5α-pregn-9-en-20-one (0·81 g.), m. p. 186—190°, $[\alpha]_D^{25}$ +32° (*c* 1·0 in dioxan). Crystallisation from aqueous methanol gave 0·543 g. (57%) of crystalline material, m. p. 194—198°, $[\alpha]_D^{25}$ +39° (in dioxan).

3β-*Acetoxy*-17-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* (IV; R = Ac, R′ = OH).—(a) *By acetylation of the* 3,17-*diol.* The diol (250 mg.), obtained as described in the preceding paragraph, was acetylated overnight at room temperature with pyridine (5 ml.) and acetic anhydride (5 ml.), giving 3β-acetoxy-17-hydroxy-16β-methyl-5α-pregn-9-en-20-one (289 mg.), m. p. 171—174°, $[\alpha]_D$ +33° (*c* 1·0 in dioxan). The infrared spectrum was in good agreement with that of an authentic sample. Attenburrow *et al.*[4e] report m. p. 177—179°, $[\alpha]_D$ +34·1° (in dioxan).

(b) *By reduction of* 3β-*acetoxy*-17-*hydroperoxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one.* This acetate (100 mg.) in acetic acid (10 ml.) was shaken with zinc (400 mg.; acid-washed) at room temperature for 4½ hr. The excess of zinc was filtered off and the precipitate was washed with ethyl acetate. The combined filtrate and washings were diluted with water and extracted with ethyl acetate, and the extract was washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated to dryness, to give a white solid (110 mg.), m. p. 158—160°. Crystallisation from aqueous methanol gave a somewhat impure specimen of 3β-acetoxy-17-hydroxy-16β-methyl-5α-pregn-9-en-20-one (63%), m. p. 163—166°, $[\alpha]_D$ +32° (*c* 1·0 in dioxan).

3β-*Hydroxy*-5α-*pregnan*-20-*one* (VIII; R = R′ = H, X = H_2).—The following selective reduction of pregnenolone provides a more convenient preparation of this compound than those described in the literature. 3β-Hydroxypregn-5-en-20-one (10 g.) in acetic acid (200 ml.) was hydrogenated in presence of 5% palladised charcoal (2 g.); after 90 min. absorption had virtually ceased. The catalyst was filtered off through kieselguhr, and the filtrate was concentrated under reduced pressure to small bulk; the solution was poured into water and the white solid filtered off and dried. Crystallisation from methanol gave 3β-hydroxy-5α-pregnan-20-one (7 g., 70%), m. p. 192—194°, $[\alpha]_D$ +92° (*c* 1·0 in EtOH) {lit., m. p. 194°, $[\alpha]_D$ +90·8° (in EtOH)}.

17-*Hydroperoxy*-3β-*hydroxy*-5α-*pregnan*-20-*one* (VIII; R = H, R′ = O_2H, X = H_2).—(a) *From* 3β-*acetoxy*-5α-*pregnan*-20-*one.* The steroid (1 g.) in t-butyl alcohol (10 ml.) was added to a solution of potassium t-butoxide (2 g. of potassium in 40 ml. of the alcohol), shaken with oxygen for 38 min., poured into water (500 ml.) containing acetic acid (10 ml.), and left overnight at 0°. The white solid (1 g.) was filtered off, washed with water, and dried [m. p. 128—138° (decomp.)]. Crystallisation from methanol gave 17-*hydroperoxy*-3β-*hydroxy*-5α-*pregnan*-20-*one* (35%), m. p. 169—172° (decomp.), $[\alpha]_D$ +54° (*c* 0·5 in MeOH), $\nu_{max.}$ (in Nujol) 3400 (bonded 3-OH), 3100 (bonded 17-O_2H), 1714 (C=O), and 852 cm.$^{-1}$ (O–O) (Found: C, 71·6; H, 10·05. $C_{21}H_{34}O_4$ requires C, 71·9; H, 9·8%).

(b) *From* 3β-*hydroxy*-5α-*pregnan*-20-*one.* The steroid (5 g.) in t-butyl alcohol (50 ml.) was added to a solution of potassium t-butoxide (5 g. of potassium in 75 ml.), oxygenated for 45 min., and worked up as described above, to give the crude hydroperoxide (5 g.), m. p. 140—142°. Trituration with a small quantity of ether gave 3·5 g. of material with m. p. 160—162°; crystallisation from ethanol then gave the 17-hydroperoxide (44%), m. p. 172—174°, $[\alpha]_D$ +54° (*c* 0·5 in MeOH).

3β,17-*Dihydroxy*-5α-*pregnan*-20-*one* (VIII; R = H, R′ = OH, X = H_2).—17-Hydroperoxy-3β-hydroxy-5α-pregnan-20-one (65 mg.) in acetic acid (25 ml.) was reduced with zinc dust (500 mg.), and the product was isolated with ethyl acetate in the usual way to give a solid (67 mg.), m. p. 233—238°. Crystallisation from ethyl acetate gave 3β,17-dihydroxy-5α-pregnan-20-one (59%), m. p. 251—256°, $[\alpha]_D$ +35° (*c* 1·0 in EtOH); the infrared spectrum resembled that of an authentic specimen {lit.,[22] m. p. 257—259°, $[\alpha]_D$ +32° (in EtOH)}.

[22] Kritchevsky and Gallagher, *J. Amer. Chem. Soc.*, 1951, **73**, 184.

17-*Hydroperoxy*-3α-*hydroxy*-5β-*pregnan*-20-*one* (IX; R = H, R′ = O_2H, X = H_2).—3α-Hydroxy-5β-pregnan-20-one (2 g.) in t-butyl alcohol (20 ml.) was added to a solution of potassium t-butoxide (4 g. of potassium in 80 ml.) and shaken with oxygen for 45 min. The solid (2·2 g.), isolated in the usual way, crystallised from ethyl acetate to give 17-*hydroperoxy*-3α-*hydroxy*-5β-*pregnan*-20-*one* (1·0 g., 40%), m. p. 162—163° (decomp.), $[\alpha]_D$ +64° (*c* 1·0 in MeOH), $\nu_{max.}$ (in Nujol) 3600 (3-OH), 3200 (bonded 17-O_2H), 1708 (C=O), and 854 cm.$^{-1}$ (O–O). Even after being dried at 100° for 2 hr. the compound had an analysis suggestive of the presence of solvent (Found: C, 70·8, 70·4, 70·8; H, 9·8, 9·75, 9·8. Calc. for $C_{21}H_{34}O_4$: C, 71·9; H, 9·8. Calc. for $C_{21}H_{34}O_4$,$\frac{1}{2}CH_3{\cdot}CO_2C_2H_5$: C, 70·0; H, 9·7%). A sample, crystallised from methanol and dried at 100° for 5 hr., corresponded approximately to a methanol *solvate* (Found: C, 69·7; H, 9·7. $C_{21}H_{34}O_4$,$CH_3{\cdot}OH$ requires C, 69·1; H, 10·0%).

3α,17-*Dihydroxy*-5β-*pregnan*-20-*one* (IX; R = H, R′ = OH, X = H_2).—17-Hydroperoxy-3α-hydroxy-5β-pregnan-20-one (90 mg.) in acetic acid (25 ml.) was reduced with zinc dust (300 mg.) in the usual way and the product was isolated with chloroform, to give a white solid (89 mg.), m. p. 206—209°. Crystallisation from aqueous methanol gave 3α,17-dihydroxy-5β-pregnan-20-one (78%), m. p. 213—216°, $[\alpha]_D$ +63° (*c* 1·0 in ethanol) {lit.,[22] m. p. 213—214°, $[\alpha]_D$ +63° (in ethanol)}.

17-*Hydroperoxy*-3β-*hydroxy*-5α-*pregnane*-11,20-*dione* (VIII; R = H, R′ = O_2H, X = O).—(a) *From* 3β-*acetoxy*-5α-*pregnane*-11,20-*dione*. The steroid (1 g.) in t-butyl alcohol (10 ml.) was added to a solution prepared from potassium (2 g.) and t-butyl alcohol (45 ml.) and shaken with oxygen for 20 min. Isolation in the usual way gave a white solid (0·72 g.), m. p. 157—160° (decomp.), $[\alpha]_D$ +66° (*c* 1·0 in MeOH). Crystallisation from ethyl acetate gave 17-*hydroperoxy*-3β-*hydroxy*-5α-*pregnane*-11,20-*dione* (49%), m. p. 161—163° (decomp.), $[\alpha]_D$ +71° (*c* 1·0 in MeOH), $\nu_{max.}$ (in Nujol) 3470 (bonded 3-OH), 3200 (bonded 17-O_2H), 1702 (C=O), and 856 cm.$^{-1}$ (O–O) (Found: C, 69·0; H, 8·9. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·85%).

(b) *From* 3β-*hydroxy*-5α-*pregnane*-11,20-*dione*. Similar hydroperoxidation of this alcohol, but with a total reaction time of 10 min., gave the hydroperoxide in 51% yield.

3β,17-*Dihydroxy*-5α-*pregnane*-11,20-*dione* (VIII; R = H, R′ = OH, X = O).—17-Hydroperoxy-3β-hydroxy-5α-pregnane-11,20-dione (100 mg.) in acetic acid (30 ml.) was reduced with zinc dust (400 mg.) for 4 hr. and the product was isolated with ethyl acetate as a white solid (86 mg.), m. p. 283—286°, $[\alpha]_D$ +65° (*c* 1·0 in dioxan). Crystallisation from aqueous methanol gave 3β,17-dihydroxy-5α-pregnane-11,20-dione (77%), m. p. 284—287°, $[\alpha]_D$ +65° (*c* 1·0 in dioxan). The infrared spectrum resembled that of an authentic specimen {lit.,[23] m. p. 267—271° and 286—289°, $[\alpha]_D$ +65° (in dioxan)}.

17-*Hydroperoxy*-3α-*hydroxy*-5β-*pregnane*-11,20-*dione* (IX; R = H, R′ = O_2H, X = O).—(a) *From* 3α-*acetoxy*-5β-*pregnane*-11,20-*dione*. The steroid (1 g.) in t-butyl alcohol (10 ml.) was added to a solution of potassium t-butoxide (2 g. of potassium in 40 ml.) and the solution was shaken with oxygen for 25 min. Isolation in the usual way gave a white solid (0·7 g.), m. p. 146—152° (decomp.), $[\alpha]_D$ +53° (*c* 1·0 in MeOH). Crystallisation from ethyl acetate gave 17-*hydroperoxy*-3α-*hydroxy*-5β-*pregnane*-11,20-*dione* (57%), m. p. 158—160° (decomp.), $[\alpha]_D$ +85° (*c* 1·0 in MeOH), $\nu_{max.}$ (in Nujol) 3520 (bonded 3-OH), 3180 (bonded 17-O_2H), 1706 (C=O), and 860 cm.$^{-1}$ (O–O) (Found: C, 69·0; H, 8·8. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·85%).

(b) *From* 3α-*hydroxy*-5β-*pregnane*-11,20-*dione*. Hydroperoxidation of the free alcohol under similar conditions, but with a total reaction time of 10 min. (absorption of oxygen was then complete), gave the same dione in 33% yield.

3α,17-*Dihydroxy*-5β-*pregnane*-11,20-*dione* (IX; R = H, R′ = OH, X = O).—17-Hydroperoxy-3α-hydroxy-5β-pregnane-11,20-dione (84 mg.) in acetic acid (25 ml.) was reduced with zinc dust (500 mg.) for 4½ hr. and the product was isolated with ethyl acetate as a white solid (79 mg.), m. p. 192—199°, $[\alpha]_D$ +62° (*c* 1·0 in acetone). Crystallisation from aqueous methanol gave 3α,17-dihydroxy-5β-pregnane-11,20-dione (66%), m. p. 203—208°, $[\alpha]_D$ +66° (*c* 1·0 in acetone) {lit.,[24] m. p. 203—204°, $[\alpha]_D$ +66° (in acetone)}.

17-*Hydroperoxy*-3β-*hydroxypregn*-5-*en*-20-*one* (X; R = O_2H).—3β-Hydroxypregn-5-en-20-one (4 g.), suspended in t-butyl alcohol (40 ml.), was added to a solution of potassium t-butoxide (4 g. of potassium in 100 ml.) and shaken with oxygen for 40 min. The mixture was worked up in the usual way; crystallisation from methanol gave 17-*hydroperoxy*-3β-*hydroxypregn*-5-*en*-20-*one*

[23] Barton, Evans, Hamlet, Jones, and Walker, *J.*, 1954, 747.
[24] Kritchevsky, Garmaise, and Gallagher, *J. Amer. Chem. Soc.*, 1952, **74**, 483.

(2·0 g., 45%), m. p. 190—192° (decomp.). After further crystallisation from methanol, it had m. p. 192—196° (decomp.), $[\alpha]_D$ −11° (*c* 0·5 in MeOH), $\nu_{max.}$ (in Nujol) 3480 (bonded 3-OH), 3200 (bonded 17-O_2H), 1698 (C=O), and 852 cm.$^{-1}$ (O–O) (Found: C, 72·1; H, 9·4. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%).

3β,17-*Dihydroxypregn-5-en*-20-*one* (X; R = OH).—17-Hydroperoxy-3β-hydroxypregn-5-en-20-one (100 mg.) in acetic acid (15 ml.) was reduced with zinc dust (300 mg.), and the product isolated in the usual way, forming a white solid (90 mg.), m. p. 235—245°. Crystallisation from acetone gave 3β,17-dihydroxypregn-5-en-20-one (52%), m. p. 259—261°, $[\alpha]_D$ −36° (*c* 0·4 in MeOH). The infrared spectrum resembled that of an authentic sample (lit., m. p. 265°,[25] 270—272° [26]).

17-*Hydroperoxy*-3β-*hydroxy*-5α-*pregn*-9-*en*-20-*one* (XI; R = O_2H).—3β-Hydroxy-5α-pregn-9-en-20-one [27] (0·5 g.), in t-butyl alcohol (10 ml.), was added to a solution of potassium t-butoxide (2 g. of potassium in 50 ml. of t-butyl alcohol) and the solution shaken with oxygen for 18 min.; the reaction mixture was worked up in the usual way. Crystallisation from methanol gave 17-*hydroperoxy*-3β-*hydroxy*-5α-*pregn*-9-*en*-20-*one* (55%), m. p. 188—191°, $[\alpha]_D$ +50° (*c* 0·4 in MeOH), $\nu_{max.}$ (in Nujol) 3500 (bonded 3-OH), 3180 (bonded 17-O_2H), 1705 (C=O), 852 (O–O), and 818 cm.$^{-1}$ (CH=CR) (Found: C, 72·8; H, 9·6. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%).

3β,17-*Dihydroxy*-5α-*pregn*-9-*en*-20-*one* (XI; R = OH).—17-Hydroperoxy-3β-hydroxy-5α-pregn-9-en-20-one (100 mg.) in acetic acid (25 ml.) was reduced with zinc dust (250 mg.), and the product was isolated in the usual way, as a white solid (90 mg.), m. p. 229—233°. Crystallisation from aqueous methanol gave 3β,17-dihydroxy-5α-pregn-9-en-20-one (47%), m. p. 238—243°, $[\alpha]_D$ −15° (*c* 0·5 in $CHCl_3$), identified by mixed m. p. and infrared with an authentic sample {lit.,[28] m. p. 236—242°, $[\alpha]_D$ −15° (in $CHCl_3$)}.

17-*Hydroperoxy*-3β-*hydroxy*-16β-*methyl*-5α-*pregnan*-20-*one* (XII; R = H, R′ = O_2H).—3β-Acetoxy-16β-methyl-5α-pregnan-20-one [4e] (0·5 g) in t-butyl alcohol (5 ml.) was added to a solution of potassium t-butoxide (2 g. of potassium in 50 ml.) and shaken with oxygen for 20 min. (1 mol. absorbed in 2 min.). The mixture was worked up as previously described, to give a white solid, m. p. 149—152°. Trituration with ether gave a product (174 mg.), m. p. 167—168°; crystallisation from methanol gave 17-*hydroperoxy*-3β-*hydroxy*-16β-*methyl*-5α-*pregnan*-20-*one* (100 mg.), m. p. 175—176°, $[\alpha]_D$ +77° (*c* 0·3 in MeOH), $\nu_{max.}$ (in Nujol) 3400 (bonded 3-OH), 3280 (bonded 17-O_2H), 1700 (C=O), and 848 cm.$^{-1}$ (O–O) (Found: C, 72·0; H, 10·2. $C_{22}H_{36}O_4$ requires C, 72·5; H, 10·0%).

3β,17-*Dihydroxy*-16β-*methyl*-5α-*pregnan*-20-*one* (XII; R = H, R′ = OH).—17-Hydroperoxy-3β-hydroxy-16β-methyl-5α-pregnan-20-one (80 mg.) in acetic acid (20 ml.) was reduced with zinc dust (300 mg.), and the product was isolated with ethyl acetate. Crystallisation from acetone gave 3β,17-dihydroxy-16β-methyl-5α-pregnan-20-one (40 mg., 52%), m. p. 214—216°, $[\alpha]_D$ +44° (*c* 0·5 in dioxan), identified by mixed m. p. and infrared spectrum with an authentic specimen {lit.,[4e] m. p. 216—221°, $[\alpha]_D$ +45·5° (in dioxan)}.

3-*Ethoxypregna*-3,5-*dien*-20-*one* (XIII; R = H).—Sulphuric acid (0·06 ml.) in dioxan (3 ml.) and ethyl orthoformate (9 ml.) were added to progesterone (3 g.), dissolved in dioxan (300 ml.), and the mixture was left at room temperature for 90 min. Pyridine (6 ml.) was added to the deep-red solution, which was then poured into water (1 l.). The mixture was extracted with ether, and the extract washed with water, dried ($MgSO_4$), and evaporated to dryness. The gummy residue in hexane–benzene (2 : 1) was chromatographed on alumina (Peter Spence's type H); elution with hexane containing increasing proportions of benzene gave white crystals (2·4 g.). Crystallisation from methanol, containing a trace of pyridine, gave the enol ether (1·8 g., 55%), m. p. 97—99°, $[\alpha]_D$ −54° (*c* 1·0 in dioxan), $\lambda_{max.}$ (in EtOH) 240—241 mμ ($E^{1\%}_{1cm.}$ 609), $\nu_{max.}$ (in CS_2) 1710 (C=O), 1655, 1630, and 1180 cm.$^{-1}$ (O·C=C·C=C) {lit.,[29] m. p. 106—107°, $[\alpha]_D$ −47° (in dioxan)}.

3-*Ethoxy*-17-*hydroperoxypregna*-3,5-*dien*-20-*one* (XIII; R = O_2H).—The foregoing enol ether (1·8 g.) was added to a solution of potassium t-butoxide (2 g. of potassium in 50 ml.) and shaken with oxygen for 30 min. The solution was poured into water and extracted with ethyl acetate, and the extract was washed with water and dried for a short time ($MgSO_4$).

[25] Julian, Meyer, and Ryden, *J. Amer. Chem. Soc.*, 1950, **72**, 367.
[26] Ringold, Löken, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 816.
[27] Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 1278.
[28] Elks, Phillipps, and Wall, *J.*, 1958, 4001.
[29] Ercoli and Gardi, *J. Amer. Chem. Soc.*, 1960, **82**, 746.

Evaporation of the solution to small bulk under reduced pressure at about 40° gave a white solid (900 mg.), m. p. 130—137°. Crystallisation from aqueous acetone gave 3-*ethoxy*-17-*hydroperoxypregna*-3,5-*dien*-20-*one* (590 mg., 30%), m. p. 135—137°, $[\alpha]_D$ −84° (*c* 0·5 in MeOH), $\lambda_{max.}$ (in EtOH) 239—240 mμ ($E^{1\%}_{1cm.}$ 484), $\nu_{max.}$ (in Nujol) 3320 (bonded 17-O_2H), 1700 (C=O), 1656, 1634, and 1026 (O·C=C·C=C), and 858 cm.$^{-1}$ (O–O) (Found: C, 73·5; H, 9·25. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·15%).

17-*Hydroperoxyprogesterone* (XIV).—3-Ethoxy-17-hydroperoxypregna-3,5-dien-20-one (500 mg.) was dissolved in warm methanol (25 ml.), acetic acid (25 ml.) added, and the solution rapidly cooled to room temperature. After 4 min. the solution had $[\alpha]_D$ −12°, and this rose to +109° during about 2 hr. After 2½ hr. the mixture was poured into water and the white solid was filtered off; crystallisation from aqueous methanol gave 17-*hydroperoxyprogesterone* (348 mg., 75%), m. p. 186—189° (decomp.), $[\alpha]_D$ +116° (*c* 0·5 in MeOH), $\lambda_{max.}$ (in EtOH) 238—239 mμ ($E^{1\%}_{1cm.}$ 483), $\nu_{max.}$ (in Nujol) 3200 (bonded 17-O_2H), 1716 (C=O), 1666, 1618, and 876 (Δ^4-3-ketone), and 852 cm.$^{-1}$ (O–O) (Found: C, 72·8; H, 8·7. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%).

3β-*Hydroxy*-16β-*methyl*-5α,17α-*pregn*-9-*en*-20-*one* (VII).—3β-Acetoxy-16β-methyl-5α-pregn-9-en-20-one (2 g.) in methanol (80 ml.) was boiled with sodium hydroxide (2 g.) in methanol (20 ml.) for 1 hr. Water (100 ml.) was added and the methanol was distilled off under reduced pressure. The mixture was diluted with water (400 ml.) and stored at 0° overnight. Crystallisation of the resulting solid from aqueous methanol gave 3β-*hydroxy*-16β-*methyl*-5α,17α-*pregn*-9-*en*-20-*one* (1·49 g., 84%), m. p. 155—158°, $[\alpha]_D$ −49° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ (in Nujol) 3520 and 3430 (bonded OH), 1704—1696 (C=O), and 820 cm.$^{-1}$ (CH=CR) (Found: C, 79·7; H, 10·45. $C_{22}H_{34}O_2$ requires C, 79·95; H, 10·4%).

In another experiment, sodium (0·2 g.) was refluxed in t-butyl alcohol (20 ml.) until dissolved, the solution was cooled, and the steroid (100 mg.) was added under nitrogen. The mixture was left at room temperature for 2 hr., acetic acid was added to neutralise the excess of sodium t-butoxide, and the mixture was poured into water. It was filtered and the precipitate dried, to give a white solid (60 mg.), m. p. 138—141°, $[\alpha]_D$ −30° (*c* 1·0 in $CHCl_3$). Both the rotation and the infrared spectrum suggested that a large proportion of the 3β-acetoxy-16β-methyl-5α-pregn-9-en-20-one had undergone hydrolysis at $C_{(3)}$ and epimerisation at $C_{(17)}$ to form the 17α-isomer.

Attempts to Use Primary and Secondary Alkoxides in the Hydroperoxidation.—(a) 3β-*Acetoxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one with sodium methoxide*. Sodium (2·5 g.) was dissolved in methanol (45 ml.), and the solution was shaken with oxygen. The steroid (0·5 g.) in methanol (5 ml.) was added and the solution was shaken with oxygen for 18 min., during which there was no apparent absorption of oxygen. Acetic acid was added to neutralise the excess of sodium methoxide and the solution was poured into water. The precipitated solid (0·52 g.), m. p. 142—147°, $[\alpha]_D$ −38° (*c* 1·0 in $CHCl_3$), appeared, from its infrared spectrum, to be essentially 3β-hydroxy-16β-methyl-5α,17α-pregn-9-en-20-one (see above).

(b) 3β-*Hydroxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one with sodium isopropoxide*. Sodium (0·5 g.) was dissolved in boiling propan-2-ol (60 ml.), and the cooled solution, in an atmosphere of oxygen, was treated with a solution of the steroid (0·5 g.) in propan-2-ol (10 ml.). On being shaken in oxygen, the mixture took up 5·2 ml. in 1 hr. The crude product had m. p. 110—115°, $[\alpha]_D$ +2° (in $CHCl_3$), suggesting partial epimerisation at $C_{(17)}$ (starting material, $[\alpha]_D$ +38°; 17α-epimer, $[\alpha]_D$ −49°).

Epimerisation of 3β-*Acetoxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one in Presence of Primary, Secondary, and Tertiary Alkoxides.*—A solution of the steroid (100 mg.) in the appropriate alcohol (2 ml.) was treated with a 0·215N-solution of the corresponding sodium alkoxide in the same solvent (10 ml.), and the rotation of the solution was followed in a 1 dm. tube. The results are shown in the Table.

Time (min.)	2	5	10	25	45	60	90	120	165	20 hr.
α; NaOMe	+0·28°	+0·27°	+0·25°	+0·22°	+0·17°	+0·13°	+0·06°	0°	−0·05°	—
α; $NaOPr^i$	+0·28	+0·27	+0·26	+0·22	+0·16	+0·12	+0·03	−0·03	—	−0·28°
α; $NaOBu^t$	+0·28	+0·27	+0·26	+0·22	+0·18	+0·14	+0·09	+0·04	−0·01	−0·22

Oxygenation of 21-*Acetoxy*-3α-*hydroxy*-5β-*pregnane*-11,20-*dione* (XV; R=CO·CH_2·OAc).—The diketone [30] (0·5 g.) in t-butyl alcohol (10 ml.) was added to a solution of potassium t-butoxide (2 g. of potassium in 50 ml.) and shaken with oxygen for 8 min., during which time

[30] von Euw, Lardon, and Reichstein, *Helv. Chim. Acta*, 1944, **27**, 1287.

1 mol. was absorbed. The solution was poured into water containing acetic acid (10 ml.) and extracted with ethyl acetate; the extract was washed with water and sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated, giving a yellow gum (360 mg.), whose infrared spectrum showed a weak band at 1730 $cm.^{-1}$, possibly due to 17-ketone.

The sodium hydrogen carbonate washings were acidified with 2N-hydrochloric acid, and the white solid (144 mg., 34%) was filtered off and dried (m. p. 281—287°). Crystallisation from aqueous methanol gave 3α-hydroxy-11-oxo-5β-androstane-17β-carboxylic acid (XV; R = CO_2H), m. p. 288—292°, $[\alpha]_D$ +80° (*c* 0·5 in MeOH), with an infrared spectrum resembling that of an authentic sample prepared as described below.

3α-Hydroxy-11-oxo-5β-androstane-17β-carboxylic Acid (XV; R = CO_2H).—3α,21-Dihydroxy-5β-pregnane-11,20-dione [31] (50 mg.) was dissolved in acetic acid (5 ml.) and water (5 ml.); sodium bismuthate (0·4 g.) was added and the solution was stirred for 45 min. Water (20 ml.) was added, followed by potassium hydroxide (2·0 g.) in water (20 ml.), and the suspension was shaken with chloroform and filtered, the solid being washed with chloroform. The combined extracts were washed with water, dried ($MgSO_4$), filtered, and evaporated to dryness, to give a solid (40 mg.), m. p. 280—288°. Crystallisation from aqueous methanol gave 3α-hydroxy-11-oxo-5β-androstane-17β-carboxylic acid (25 mg., 52%), m. p. 288—292°, $[\alpha]_D$ +80° (*c* 0·5 in MeOH), $\nu_{max.}$ (in Nujol) 3370 (bonded OH), 2600, and 1700 (CO_2H), and 1705 $cm.^{-1}$ (C=O) {lit.,[32] m. p. 290—292°, $[\alpha]_D$ +80° (in EtOH)}.

5-Hydroperoxy-3β-hydroxy-5α-cholestan-6-one (XVI; R = O_2H).—3β-Hydroxy-5α-cholestan-6-one (0·5 g.), in t-butyl alcohol (10 ml.), was added to a solution of potassium t-butoxide (1·5 g. of potassium in 45 ml.) and shaken with oxygen for 36 min. (1 mol. absorbed after 26 min.). The solution was poured into water (1000 ml.) containing acetic acid (10 ml.) and extracted with methylene chloride. The extract was washed with water, dried ($MgSO_4$), and evaporated. The gummy residue crystallised from ethyl acetate (charcoal) to give *5-hydroperoxy-3β-hydroxy-5α-cholestan-6-one* (20%), m. p. 192—195° (decomp.), $[\alpha]_D$ −5° (*c* 1·0 in MeOH), $\nu_{max.}$ (in CS_2) 3430 (bonded 3-OH), 3210 (bonded 5-O_2H), and 1720 $cm.^{-1}$ (C=O) (Found: C, 74·35; H, 10·6. $C_{27}H_{46}O_4$ requires C, 74·6; H, 10·7%).

3β,5-Dihydroxy-5α-cholestan-6-one (XVI; R = OH).—5-Hydroperoxy-3β-hydroxy-5α-cholestan-6-one (25 mg.) was dissolved in acetic acid (10 ml.) and shaken with zinc dust (300 mg.) for 4 hr. The zinc was filtered off and the precipitate washed with ethyl acetate; the combined filtrates were washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated, to give a white solid (26 mg.), m. p. 229—234°. Crystallisation from aqueous methanol gave 3β,5-dihydroxy-5α-cholestan-6-one (54%), m. p. 232—234°, $[\alpha]_D$ −24° (*c* 0·5 in $CHCl_3$) {lit.,[33] m. p. 232°, $[\alpha]_D$ −22·6° (in $CHCl_3$)}.

Oxygenation of Hecogenin.—Hecogenin (1 g.) in t-butyl alcohol (30 ml.) was added to a solution of potassium t-butoxide (4 g. of potassium in 90 ml.) and shaken with oxygen for 3½ hr., during which nearly 2 mol. of oxygen were absorbed. The solution was poured into water (1 l.) containing acetic acid (10 ml.), and the product was stored at 0° for 2 hr., filtered off, and dried. It had m. p. 158—163°, $[\alpha]_D$ −22° (*c* 1·0 in $CHCl_3$), $\lambda_{max.}$ 281 mμ ($E^{1\%}_{1\,cm.}$ 55·2). It gave a green colour with ferric chloride.

This crude material (1·1 g.) in pyridine (6 ml.) and acetic anhydride (8 ml.) was heated on the steam-bath for 4 hr.; the solution was poured on ice, and the solid filtered off and dried. The product (0·9 g.) in benzene was chromatographed on Florisil (100 g.), the column being eluted with benzene and benzene–ethyl acetate. Crystallisation of the eluted material from ethanol gave, as first crop, hecogenin acetate (100 mg.), m. p. 238—242°, $[\alpha]_D$ −2° (*c* 1·0 in $CHCl_3$). Concentration of the mother-liquors gave 3β,11-diacetoxy-5α,25D-spirost-9-en-12-one (XVII) (152 mg.), m. p. 187—191°, $[\alpha]_D$ +19° (*c* 1·0 in $CHCl_3$), $\lambda_{max.}$ 243 mμ ($E^{1\%}_{1\,cm.}$ 189), whose infrared spectrum resembled that of an authentic sample (Found: C, 70·15; H, 8·6. Calc. for $C_{31}H_{44}O_7$: C, 70·4; H, 8·4%) {lit.,[34] m. p. 188—192°, $[\alpha]_D$ +14° (in $CHCl_3$), $\lambda_{max.}$ 244 mμ ($E^{1\%}_{1\,cm.}$ 213)}.

Oxygenation of Cholestan-3-one in Presence of Potassium t-Butoxide.—Cholestan-3-one (1·0 g.) in t-butyl alcohol (100 ml.) containing potassium t-butoxide (made 1N) was shaken in oxygen for 20 min. (1 mol. uptake). Water (10 ml.) and excess of acetic acid (6 ml.) were added and

[31] Oliveto, Smith, Gerold, Rausser, and Hershberg, *J. Amer. Chem. Soc.*, 1956, **78**, 1414.
[32] Belleau and Gallagher, *J. Amer. Chem. Soc.*, 1952, **74**, 2816.
[33] Fieser and Fieser, "Steroids," Reinhold Publishing Corporation, New York, 1959, p. 297.
[34] Djerassi, Ringold, and Rosenkranz, *J. Amer. Chem. Soc.*, 1954, **76**, 5533.

the alcohol was removed by evaporation *in vacuo*. The residue was extracted with ether, and the extract washed with aqueous sodium hydrogen carbonate and then with 20% aqueous potassium hydroxide (4 × 25 ml.). The yellow solid that collected at the interface was separated, acidified with 6N-hydrochloric acid, and extracted with ether. Removal of the ether, after drying (Na_2SO_4), gave cholestane-2,3-dione (XVIII) (900 mg.) as a mixture of the two enolic forms (ultraviolet). The two forms were identified by the procedure of Stiller and Rosenheim.[17]

Oxygenation of Lanost-8-en-3-one.—Lanost-8-en-3-one (500 mg.) in t-butyl alcohol (50 ml.) containing potassium t-butoxide (N) was shaken in oxygen for 16 min. (1 mol. uptake). Water (5 ml.) was added and the solution at once acidified with 6N-hydrochloric acid. The product was extracted with chloroform and washed with water and saturated aqueous sodium hydrogen carbonate. Removal of the solvent *in vacuo* gave 2-hydroxylanosta-1,8-dien-3-one (XX) (477 mg.). Recrystallisation from ether–ethanol gave 250 mg. (48%) of material with $[\alpha]_D$ +48° (*c* 1·26 in $CHCl_3$) and m. p. 155—157·5°, undepressed on admixture with an authentic specimen kindly provided by Dr. J. F. McGhie (Chelsea College of Science and Technology). The identity was confirmed by conversion (pyridine–acetic anhydride overnight at room temperature) into the acetate (m. p. and mixed m. p.).

Oxygenation of Cholestan-3-one in Presence of Triphenylmethylsodium.—Triphenylmethyl chloride (5 g.) in dry tetrahydrofuran (120 ml.) was treated with freshly prepared 1% sodium amalgam (92 g.) under nitrogen with shaking overnight. After decantation under nitrogen this solution was added to cholestan-3-one (2·1 g.). The nitrogen was removed and the solution stirred under dry oxygen for 90 min. (150 ml. uptake). Water (10 ml.) and excess of acetic acid were added and the solvent was removed *in vacuo*. The residue was taken up in ether and separated into acidic (solid potassium salt at interface) and neutral fractions. Acidification of the potassium salt gave the *hydroxy-acid* (XXI; R = CO_2H) (1·176 g.). Recrystallisation from ether and sublimation at 200—225°/10^{-5} mm. gave material with m. p. 235—240° after sintering at 200°, $[\alpha]_D$ +25° (*c* 0·63 in EtOH) (Found: C, 77·95, 77·9; H, 10·95, 10·9; active H, 0·50. $C_{27}H_{46}O_3$ requires C, 77·45; H, 11·1; active H, 0·48%). Treatment with ethereal diazomethane gave the *methyl ester* (XXI; R = CO_2Me) which, after crystallisation from aqueous ethanol, had m. p. 83—83·5°, $[\alpha]_D$ +20° (*c* 0·93 in $CHCl_3$), $\nu_{max.}$ (in $CHCl_3$) 3522 (OH) and 1718 $cm.^{-1}$ (ester) (Found: C, 77·05; H, 10·95. $C_{28}H_{48}O_3$ requires C, 77·7; H, 11·2%).

The hydroxy-acid (110 mg.) in acetic acid (20 ml.) containing sodium dichromate dihydrate (500 mg.) was left at room temperature for 24 hr. Working up in the usual way gave A-norcholestan-2-one (XXII) (100 mg.). Crystallised from ether–ethanol this had m. p. 103—104°, $[\alpha]_D$ +150° (*c* 0·99 in $CHCl_3$), $\nu_{max.}$ 1727 $cm.^{-1}$ (cyclopentanone) (Found: C, 83·95; H, 12·0. Calc. for $C_{26}H_{44}O$: C, 83·8; H, 11·9%) {lit., m. p. 100—100·5°;[19a] 95—96°, $[\alpha]_D$ +142° ($CHCl_3$) [19b]}. The derived 2,4-dinitrophenylhydrazone had m. p. 170—172° (lit.,[19b] m. p. 166—167°).

The hydroxy-acid (XXI; R = CO_2H) (134 mg.) in ether (50 ml.) was refluxed overnight with an excess of lithium aluminium hydride. The excess of reductant was destroyed with ethyl acetate. Working up in the usual way afforded the *diol* (XXI; R = CH_2·OH) (110 mg.). Recrystallised from aqueous ethanol this had m. p. 178—180°, $[\alpha]_D$ +29° (*c* 1·48 in $CHCl_3$), having only hydroxyl absorption in the infrared region (Found: C, 79·9; H, 11·7. $C_{27}H_{48}O_2$ requires C, 80·1; H, 12·0%).

Oxygenation of Cholestanol in Presence of Potassium t-Butoxide in Benzene.—Potassium t-butoxide (sublimed; 1·5 g.) was dissolved in dry benzene (120 ml.) by shaking at room temperature, cholestanol (1 g.) was added, and the mixture was shaken overnight in oxygen. An excess of acetic acid was added and the solution was washed with water, dried, and evaporated to dryness. The residual gum was dissolved in ether and the solution was extracted with 2N-aqueous sodium hydroxide. The alkaline extract was acidified with hydrochloric acid and re-extracted with ether. The washed and dried extract was evaporated to dryness and the gummy residue (520 mg.) was crystallised from ethyl acetate to give 2ξ-hydroxy-A-norcholestane-2ξ-carboxylic acid (XXI; R = CO_2H) (37 mg.), m. p. 240—243°, $[\alpha]_D$ +25° (in EtOH), identified by m. p. and infrared spectrum with the compound prepared as described above.

Oxygenation of Tigogenin in Presence of Potassium t-Butoxide in Benzene.—Tigogenin (1 g.) in benzene (140 ml.) containing potassium t-butoxide (1 g.) was shaken overnight in oxygen. The mixture was acidified with acetic acid, washed with water, dried, and evaporated. Crystallisation of the residue from methanol gave, as first crop, unchanged tigogenin (300 mg.), m. p. 203—206°. A second crop of crystals (100 mg.) crystallised from methanol to give

the presumed 2ξ-*hydroxy*-A-*nor*-5α,25D-*spirostan*-2ξ-*carboxylic acid* (XXIII) as plates (24 mg.), m. p. 266—272°, $\nu_{max.}$ (in Nujol) 3500 (OH), 1710 (CO_2H), 982, 922, and 902 cm.$^{-1}$ (25D-spirostan) (Found: C, 72·3; H, 9·5. $C_{27}H_{42}O_5$ requires C, 72·6; H, 9·5%).

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