The Hydration of Unsaturated Steroids by the Brown Hydroboration Reaction. I. Monounsaturated Steroids

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A wide variety of monounsaturated steroids was subjected to hydration by the Brown method (involving hydroboration and subsequent oxidation with alkaline hydrogen peroxide), in order to investigate the scope and steric course of the reaction. The hydroboration step was carried out either by means of lithium aluminum hydride and boron trifluoride *in situ* or alternatively by passing in diborane gas. It was found that nearly all of the unsaturated steroids studied could be hydrated successfully by this method, the only exceptions noted being the highly hindered Δ^{7}-, $\Delta^{9(11)}$-5β-, and $\Delta^{8(14)}$-ethylenes. The hydration in all cases proceeded by over-all *cis* addition of the elements of water, predominantly from the less hindered side (usually the α side) of the molecule. In the case of steroids containing 1,2-disubstituted double bonds, approximately equal amounts of both possible positionally isomeric alcohols were obtained, while steroidal trisubstituted ethylenes gave only the secondary alcohols (anti-Markownikoff addition). The hydroboration of certain 1,2-disubstituted steroidal ethylenes with bis-3-methyl-2-butylborane (disiamylborane) was also investigated, and it was found that in the case of 5α-cholest-1-ene this reagent resulted in the formation of only 5α-cholestan-2α-ol.

An excellent method for the hydration of olefins has been discovered by H. C. Brown and co-workers,[2] involving hydroboration of the double bond and subsequent oxidation of the resulting alkylborane with alkaline hydrogen peroxide. Most of the examples studied by Brown involved acyclic or simple cyclic olefins. It was of interest to investigate this hydration method in the steroid series, since the results were expected to provide valuable information regarding the scope and steric course of this important reaction. Consequently, a variety of unsaturated steroids, both hydrocarbons and compounds incorporating various functional groups, were subjected to hydration by the Brown method.[3a-d] The results obtained with monounsaturated steroids are described in the present paper, and those obtained with steroidal conjugated dienes in the following paper.[3e] No steroid had been hydrated by this method when we started our studies in 1958. Subsequently other workers have subjected various steroids to the hydration reaction, as will be mentioned later where relevant.

Nearly all of the unsaturated steroids investigated could be hydrated successfully by the hydroboration procedure, and this represents a useful, generally stereospecific, method of synthesis of hydroxy steroids from steroidal olefins. The only exceptions noted were the highly hindered Δ^{7}-, $\Delta^{9(11)}$-5β-, and $\Delta^{8(14)}$-ethylenes. As found in other series,[2] the hydration in all cases proceeded by over-all *cis* addition of the elements of water, predominantly from the less hindered side (usually the α side) of the molecule. In the case of steroids containing 1,2-disubstituted double bonds, approximately equal amounts of both possible positionally isomeric alcohols were usually obtained, while steroidal trisubstituted ethylenes gave the secondary alcohols (anti-Markownikoff addition) as the only products isolated. These results parallel those obtained with 1,2-disubstituted and trisubstituted ethylenes in the acyclic and simple cyclic series.

Methods.—The hydroboration experiments were carried out either by adding an ethereal solution of lithium aluminum hydride to a solution of the steroidal olefin and boron trifluoride etherate in ether or tetrahydrofuran (method a)[3a,4] or alternatively by passing diborane gas (generated by adding a solution of sodium borohydride in diglyme to boron trifluoride etherate in diglyme)[5] through a solution of the olefin in tetrahydrofuran (method b).[6] Method a possesses the advantage that the necessity of generating diborane separately is avoided, and, unlike the earlier Brown *in situ* procedures,[7] the high-boiling diglyme is not employed.[8] Moreover, in a number of cases when method b resulted in the recovery of comparatively large amounts of starting materials (despite the use of a considerable excess of diborane), a more complete conversion was achieved by use of method a. Method a, however, generally cannot be used with ketals or with esters,[9] and in these cases method b was the method of choice. In addition to these two methods of hydroboration, some experiments were performed with bis-3-methyl-2-butylborane (disiamylborane), as described at the end of this paper.

In no case was the hydroboration product investigated (*e.g.*, whether it consisted of the mono-, di-, or trialkylborane),[2] the total material always being oxidized directly with alkaline hydrogen peroxide. This oxidation step was generally carried out by addition of 10% aqueous sodium hydroxide to a solution of the alkylborane in tetrahydrofuran, followed by 30% aqueous hydrogen peroxide at 0°. In some early experiments, however, the reaction was performed by addition of 30% aqueous hydrogen peroxide to a solution containing the alkylborane and potassium hydroxide in ethanol, followed by boiling under reflux.

(1) Taken in part from a Ph.D. thesis submitted by M. Nussim to the Hebrew University, Jerusalem, April, 1961.

(2) See H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, and references cited there.

(3) For preliminary communications, see (a) S. Wolfe, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **24**, 1034 (1959); (b) Y. Mazur, M. Nussim, and F. Sondheimer, *Proc. Chem. Soc.*, 314 (1959); (c) M. Nussim and F. Sondheimer, *Chem. Ind.* (London), 400 (1960); (d) F. Sondheimer and M. Nussim, *J. Org. Chem.*, **26**, 630 (1961); (e) M. Nussim, Y. Mazur, and F. Sondheimer, *ibid.*, **29**, 1131 (1964).

(4) F. Sondheimer and S. Wolfe, *Can. J. Chem.*, **37**, 1870 (1959). The lithium aluminum hydride was added to the boron trifluoride, rather than vice versa, to ensure a steady evolution of diborane [see I. Shapiro, H. G. Weiss, M. Schmich, S. Skolnik, and G. B. L. Smith, *J. Am. Chem. Soc.*, **74**, 901 (1952)].

(5) H. C. Brown and P. A. Tierney, *ibid.*, **80**, 1552 (1958).

(6) *Inter alia*, see H. C. Brown and G. Zweifel, *ibid.*, **83**, 2544 (1961).

(7) (a) H. C. Brown and B. C. Subba Rao, *ibid.*, **81**, 6423 (1959); (b) 6428 (1959).

(8) For other methods for avoiding the necessity of generating diborane separately or of using diglyme, see H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover, and G. Zweifel, *ibid.*, **82**, 4233 (1960).

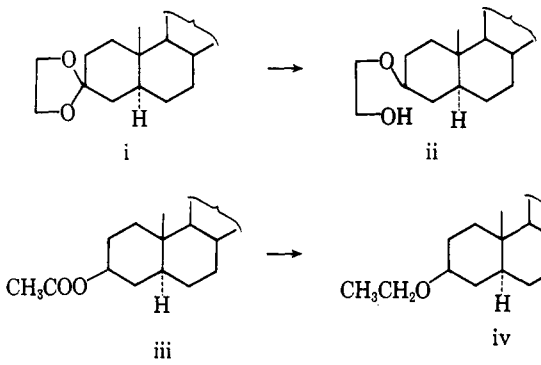
The two oxidation procedures are equally convenient. However the first-mentioned one, unlike the second, caused only slow hydrolysis of 3β-acetoxy steroids, and, therefore, is the method of choice when saponification of esters is to be avoided.

The alcohols obtained by the hydroboration–oxidation sequence were usually isolated by chromatography on alumina. The yields, given to the nearest 5%, are those of materials actually obtained in reasonably pure form. No complete analytical study of the product composition was made in any case, and small amounts of by-products may well have been formed but were not detected.

1,2-Disubstituted Ethylenes.[3d]—All the possible types of steroidal 1,2-disubstituted ethylenes containing the double bond in the normal 5α steroid nucleus, except for ring D ethylenes, were subjected to the hydration reaction. Approximately equal amounts of both possible positionally isomeric alcohols were obtained in all the cases studied, except when bis-3-methyl-2-butylborane was used (following). Attack appeared to occur invariably at the less hindered α side of the steroid nucleus, giving rise to the α alcohols. A clear-cut chromatographic separation between the two isomeric alcohols formed in each case usually could be effected, since one of the products contains an equatorial hydroxyl group and the other an axial hydroxyl group.

5α-Cholest-1-ene (I) on hydration by method a yielded 35% of 5α-cholestan-1α-ol (IIa)[11] and 40% of 5α-cholestan-2α-ol (Va)[12]; 20% of unchanged starting material was recovered. 5α-Cholest-2-ene (IV) either by method a or b afforded 35% of 5α-cholestan-2α-ol (Va) (identical with the previously described compound) and 45% of 5α-cholestan-3α-ol (VIIIa),[13] as well as 10% of unchanged starting material.[14]

(9) This was established by blank experiments. Thus, 3-cycloethylenedioxy-5α-cholestane (i) on being subjected to the reaction conditions of method a yielded 90% of the hydroxy ether (ii).[10] 5α-Cholestan-3β-yl acetate under these conditions was reduced to 3β-ethoxy-5α-cholestane (iv)[10] in 20% yield.



(10) For similar reductions of ketals and esters with lithium aluminum hydride–boron trifluoride and lithium aluminum hydride–aluminum trichloride combinations, see (a) G. R. Pettit and W. J. Bowyer, *J. Org. Chem.*, **25**, 84 (1960); (b) G. R. Pettit and T. R. Kasturi, *ibid.*, **26**, 4553 (1961); (c) E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Am. Chem. Soc.*, **84**, 2371 (1962).

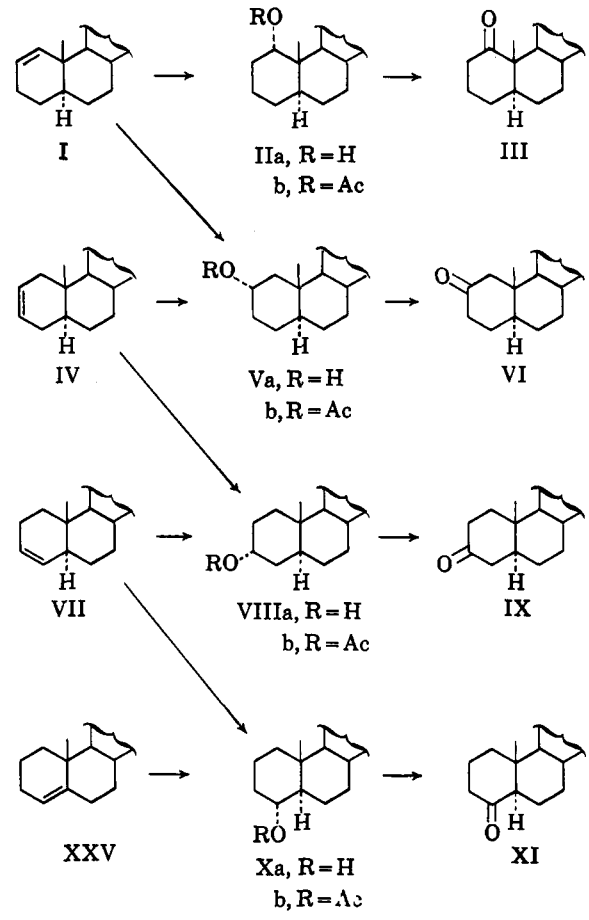
(11) *Inter alia*, P. Striebel and C. Tamm, *Helv. Chim. Acta*, **37**, 1094 (1954).

(12) *Inter alia*, A. Fürst and P. A. Plattner, *ibid.*, **32**, 275 (1949).

(13) *Inter alia*, C. W. Shoppee, *J. Chem. Soc.*, 1138 (1946).

(14) These results[3d] are in agreement with the recent findings of Cross, *et al.*,[15] that the hydration of 17α-methyl-5α-androst-2-en-17β-ol by method b yields 30% of the corresponding 2α-ol and 35% of the 3α-ol. They also agree in essence with the results obtained by Hassner and Pillar[16] from the hydration of Δ²-cholestene by method b; these workers showed that this reaction in addition to the predominantly formed α-ols gives rise to appreciable amounts of the β-ols.

CHART I



5α-Cholest-3-ene (VII) by method a yielded 40% of 5α-cholestan-3α-ol (VIIIa) (identical with the compound obtained before) and 45% of 5α-cholestan-4α-ol (Xa).[17] The structures assigned to the 1α-ol IIa, the 2α-ol Va, the 3α-ol VIIIa, and the 4α-ol Xa follow from the good agreement of the physical properties of the alcohols, as well as of the corresponding acetates IIb, Vb, VIIIb, and Xb, with those reported,[11,12,13,17] while oxidation with chromium trioxide in acetic acid led to 5α-cholestan-1-one (III),[11] 5α-cholestan-2-one (VI),[12] 5α-cholestan-3-one (IX) (identical with an authentic sample), and 5α-cholestan-4-one (XI),[17] respectively. (See Chart I.)

5α-Cholest-6-en-3β-ol (XII) on hydration by method a gave a 55% yield of a mixture apparently consisting of about equal amounts of 5α-cholestane-3β,6α-diol (XIIIa)[18a] and 5α-cholestane-3β,7α-diol (XVa).[17c,18b] The hydration of XII is assumed to have proceeded from the α side, since this appears to be the less hindered side of the molecule.[19] Unfortunately neither the mixture of diols XIIIa and XVa nor the corresponding diacetates XIIIb and XVb could be separated by

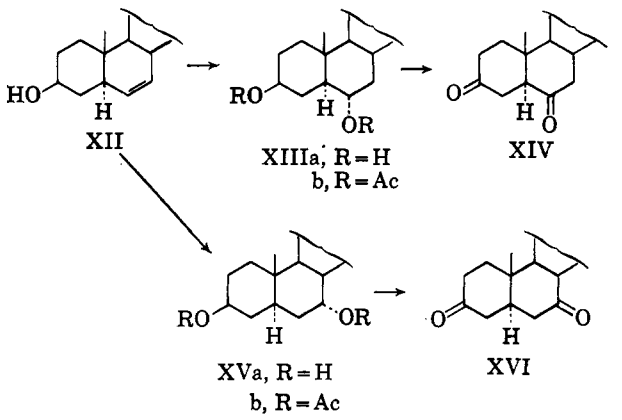
(15) A. D. Cross, J. A. Edwards, and A. Bowers, *J. Med. Chem.*, **5**, 406 (1962); A. D. Cross, J. A. Edwards, J. C. Orr, B. Berköz, L. Cervantes, M. C. Calzada, and A. Bowers, *ibid.*, **6**, 162 (1963).

(16) A. Hassner and C. Pillar, *J. Org. Chem.*, **27**, 2914 (1962).

(17) *Inter alia*, (a) R. Tschesche and A. Hagedorn, *Ber.*, **68**, 2247 (1935); (b) L. Ruzicka, P. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, **27**, 727 (1944); (c) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

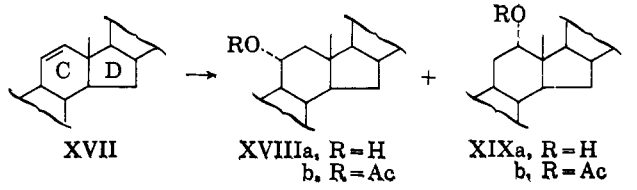
(18) *Inter alia*, (a) P. A. Plattner and W. Lang, *Helv. Chim. Acta*, **27**, 1872 (1944); (b) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **65**, 1503 (1943).

(19) See D. R. James, R. W. Rees, and C. W. Shoppee, *J. Chem. Soc.*, 1370 (1955).



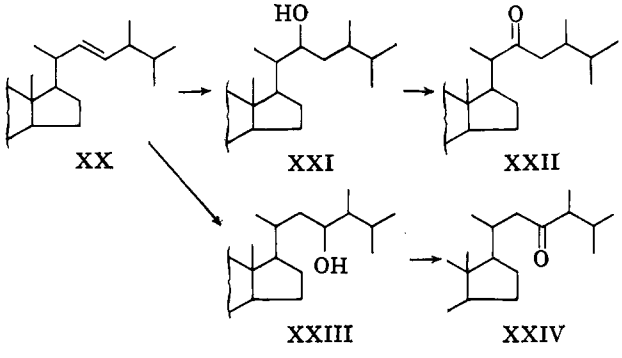
chromatography or by crystallization. Oxidation of the mixed diols XIIIa and XVa with chromium trioxide in acetic acid gave *ca.* a 1:1 mixture of 5α-cholestane-3,6-dione (XIV)[20] and 5α-cholestane-3,7-dione (XVI),[20a] as evidenced by thin layer chromatography (comparison with authentic samples). Small quantities of the pure 3,6-dione XIV as well as of the 3,7-dione XVI could be isolated by fractional crystallization.

5α-25D-Spirost-11-en-3β-ol acetate (XVII) on hydration by method b, followed by saponification and chromatography, afforded 40% of 5α-25D-spirostane-3β,11α-diol (XVIIIa) and 40% of 5α-25D-spirostane-3β,12α-diol (12-epirockogenin) (XIXa), in addition to 10% of unchanged Δ^{11} compound. The 3β,11α-diol



XVIIIa and the 3β,12α-diol XIXa, as well as the derived diacetates XVIIIb and XIXb, agreed well in physical properties with those reported,[21] and were identified by direct comparison with authentic samples.

One example of the hydration of a steroid containing a 1,2-disubstituted double bond in the side chain was investigated. 5α-Ergost-22-en-3β-ol (XX) by method a was converted in 70% yield to what appears to be a mixture of 5α-ergostane-3β,22ξ-diol (XXI) and 5α-ergostane-3β,23ξ-diol (XXIII). This mixture could

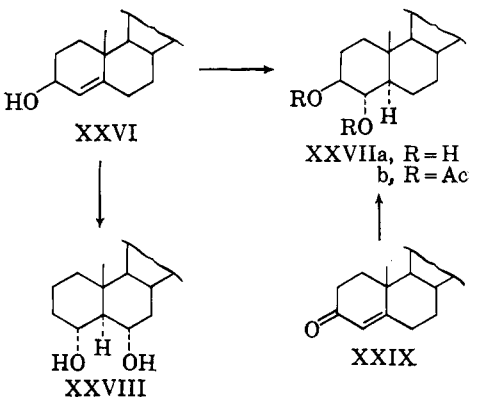


not be resolved by chromatography on alumina, but an apparently pure substance, either XXI or XXIII, was separated by repeated crystallization. That the diols obtained by hydration of XX were positional isomers rather than stereoisomers was shown by the fact that oxidation with chromium trioxide again gave a mixture, presumably of 5α-ergostane-3,22-dione (XXII) and 5α-ergostane-3,23-dione (XXIV).

Trisubstituted Ethylenes.[3a,c]—All the possible types of steroidal trisubstituted ethylenes containing the double bond in the normal 5α steroid nucleus were investigated.

Cholest-4-ene (XXV) on hydration by method a gave 60% of 5α-cholestan-4α-ol (Xa) [identical with that obtained from 5α-cholest-3-ene (VII)], besides 25% of unchanged starting material. By use of method b, the yield of 5α-cholestan-4α-ol (Xa) was only 30%, and 60% of starting material was recovered, despite the fact that a considerable excess of diborane was employed.

Cholest-4-en-3β-ol (XXVI) on hydroboration by a modification of method a, involving addition of ethereal boron trifluoride to a solution of the steroid and lithium aluminum hydride in ether (inverse addition),[4] followed by peroxide oxidation and acetylation, yielded 60% of 5α-cholestane-3β,4α-diol diacetate (XXVIIb). The properties of this diacetate, as well as of the corresponding diol XXVIIa obtained by saponification, agreed well with those reported.[22] Very similar results were obtained when XXVI was hydrated by method b.



However cholest-4-en-3β-ol (XXVI) on hydration by the unmodified method a furnished 50% of 5α-cholestane-4α,6α-diol (XXVIII) as sole crystalline product. This diol is obtained in about the same yield by the hydration of cholesta-3,5-diene (see following paper[3c]), and the latter diene is clearly formed first in the conversion of XXVI to XXVIII through dehydration by means of the boron trifluoride prior to addition of the lithium aluminum hydride.

Cholest-4-en-3-one (XXIX) by either method a or b yielded, after acetylation, *ca.* 60% of 5α-cholestane-3β,4α-diol diacetate (XXVIIb), identical with that obtained from the Δ^4-3β-ol XXVI.[23] This reaction involves reduction of the 3-ketone group as well as hydration of the Δ^4 double bond.

(20) *Inter alia*, (a) D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 783 (1948); (b) P. A. Plattner, A. Fürst, F. Koller, and H. H. Kuhn, *Helv. Chim. Acta*, **37**, 258 (1954).

(21) *Inter alia*, (a) C. Djerassi, E. Batres, M. Velasco, and G. Rosenkranz *J. Am. Chem. Soc.*, **74**, 1712 (1952); (b) R. Hirschmann, C. S. Snoddy, and N. L. Wendler, *ibid.*, **74**, 2693 (1952).

(22) L. F. Fieser and R. Stevenson, *ibid.*, **76**, 1728 (1954).

(23) The conversion of both cholest-4-en-3β-ol (XXVI) and cholest-4-en-3-one (XXIX) to 5α-cholestane-3β,4α-diol (XXVIIa) by method b has been carried out independently by L. Caglioti and G. Cainelli, *Atti accad. nazl. Lincei Rend. Classe sci. fis. mat. e nat.*, [8]**29**, 555 (1960).

With cholest-5-ene derivatives, it was found that the direction of attack of the double bond depends on the nature of the substituent at C-3. Cholest-5-ene (XXX) by method a produced 75% of 5α-cholestan-6α-ol (XXXIa), besides 20% of unchanged starting material. By method b the yield of the 6α-ol XXXIa was only 40%, 45% of the Δ^5-ene XXX being recovered. In neither case could any isomeric alcohol be detected. The resulting 5α-cholestan-6α-ol (XXXIa) and the corresponding acetate XXXIb possessed physical properties in good agreement with those reported.[24,25]

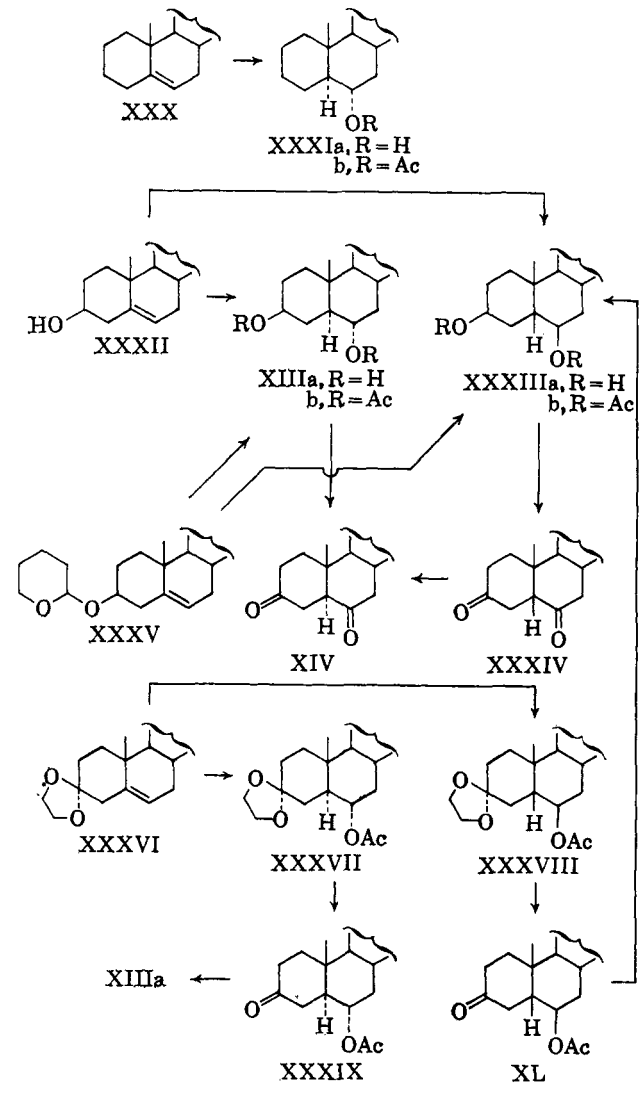
On the other hand, cholesterol (XXXII) on hydration by method a or b yielded, after acetylation, 70% of 5α-cholestane-3β,6α-diol diacetate (XIIIb), as well as *ca.* 20% of 5β-cholestane-3β,6β-diol diacetate (XXXIIIb) (besides 10% of unchanged cholesteryl acetate).[26] Saponification of the diacetates XIIIb and XXXIIIb led to the corresponding diols XIIIa and XXXIIIa, respectively. The structures assigned to these substances follow from the good correspondence of the physical properties with those reported.[18a,29] Moreover oxidation of the diols XIIIa and XXXIIIa with chromium trioxide in acetic acid led to 5α-cholestane-3,6-dione (XIV)[20] and 5β-cholestane-3,6-dione (XXXIV),[29] respectively. The latter diketone could be epimerized to the former by adsorption on basic alumina. (See Chart II.)

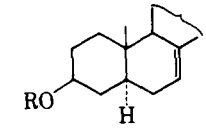
Cholesterol 3-(2′-tetrahydropyranyl) ether (XXXV) on hydration by method a, followed by acid treatment and acetylation, produced 45% of the 3β,6α-diacetate XIIIb and 35% of the 3β,6β-diacetate XXXIIIb, identical with the substances obtained previously.

3-Cycloethylenedioxycholest-5-ene (XXXVI) on hydration by method b and subsequent acetylation gave 95% of an apparently pure substance, which in view of further transformations must be *ca.* a 1:2 mixture of 3-cycloethylenedioxy-5α-cholestan-6α-ol acetate (XXXVII) and 3-cycloethylenedioxy-5β-cholestan-6β-ol acetate (XXXVIII).[30] Removal of ketal groupings by means of boiling aqueous acetic acid led to a mixture which by chromatography now could be separated, affording both 6α-acetoxy-5α-cholestan-3-one (XXXIX) and 6β-acetoxy-5β-cholestan-3-one (XL) in 30% and 60% yields (based on the Δ^5-ketal XXXVI), respectively. The structures of the 6-acetoxy-3-ketones XXXIX and XL follow from the fact that lithium aluminum hydride reduction yielded 5α-cholestane-3β,6α-diol (XIIIa) and 5β-cholestane-3β,6β-diol (XXXIIIa), respectively. Both of these diols, as well as the derived diacetates XIIIb and XXXIIIb, proved to be identical with the corresponding substances derived from cholesterol. Moreover the physical properties of the 6β-acetoxy 3-ketone XL agreed well with those reported.[31] The fact that lithium aluminum hydride reduction of the keto group in this acetoxy ketone XL led to the axial 3β-ol was unexpected and must be due to the presence of the 6β-acetoxy group, since the corresponding reduction of 5β-cholestan-3-one leads mainly to the equatorial 3α-ol.[32] The finding that hydroboration of the ketal XXXVI proceeds mainly from the β side is understandable in view of the presence of an axial 3α-oxygen substituent in this substance.

Attempted hydration of 5α-cholest-7-en-3β-ol (XLIa) by method a led to an 80% recovery of starting material, as well as 20% of an unidentified oil. Method b gave back starting material quantitatively. Similar results were obtained with 5α-ergosten-7-en-3β-ol (type XLIa) using method a, and with 5α-25D-spirost-

CHART II





XLIa, R=H
b, R=Ac

(24) *Inter alia*, R. Tschesche, *Ber.*, **65**, 1842 (1932).

(25) *Inter alia*, C. W. Shoppee, *et al.*, *J. Chem. Soc.*, 3361 (1952).

(26) W. J. Wechter [*Chem. Ind.* (London), 294 (1959)] independently has performed the reaction with cholesterol, using method b, and obtained results similar to ours. Moreover the hydroboration of certain Δ^5-3β-acetoxy steroids[27] and Δ^5-3β-dimethylamino steroids[28] have been described; the products were oxidized directly with sodium dichromate or chromium trioxide, whereby the corresponding 5α-6-keto compounds were obtained.

(27) J. Bagli, P. F. Morand, and R. Gaudry, *J. Org. Chem.*, **27**, 2938 (1962).

(28) R. Pappo, *J. Am. Chem. Soc.*, **81**, 1010 (1959).

(29) V. Prelog and E. Tagmann, *Helv. Chim. Acta*, **27**, 1880 (1944).

(30) The hydration of 3,20-biscycloethylenedioxypregn-5-ene (type XXXVI) through hydroboration has been described by Bagli, *et al.*[27] The steric course of addition was not determined, the product being oxidized at C-6 and then treated with sodium methoxide, whereby the 5α-6-ketone was obtained.

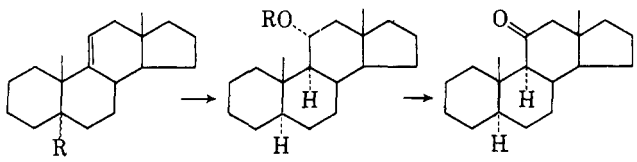
(31) D. N. Jones, J. R. Lewis, C. W. Shoppee, and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955).

(32) C. W. Shoppee and G. H. R. Summers, *ibid.*, 687 (1950).

7-en-3β-ol acetate (type XLIIb) using method b. This lack of reactivity of Δ^7 steroids is not surprising, since this type of ethylene is known to be inert; *e.g.*, it cannot be hydrogenated without prior rearrangement.[33a]

We turn now to the hydration of $\Delta^{9(11)}$ steroids. It has been reported by Wechter[26] that 3,20-biscycloethylenedioxy-5β-pregn-9(11)-ene (XLVb) is inert to hydroboration. We have found similarly that 5β-androst-9(11)-ene (XLIIb)[34] on attempted hydration by method a or b was recovered completely unchanged. This lack of reactivity must be due to the A/B-*cis* junction in compounds XLIIb and XLVb, resulting in hindrance of the $\Delta^{9(11)}$ double bond from the α as well as from the β side. On the other hand, 5α-$\Delta^{9(11)}$ steroids are not appreciably hindered from the α side, and such compounds in fact have been found by us to undergo smooth hydration to give the expected 11α-hydroxy steroids with the normal (α) hydrogen configuration at C-9. This represents a useful new method for introducing an 11-oxygen group into steroids.

5α-Androst-9(11)-ene (XLIIa)[34] on hydration by method a gave over 90% of 5α-androstan-11α-ol (XLIIIa). The structure of this product, which could not be crystallized, follows from the facts that it could be acetylated to XLIIIb on treatment with acetic



XLIIa, R = ···H
b, R = —H

XLIIIa, R = H
b, R = Ac

XLIV

anhydride in pyridine, and that oxidation with chromium trioxide in acetic acid led to 5α-androstan-11-one-(XLIV), identical with an authentic sample.[35] Hydration of XLIIa by method b furnished the 11α-ol XLIIIa in only 55% yield, and 40% of starting material was recovered.

XLVa, 3,20-biscycloethylenedioxy-5α-pregn-9(11)-ene,[34] which is the 5α isomer of the 5β compound XLVb that had been found to be unreactive,[26] on hydration by method b yielded 60% of 3,20-biscycloethylenedioxy-5α-pregnan-11α-ol (XLVI) besides 30% of unchanged starting material. The structure of the amorphous 11α-hydroxy bisketal XLVI is based on the fact that removal of the ketal groupings with aqueous sulfuric acid led in 90% yield to 11α-hydroxy-5α-pregnane-3,20-dione (XLVIIa). The physical properties of this latter substance, as well as of the derived acetate XLVIIb, agreed well with those reported,[36] and oxidation of the hydroxydione XLVIIa with chromium trioxide in acetic acid led to 5α-pregnane-3,11,20-trione,[37] identified by direct comparison with an authentic sample.

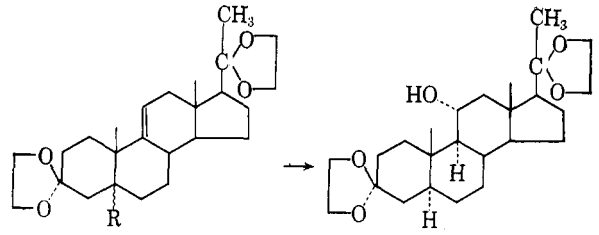
(33) See L. F. Fieser and M. Fieser, "Steroids," 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1959: (a) p. 260; (b) pp. 667–671.

(34) The preparation of this previously unknown compound is described in Experimental.

(35) F. Sondheimer, E. Batres, and G. Rosenkranz, *J. Org. Chem.*, **22**, 1090 (1957).

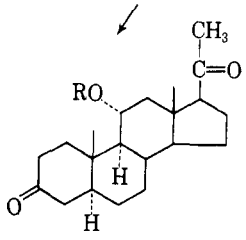
(36) *Inter alia*, O. Mancera, J. Romo, F. Sondheimer, G. Rosenkranz, and C. Djerassi, *ibid.*, **17**, 1066 (1952).

(37) *Inter alia*, (a) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **21**, 161 (1938); (b) C. Djerassi, O. Mancera, J. Romo, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 3505 (1953).



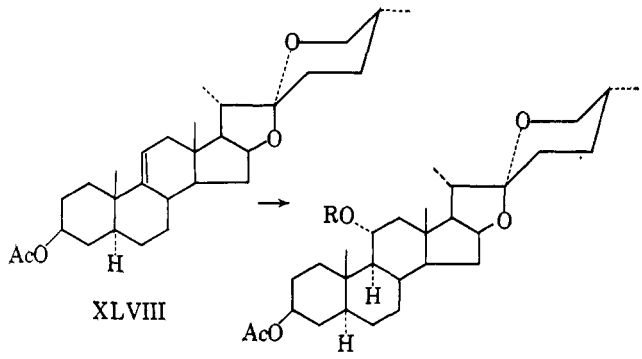
XLVa, R = ···H
b, R = —H

XLVI



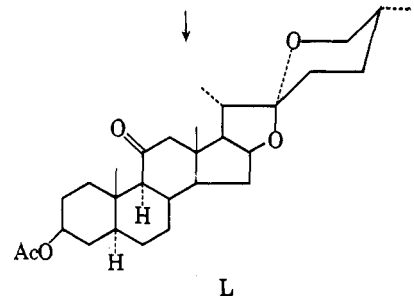
XLVIIa, R = H
b, R = Ac

A practical example of the utility of the hydration of 5α-$\Delta^{9(11)}$ steroids is the hydration of 5α-25D-spirost-9(11)-en-3β-ol acetate (XLVIII),[38] which by method b and subsequent acetylation gave 60% of 5α-25D-spirostane-3β,11α-diol diacetate (ILb), as well as 30% of recovered starting material. The physical properties



XLVIII

ILa, R = H
b, R = Ac



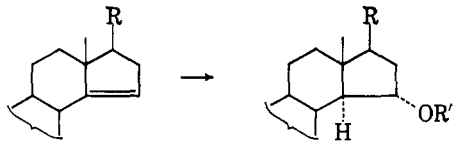
L

of the diacetate ILb, as well as of the corresponding 3β,11α-diol obtained by saponification, agreed well with those reported,[21a] and these substances proved to be identical with the corresponding ones (XVIIIb and XVIIIa) obtained by the previously mentioned

(38) Prepared from hecogenin acetate by selenium dioxide dehydrogenation [A. Bowers, E. Denot, M. B. Sanchez, F. Neumann, and C. Djerassi, *J. Chem. Soc.*, 1859 (1961)], and subsequent removal of the 12-ketone group by Wolff–Kishner reduction [C. Djerassi, H. Martinez, and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951)], as well as *via* the ethylenethioketal [(R. Hirschmann, C. S. Snoddy, and N. L. Wendler, *J. Am. Chem. Soc.*, **75**, 3252 (1953)].

hydration of 5α-25D-spirost-11-en-3β-ol acetate (XVII). In another experiment the total hydration product derived from the $\Delta^{9(11)}$-ethylene XLVIII was oxidized with chromium trioxide in acetic acid, whereby 50% of 3β-acetoxy-5α-25D-spirostan-11-one (L) (identical with an authentic sample)[21a] besides 35% of recovered starting material was obtained. This last experiment demonstrates that a 3β-acetoxy grouping can be kept intact in the hydration reaction when method b is used. The $\Delta^{9(11)}$ compound XLVIII is readily prepared in two or three steps from hecogenin acetate,[38] and its conversion to the 11-ketone L by the present method constitutes a short and convenient way for shifting the 12-carbonyl group to the 11-position, a transformation of importance for the production of hormones of the cortisone type.[33b]

5α-Cholest-14-en-3β-ol (LIa) on hydration by method a yielded 75% of 5α-cholestane-3β,15α-diol (LIIa), converted by acetylation to the diacetate LIIb. That hydration of the Δ^{14}-ene LIa, like catalytic hydrogena-



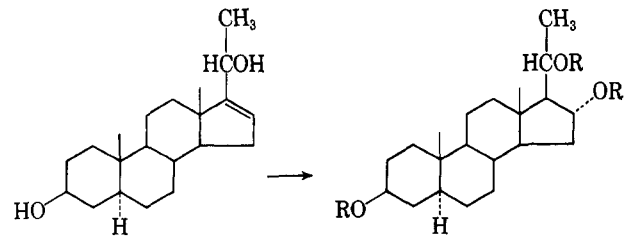
LIa, R = C_8H_{17}
b, R = OH

LIIa, R = C_8H_{17}, R′ = H
b, R = C_8H_{17}, R′ = Ac
c, R = OH, R′ = H

tion,[33a] has proceeded from the α side to produce the 3β,15α-diol LIIa follows from the fact that the physical properties of the diacetate LIIb agreed reasonably well with those of a substance considered most probable to possess this structure,[39] as well as from a consideration of molecular rotation ([M]D) differences. Thus, the shift in [M]D on passing from 5α-cholestan-3β-ol to the diol LIIa is +184, in accord with the positive value (*ca.* +100) observed for the shift in passing from a pregnan-20-one to the corresponding 15α-ol, and not with the negative value (*ca.* −100) for passing to the 15β-ol.[40]

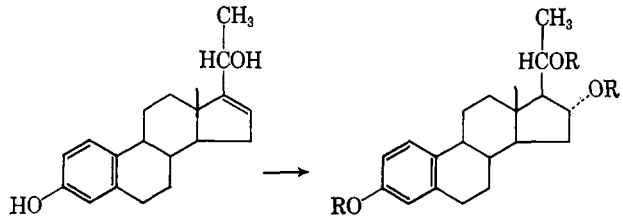
Similarly, hydration of 5α-androst-14-ene-3β,17β-diol (LIb) by method a gave 70% of 5α-androstane-3β,15α,17β-triol (LIIc). The shift in [M]D on passing from 5α-androstane-3β,17β-diol to this triol is +133, again confirming the 15α configuration of the new hydroxyl group.[43]

5α-Pregn-16-ene-3β,20α-diol (LIII)[34] was hydrated by method a, whereby 5α-pregnane-3β,16α,20α-triol (LIVa)[44] was obtained in 80% yield. This represents a convenient synthetic route to this urinary constit-



LIII

LIVa, R=H
b, R=Ac

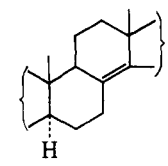


LV

LVIa, R=H
b, R=Ac

uent.[44b] The physical properties of the triol LIVa, as well as those of its triacetate LIVb, agreed reasonably well with those reported.[44] In similar fashion, 19-norpregna-1,3,5(10),16-tetraene-3,20α-diol (LV)[34] on hydration by method a was converted in 90% yield to a triol, by analogy assigned the structure of 19-norpregna-1,3,5(10)-triene-3,16α,20α-triol (LVIa); acetylation gave the corresponding 3,16,20-triacetate LVIb.

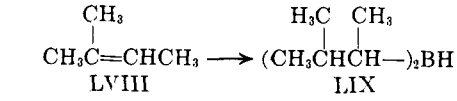
Tetrasubstituted Ethylenes.—The only steroidal tetrasubstituted ethylene investigated was 5α-cholest-8(14)-en-3β-ol (LVII), which on attempted hydration either by method a or b was recovered completely



LVII

unchanged. This result was not unexpected in view of the known lack of reactivity of steroidal $\Delta^{8(14)}$-ethylenes, *e.g.*, towards catalytic hydrogenation.[33a]

Hydroboration with Bis(3-methyl-2-butyl)borane (Disiamylborane) (LIX).[3d]—It has been shown by Brown and Zweifel[2,45] that the hydroboration of simple olefins with the bulky bis(3-methyl-2-butyl)borane (disiamylborane) [LIX, obtained by hydroboration of 2-methyl-2-butene (LVIII)] results in greater steric



control than if diborane is used. Since the previously described hydration experiments with steroidal 1,2-disubstituted ethylenes had given rise to comparable amounts of both possible positionally isomeric alcohols, it was decided to investigate with certain of these ethylenes whether use of disiamylborane would change the ratio of the products.

(39) D. H. R. Barton and G. F. Laws, *J. Chem. Soc.*, 52 (1954); W. Klyne and W. M. Stokes, *ibid.*, 1979 (1954). Unfortunately no sample was available for direct comparison.

(40) These values are based on the fact that the shift in [M]D on passing from progesterone and desoxycorticosterone to the corresponding 15α-hydroxy derivative is +117[41] and +92,[42] respectively, while the shift associated with passage to the corresponding 15β derivative is −108[41] and −95,[42] respectively.

(41) J. Fried, R. W. Thoma, D. Perlman, J. E. Herz, and A. Borman, *Recent Progr. Hormone Res.*, **11**, 149 (1955).

(42) C. Meystre, E. Vischer, and A. Wettstein, *Helv. Chim. Acta*, **38**, 381 (1955); for reassignment of configuration, see A. Wettstein, *Experientia*, **11**, 465 (1955).

(43) The corresponding shift in passing from testosterone to 15α-hydroxytestosterone is +100 [A. Gubler and C. Tamm, *Helv. Chim. Acta*, **41**, 301 (1958)].

(44) (a) H. Hirschmann and F. B. Hirschmann, *J. Biol. Chem.*, **184**, 259 (1950); (b) S. Lieberman, B. Praetz, P. Humphries, and K. Dobriner, *ibid.*, **204**, 491 (1953).

(45) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 3222, 3223 (1960); **83**, 1241, 2544 (1961).

Disiamylborane (LIX) was prepared by hydroboration of 2-methyl-2-butene (LVIII)[46] through addition of ethereal lithium aluminum hydride to an ether solution of the ethylene LVIII and boron trifluoride,[3a,4] as well as through addition of boron trifluoride etherate to a solution of the ethylene LVIII and sodium borohydride in diglyme.[45] 5α-Cholest-1-ene (I) was allowed to react with this reagent, prepared by either method, and the product was oxidized with alkaline hydrogen peroxide in the usual way. Chromatography then yielded 75% of 5α-cholestan-2α-ol (Va), the less hindered isomer, and no detectable amount of 5α-cholestan-1α-ol (IIa). On the other hand, no significant change from the previous results was observed when 5α-cholest-2-ene (IV) and 5α-cholest-3-ene (VII) were hydrated under these conditions, the former giving 35% of 5α-cholestan-2α-ol (Va) and 45% of 5α-cholestan-3α-ol (VIIIa), while the latter gave 45% of 5α-cholestan-3α-ol (VIIIa) and 35% of 5α-cholestan-4α-ol (Xa). These results are in keeping with the fact that the two possible sites of attack in the Δ^1 compound differ sterically to a greater extent than in the Δ^2 or the Δ^3 compound.

Experimental[48]

Hydroboration Procedures. i. **Method a.**—The following is a typical example of the use of method a. Boron trifluoride etherate (5 g., 35.2 mmoles) was added to a solution of 1 g. of the steroidal olefin in 40 cc. of dry ether (or tetrahydrofuran where indicated). A solution of 0.6 g. (15.8 mmoles) of lithium aluminum hydride in 30 cc. of ether was then added dropwise during 1 hr. under nitrogen with stirring and continuous cooling in ice–water. The ice bath was removed and the mixture was stirred for 1 hr. Water was added carefully, and the organic layer, after being washed with sodium bicarbonate solution and water, was dried over sodium sulfate and evaporated.

ii. **Method b.**—The following is a typical example of the use of method b. Diborane was generated by adding a solution of 0.6 g. (15.9 mmoles) of sodium borohydride in 30 cc. of diglyme to a solution of 5 g. (35.2 mmoles) of boron trifluoride etherate in 20 cc. of diglyme, in the type of apparatus described by Brown and Subba Rao.[7b] The gas was passed into a solution of 1 g. of the steroidal olefin in 40 cc. of dry tetrahydrofuran during *ca.* 1 hr. by means of a slow stream of nitrogen. After an additional hour at room temperature, *ca.* 5 cc. of water was added to destroy excess diborane, and the mixture was oxidized directly.

Oxidation of Organoboranes.—Unless stated otherwise, all oxidations were carried out by the following procedure. Aqueous sodium hydroxide (20 cc. of a 10% solution) was added to a solution of the organoborane (derived from 1 g. of olefin) in 40 cc. of tetrahydrofuran. The solution was then cooled in ice–water, and 15 cc. of 30% aqueous hydrogen peroxide was added dropwise with stirring and continued cooling. The mixture was stirred for 1 hr. at 0° and diluted with water and ether; the organic layer was washed with sodium bisulfite solution and water. The extract was then dried over sodium sulfate and evaporated.

Blank Experiments (Carried Out by Dr. E. Levy). a. 3-Cycloethylenedioxy-5α-cholestane (i).—This ketal (2.15 g., 5 mmoles) was subjected to the reaction conditions of method a, and the product was chromatographed on 100 g. of Alcoa activated alumina (grade F-20). Elution with benzene–ether (1:1) gave 1.95 g. (90%) of 3β-(β-hydroxyethoxy)-5α-cholestane (ii), m.p. 144–147°. Crystallization from hexane yielded 1.60 g., m.p. 148–149°, $[\alpha]_D$ +20°; strong hydroxyl band in the infrared (potassium bromide).

Anal. Calcd. for $C_{29}H_{52}O_2$: C, 80.49; H, 12.11. Found: C, 80.80; H, 11.98.

b. 5α-Cholestan-3β-yl Acetate (iii).—Cholestanyl acetate (4.3 g.) was subjected to the reaction conditions of method a, and the product was chromatographed on 200 g. of Alcoa activated alumina (grade F-20). Elution with pentane–benzene (4:1) and crystallization from ether–methanol yielded 0.83 g. (20%) of 3β-ethoxy-5α-cholestane (iv), m.p. 80–81°, identified by direct comparison with an authentic sample (m.p. 81–82°).[10b] Elution with benzene–ether (9:1) yielded 2.82 g. (73%) of 5α-cholestan-3β-ol, m.p. 140–142°.

Hydration of 5α-Cholest-1-ene (I).—5α-Cholest-1-ene (I) was prepared according to Henbest and Wilson[49]; after regeneration from the dibromide, it showed m.p. 69–70°, $[\alpha]_D$ +14°. Hydration of 1 g. of this olefin was carried out by method a, and the product was chromatographed on 35 g. of alumina. Elution with pentane gave 210 mg. (21%) of unchanged starting material. Elution with pentane–benzene (1:1) yielded 345 mg. (33%) of 5α-cholestan-1α-ol (IIa), m.p. 97–100°, which after crystallization from acetone–methanol showed m.p. 103–104°, $[\alpha]_D$ +36°; lit.[11] m.p. 102–103°, $[\alpha]_D$ +35°. The corresponding acetate IIb was obtained as a colorless oil, $[\alpha]_D$ +40°; lit.[11] $[\alpha]_D$ +39°, oil; lit.[49] m.p. 73–75°, $[\alpha]_D$ +43°. Elution with benzene gave 395 mg. (38%) of 5α-cholestan-2α-ol (Va), m.p. 175–178°, which after crystallization from methanol showed m.p. 181–182°, $[\alpha]_D$ +28°; lit.[12] m.p. 181°, $[\alpha]_D$ +27°. The corresponding acetate Vb on crystallization from methanol exhibited m.p. 89–91°, $[\alpha]_D$ 0°; lit.[12] m.p. 90°, $[\alpha]_D$ −1°.

Oxidation of the 1α-ol IIa (60 mg.) with chromium trioxide in acetic acid for 1 hr. at room temperature, followed by crystallization from methanol, gave 41 mg. of 5α-cholestan-1-one (III), m.p. 86–88°, $[\alpha]_D$ +114°; lit.[49] m.p. 87–89°, $[\alpha]_D$ +114°. Similar oxidation of the 2α-ol Va (100 mg.) and crystallization from methanol led to 70 mg. of 5α-cholestan-2-one (VI), m.p. 129–130°, $[\alpha]_D$ +50°; lit.[12] m.p. 130°, $[\alpha]_D$ +51°. The corresponding oxime on crystallization from methanol exhibited m.p. 197–198°, $[\alpha]_D$ +12°; lit.[12] m.p. 200°, $[\alpha]_D$ +14°.

Hydration of 5α-Cholest-2-ene (IV).—5α-Cholest-2-ene (IV) was prepared according to Fieser and Dominguez[50]; after regeneration from the dibromide, it showed m.p. 74–75°, $[\alpha]_D$ +67°. Hydration of 1 g. of this olefin by method a, followed by chromatography on 30 g. of alumina, yielded three different substances. The first, eluted with pentane, proved to be unchanged starting material (120 mg., 12%). The second, eluted with pentane–benzene (1:1), was 5α-cholestan-3α-ol (VIIIa) (450 mg., 43%), m.p. 185–187°, which after crystallization from methanol showed m.p. 187–188°, $[\alpha]_D$ +24°, no precipitate with digitonin; lit.[13] m.p. 186–187°, $[\alpha]_D$ +26°. The corresponding acetate VIIIb after crystallization from methanol exhibited m.p. 97–98°, $[\alpha]_D$ +28°; lit.[13] m.p. 94–95°, $[\alpha]_D$ +30°. The third substance, eluted with benzene, was 5α-cholestan-2α-ol (Va) (350 mg., 33%), m.p. 176–180°, which on crystallization from methanol showed m.p. 181–183°; it was identical with the previously described sample derived from 5α-cholest-1-ene (I).

Oxidation of the 3α-ol VIIIa (100 mg.) with chromium trioxide in acetic acid and crystallization of the product from methanol gave 60 mg. of 5α-cholestan-3-one (IX), m.p. 127–128°, $[\alpha]_D$ +41°. This ketone was identified by direct comparison with an authentic sample (m.p. 128–129°, $[\alpha]_D$ +42°).

Hydration of the Δ^2-ene IV by method b gave almost identical results.

5α-Cholest-3-ene (VII).—This olefin previously has been prepared from cholest-4-en-3-one by Wolff–Kishner reduction.[51]

(46) This olefin was obtained from *t*-amyl alcohol by dehydration with aqueous sulfuric acid to give a mixture consisting of 87% of 2-methyl-2-butene and 13% of 2-methyl-1-butene.[47] The latter olefin was then removed through hydroboration of part of this mixture with sodium borohydride–boron trifluoride to give mainly disiamylborane (LIX), followed by addition of the rest of the olefin mixture, whereby the 2-methyl-1-butene component was attacked preferentially (see second reference in ref. 45).

(47) F. C. Whitmore, C. S. Rowland, S. N. Wrenn, and G. W. Kilmer, *J. Am. Chem. Soc.*, **64**, 2970 (1942).

(48) Melting points are uncorrected. All chromatograms were carried out with Merck "acid-washed" alumina unless otherwise stated. Rotations were determined at room temperature in chloroform solution, unless specified otherwise. Ultraviolet spectra were measured in 95% ethanol solution on a Unicam Model S.P. 500 spectrophotometer. Infrared spectra were determined in chloroform solution (except those marked "KBr", which were measured as potassium bromide pellets) with a Perkin-Elmer Infracord recording spectrophotometer with sodium chloride optics. Analyses were carried out in our microanalytical department under the direction first of Mr. Erich Meier and recently of Mr. Raoul Heller. All acetylations were performed by means of acetic anhydride in pyridine at room temperature for 16 hr.

(49) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 3289 (1956).

(50) L. F. Fieser and X. A. Dominguez, *J. Am. Chem. Soc.*, **75**, 1704 (1953).

(51) G. Lardelli and O. Jeger, *Helv. Chim. Acta*, **32**, 1817 (1949).

We have carried out this reduction under the Huang-Minlon conditions.[52] Careful chromatography of the product on alumina followed by repeated crystallization from ether–methanol yielded 25% of 5α-cholest-3-ene (VII), m.p. 71–72°, $[\alpha]_D$ +55°; lit.[17c] m.p. 72–72.5°, $[\alpha]_D$ +57°. The melting point was depressed on admixture with 5α-cholest-2-ene (IV), as well as with cholest-4-ene (XXV). Hydrogenation in acetic acid over platinum smoothly gave 5α-cholestane, m.p. 78–79°, identical with an authentic sample (m.p. 79–80°) by mixture melting point determination and infrared comparison.

Hydration of 5α-Cholest-3-ene (VII).—Hydration of 1 g. of the Δ^3-ene VII was carried out by method a, and the product was chromatographed on 30 g. of alumina. Elution with pentane–benzene (1:1) furnished 400 mg. (38%) of 5α-cholestan-3α-ol (VIIIa), m.p. 187–188°, $[\alpha]_D$ +24°, identical with the previously described sample derived from 5α-cholest-2-ene (IV). Elution with pentane–benzene (1:4) afforded 460 mg. (44%) of 5α-cholestan-4α-ol (Xa), m.p. 182–185°, which after crystallization from ether–methanol showed m.p. 188–189°, $[\alpha]_D$ +3°; lit.[17a] m.p. 189°, $[\alpha]_D$ +4°. The corresponding acetate Xb after crystallization from methanol exhibited m.p. 110–112°, $[\alpha]_D$ +15°; lit.[17b] m.p. 112.5–113°, $[\alpha]_D$ +16°.

Oxidation of the 4α-ol Xa (100 mg.) with chromium trioxide in acetic acid, followed by crystallization from methanol, led to 65 mg. of 5α-cholestan-4-one (XI), m.p. 99–100°, $[\alpha]_D$ +30°; lit.[17b] m.p. 99–99.5°, $[\alpha]_D$ +30°.

Hydration of 5α-cholest-6-en-3β-ol (XII) (Experiment Carried Out by Dr. E. Levy).—5α-Cholest-6-en-3β-ol (XII) was prepared by the hydroboration of 7-dehydrocholesterol, as described in the following paper.[3e] Hydration of 250 mg. of this olefin was carried out by method a, and the product was chromatographed on 15 g. of Alcoa activated alumina (grade F-20). Elution with ether–chloroform (1:1) yielded 150 mg. (57%) of a crystalline material, m.p. 130–135°, $[\alpha]_D$ +24°. The value of the optical rotation suggests this to be *ca.* a 1:1 mixture of 5α-cholestane-3β,6α-diol (XIIIa) (lit.[18a] m.p. 216–217°, $[\alpha]_D$ +38°) and of the 3β,7α-diol XVa (lit.[18b] m.p. 152–153°, $[\alpha]_D$ +8°; lit.[17c] m.p. 149–150°, $[\alpha]_D$ +12°). Recrystallization or rechromatography of this diol mixture did not lead to a pure substance nor could the corresponding diacetates XIIIb and XVb be separated.

The diol mixture (150 mg.) was oxidized with 150 mg. of chromium trioxide in 40 cc. of 90% acetic acid for 16 hr. at room temperature. Isolation with ether led to a crystalline residue, which was chromatographed on 10 g. of Alcoa activated alumina (grade F-20). Elution with pentane–ether (1:1) gave 110 mg. of *ca.* a 1:1 mixture of 5α-cholestane-3,6-dione (XIV) and 5α-cholestane-3,7-dione (XVI), as evidenced by the fact that thin layer chromatography (development with 2,4-dinitrophenylhydrazine solution) revealed two substances to be present in about equal amounts, which were shown to be the diketones XIV and XVI through chromatographic comparison with the respective authentic samples.[20] Several crystallizations of the diketone mixture from ether–pentane gave 24 mg. of the 3,7-dione XVI, m.p. 187–188°, while repeated crystallizations of the mother liquors from methanol afforded 12 mg. of the 3,6-dione XIV, m.p. 171–172°. The two diketones were identified by direct comparison with the authentic samples (m.p. 189–190° and 172–173°, respectively).

5α-25D-Spirost-11-en-3β-ol Acetate (XVII).—Hecogenin acetate was successively brominated to 3β-acetoxy-11α,23ξ-dibromo-5α-25D-spirostan-12-one, reduced with lithium aluminum hydride to 11α,23ξ-dibromo-5α-25D-spirostane-3β,12ξ-diol, and acetylated to the corresponding 3,12-diacetate, as described by Cornforth, *et al.*[53] A solution of the last-mentioned diacetate (1.7 g.) in 60 cc. of glacial acetic acid was heated to boiling, 15 g. of zinc powder was added in several portions, and the mixture was then boiled under reflux for 4 hr. The mixture was filtered, evaporated under reduced pressure, and diluted with water. Extraction with ether led to 1.2 g. of product, m.p. 195–200°, negative Beilstein test, which was chromatographed on 30 g. of alumina. Elution with pentane–benzene (1:1), followed by crystallization from acetone, yielded 0.82 g. of 5α-25D-spirost-11-en-3β-ol acetate (XVII), m.p. 207–210°, $[\alpha]_D$ −45°; lit.[54] m.p. 206–210°, $[\alpha]_D$ −44°.[55]

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.37; H, 9.77.

Hydration of 5α-25D-Spirost-11-en-3β-ol Acetate (XVII).—The Δ^{11}-ene XVII (500 mg.) was hydrated by method b and then saponified through 2-hr. boiling with 60 cc. of 3% methanolic potassium hydroxide. The product was chromatographed on 20 g. of alumina. Elution with benzene–ether (9:1) afforded 45 mg. (10%) of unchanged 5α-25D-spirost-11-en-3β-ol, which after crystallization from acetone showed m.p. 198–200°, $[\alpha]_D$ −38°; lit.[54] m.p. 193–195°, $[\alpha]_D$ −36°. Elution with ether gave 200 mg. (42%) of 5α-25D-spirostane-3β,11α-diol (XVIIIa), m.p. 213–216°, which after crystallization from acetone exhibited m.p. 216–218°, $[\alpha]_D$ −68°; lit.[21a] m.p. 217–218°, $[\alpha]_D$ −69°. The corresponding diacetate XVIIIb showed m.p. 175–177°, $[\alpha]_D$ −86°; lit.[21a] m.p. 175–177°, $[\alpha]_D$ −84°. Both XVIIIa and XVIIIb were identified by direct comparison with the respective authentic samples.

Elution with ether–chloroform (4:1) yielded 195 mg. (41%) of 5α-25D-spirostane-3β,12α-diol (12-epirockogenin) (XIXa), m.p. 208–212°, which after crystallization from methanol showed m.p. 214–217°, $[\alpha]_D$ −30° (acetone); lit.[21b] m.p. 216–220°, $[\alpha]_D$ −32° (acetone). The corresponding diacetate XIXb exhibited m.p. 153–155°, $[\alpha]_D$ −12° (acetone); lit.[21b] m.p. 156–159°, $[\alpha]_D$ −15° (acetone). Both XIXa and XIXb were identified by direct comparison with the respective authentic samples derived from hecogenin.

5α-Ergost-22-en-3β-ol (XX).—Ergosterol was converted to ergosta-4,6,22-trien-3-one (isoergosterone) in *ca.* 65% yield by the two-step method described by Shepherd, *et al.*[56] The reduction of this trienone to ergosta-4,22-dien-3-one by means of lithium in liquid ammonia and alcohol has been reported by Johnson, *et al.*,[57] as well as by Daglish, *et al.*[58] We have found this reduction (carried out in the absence of alcohol) to give mainly the unconjugated ergosta-5,22-dien-3-one, which then can be conjugated, as described in the sequel.[59]

A solution of 5 g. of ergosta-4,6,22-trien-3-one in 200 cc. of dry ether was added to a stirred solution of 1 g. of lithium in 400 cc. of liquid ammonia. After a further 15-min. stirring, ammonium chloride was added until the blue color disappeared, and the ammonia then was evaporated. Ether and water were added to the residue; the organic layer was washed with dilute hydrochloric acid and water, then dried, and evaporated. The resulting material (4.75 g.) consisted mainly of ergosta-5,22-dien-3-one, as shown by the spectral properties [λ_{max} 242 mμ (ε 1,500), indicative of *ca.* 10% of Δ^4-3-one; strong infrared band at 1710 (Δ^5-3-one) and weak band at 1670 cm.$^{-1}$ (Δ^4-3-one)]. This material was dissolved in 50 cc. of methanol containing 0.2 cc. of 10% aqueous potassium hydroxide, and the solution was boiled for 5 min. Dilution with water and extraction with ether afforded 4.65 g. of a product which possessed only a strong band at 1670 cm.$^{-1}$ in the carbonyl region of the infrared. Crystallization from ethanol yielded 3.95 g. (79% based on isoergosterone) of ergosta-4,22-dien-3-one, m.p. 129–131°, $[\alpha]_D$ +44°, λ_{max} 242 mμ (ε 16,500); lit.[56] m.p. 127–131°, $[\alpha]_D$ +43°, λ_{max} 242 mμ (ε 16,600).

Ergosta-4,22-dien-3-one (3.6 g.) in 150 cc. of dry ether was reduced with 0.7 g. of lithium in 300 cc. of liquid ammonia, and the excess lithium was then destroyed with ammonium chloride, exactly as described before for the reduction of ergosta-4,6,22-trien-3-one. Isolation with ether afforded 3.45 g. of a mixture of 5α-ergost-22-en-3-one and 5α-ergost-22-en-3β-ol (hydroxyl band

(52) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949). This investigator has reported that reduction of cholest-4-en-3-one under these conditions yielded 61% of a hydrocarbon, m.p. 77–78°, $[\alpha]_D$ +64°, considered to be cholest-4-ene. The course of the reduction of 25D-spirost-4-en-3-one under the Huang-Minlon conditions has been studied by C. Djerassi and J. Fishman [*J. Am. Chem. Soc.*, **77**, 4291 (1955)], who showed that the 5α-Δ^3-ene was the major product.

(53) J. W. Cornforth, J. M. Osbond, and G. H. Phillips, *J. Chem. Soc.*, 907 (1954).

(54) J. Elks, G. H. Phillips, D. A. H. Taylor, and L. J. Wyman, *ibid.*, 1739 (1954).

(55) It has been reported by Cornforth, *et al.*, in ref. 53 that, when this zinc reduction was carried out for 1 hr. on the steam bath, the product was the 23-bromo derivative of the olefin XVII. However, Elks, *et al.*,[54] have shown that treatment of 12α,23ξ-dibromo-5α-25D-spirostane-3β,11β-diol 3-acetate with zinc in boiling acetic acid for 3.5 hr. resulted in the olefin XVII, the 23-bromo group being reduced.

(56) D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, J. E. Stafford, R. L. Pedersen, and A. C. Ott, *J. Am. Chem. Soc.*, **77**, 1212 (1955).

(57) F. Johnson, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 1302 (1954).

(58) A. F. Daglish, J. Green, and V. D. Poole, *ibid.*, 2627 (1954).

(59) Since completion of this part of the work, R. E. Schaub and M. J. Weiss [*Chem. Ind.* (London), 2003 (1961)] have reported the analogous reduction of 17β-hydroxyandrosta-4,6-dien-3-one to 17β-hydroxyandrost-5-en-3-one under conditions similar to those used by ourselves.

and comparatively weak carbonyl band at 1710 cm.$^{-1}$ in the infrared).[60] This mixture was then reduced through 2-hr. boiling with 0.7 g. of lithium aluminum hydride in 300 cc. of dry tetrahydrofuran. Isolation with ether, followed by crystallization from chloroform–methanol, yielded 2.65 g. (73% based on the $\Delta^{4,22}$-dien-3-one) of 5α-ergost-22-en-3β-ol (XX), m.p. 155–156°, $[\alpha]_D$ −9°; lit.[61a] m.p. 152°, $[\alpha]_D$ −9°; lit.[61b] m.p. 154–156°, $[\alpha]_D$ −11°. The corresponding acetate after crystallization from methanol showed m.p. 155–156°, $[\alpha]_D$ −20°; lit.[61a] m.p. 155.5°, $[\alpha]_D$ −17°; lit.[61c] m.p. 157°, $[\alpha]_D$ −19°.

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.30; H, 11.15.

Hydration of 5α-Ergost-22-en-3β-ol (XX).—This olefin (1 g. in 80 cc. of tetrahydrofuran) was hydrated by method a, and the product was chromatographed on 40 g. of alumina. Elution with benzene–ether (1:1) yielded 720 mg. (69%) of a crystalline material, m.p. 184–190°, which appears to be a mixture of 5α-ergostane-3β,22ξ-diol (XXI) and 5α-ergostane-3β,23ξ-diol (XXIII). This mixture could not be separated by further chromatography; however, several crystallizations from aqueous acetone afforded an apparently pure substance, m.p. 199–201°, $[\alpha]_D$ −6°, which seems to be a hydrate of either XXI or XXIII.

Anal. Calcd. for $C_{28}H_{50}O_2 \cdot H_2O$: C, 77.00; H, 12.00. Found: C, 77.17; H, 12.03.

Oxidation of the mixture of diols with chromium trioxide in acetic acid led to a mixture of the 3,22-dione XXII and the 3,23-dione XXIV, m.p. 123–128°, which also could not be separated by chromatography.

Hydration of Cholest-4-ene (XXV).—Cholest-4-ene (XXV) was prepared from cholest-4-en-3-one by conversion to the ethylenethioketal by the method of Fieser[62] and subsequent Raney nickel desulfurization,[63] as well as by direct reduction of the Δ^4-3-one with lithium aluminum hydride and aluminum chloride.[64] The olefin, after purification *via* the corresponding dibromide as described by Bladon, *et al.*,[65] showed m.p. 83–84°, $[\alpha]_D$ +75°.

Cholest-4-ene (1 g.) was hydrated by method a. The oxidation was carried out by dissolving the organoborane in 100 cc. of 10% ethanolic potassium hydroxide, and 30 cc. of 30% aqueous hydrogen peroxide was then added during 5 min. without external cooling. The solution was boiled under reflux for 15 min., and the product was then isolated with ether as usual. Chromatography on 30 g. of alumina and elution with pentane gave 255 mg. (25%) of unchanged starting material. Elution with pentane–benzene (1:4), followed by crystallization from ether–methanol, produced 615 mg. (59%) of 5α-cholestan-4α-ol (Xa), m.p. 187–188°, $[\alpha]_D$ +3°. This substance proved to be identical with the one described previously, derived from 5α-cholest-3-ene (VII).

By use of method b and subsequent oxidation, as described directly preceding, 500 mg. of cholest-4-ene yielded 155 mg. (30%) of 5α-cholestan-4α-ol (Xa) and 305 mg. (61%) of unchanged starting material.

Hydration of Cholest-4-en-3β-ol (XXVI). a. Inverse Addition.—Cholest-4-en-3β-ol (XXVI) (m.p. 130–132°, $[\alpha]_D$ +44°) was prepared by the reduction of cholest-4-en-3-one with lithium tri-*t*-butoxy aluminum hydride.[66] A solution of 500 mg. of this unsaturated alcohol in 20 cc. of ether was added to a solution of 300 mg. of lithium aluminum hydride in 30 cc. of ether. Boron trifluoride etherate (2.5 g.) in 20 cc. of ether was then added dropwise during 10 min., with stirring and ice cooling. The mixture was stirred for 1 hr. at room temperature, and the organoborane was then isolated and oxidized in the usual manner. The product was acetylated and then chromatographed on 15 g. of alumina. Elution with pentane–benzene (2:1) furnished 385 mg. (61%) of 5α-cholestane-3β,4α-diol diacetate (XXVIIb), m.p. 159–161°, which on crystallization from methanol showed m.p. 161–162°, $[\alpha]_D$ +32°; lit.[22] m.p. 161.5–162.5°, $[\alpha]_D$ +30°. Saponification with boiling 3% methanolic potassium hydroxide for 1 hr. and crystallization from ether–methanol yielded the free diol XXVIIa, m.p. 236–238°, $[\alpha]_D$ +20°; lit.[22] m.p. 236–237°, $[\alpha]_D$ +20°.

Hydration of cholest-4-en-3β-ol by method b yielded the diacetate XXVIIb in 55% yield.

b. Normal Addition.—Cholest-4-en-3β-ol (500 mg.) was hydrated by the unmodified method a, and the product was chromatographed on 15 g. of alumina. The only crystalline product isolated (260 mg., 50%) was 5α-cholestane-4α,6α-diol (XXVIII), m.p. 186–190°, which after crystallization from acetone showed m.p. 193–195°, $[\alpha]_D$ +20°. It was identical with the diol obtained by the hydration of cholesta-3,5-diene (see following paper[3e]).

Hydration of Cholest-4-en-3-one (XXIX).—Hydration of 1 g. of cholest-4-en-3-one by method a, acetylation of the product, and chromatography on 30 g. of alumina led to 760 mg. (60%) of 5α-cholestane-3β,4α-diol diacetate (XXVIIb), m.p. 160–161°, identified with the previously described substance obtained from cholest-4-en-3β-ol (inverse addition). None of the diacetate of the 4α,6α-diol XXVIII could be detected. The yield of the 3β,4α-diacetoxy compound XXVIIb was 56% when the hydration of cholest-4-en-3-one was carried out by method b.

Hydration of Cholest-5-ene (XXX).—Cholest-5-ene (XXX) (m.p. 93–94°, $[\alpha]_D$ −56°) was prepared by the reduction of cholesteryl chloride with sodium in liquid ammonia, according to Ireland, *et al.*[67] This olefin (1 g.) was hydrated by method a, the oxidation being carried out as described for the hydration of cholest-4-ene (XXV). The product was chromatographed on 30 g. of alumina. Elution with pentane yielded 210 mg. (21%) of unchanged starting material. Elution with benzene then produced 765 mg. (73%) of 5α-cholestan-6α-ol (XXXIa), m.p. 124–126°, which after crystallization from ether–methanol showed m.p. 128–129°, $[\alpha]_D$ +35°; lit.[24] m.p. 128–129°, $[\alpha]_D$ +35°. The corresponding acetate XXXIb after crystallization from ethyl acetate–ethanol exhibited m.p. 94–96°, $[\alpha]_D$ +69°; lit.[24] m.p. 95°, $[\alpha]_D$ +69°. No isomeric alcohol could be detected from the hydration reaction.

Hydration of cholest-5-ene (500 mg.) by method b, followed by chromatography, yielded 230 mg. (46%) of unchanged starting material and 205 mg. (39%) of 5α-cholestan-6α-ol. No isomeric alcohol could again be detected.

Hydration of Cholesterol (XXXII).—Cholesterol (1 g.) was hydrated by method a, the oxidation begin carried out as described for the hydration of cholest-4-ene (XXV). The product was acetylated and then chromatographed on 40 g. of alumina. Elution with pentane–benzene (9:1) yielded 100 mg. (9%) of unchanged cholesteryl acetate, m.p. 113–114°. Elution with pentane–benzene (1:1) gave 855 mg. (68%) of 5α-cholestane-3β,6α-diol diacetate (XIIIb), m.p. 100–102°, which after crystallization from methanol showed m.p. 106–107°, $[\alpha]_D$ +41°; lit.[18a] m.p. 107–108°, $[\alpha]_D$ +39°.

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72. Found: C, 75.90; H, 10.54.

Elution with benzene furnished 235 mg. (19%) of 5β-cholestane-3β,6β-diol diacetate (XXXIIIb), m.p. 129–133°, which on crystallization from methanol exhibited m.p. 136–138°, $[\alpha]_D$ +16°; lit.[29] m.p. 137–139°, $[\alpha]_D$ +13°.

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72. Found: C, 76.00; H, 10.61.

Hydration of cholesterol by method b and subsequent acetylation yielded 70% of the 3β,6α-diacetate XIIIb and 16% of the 3β,6β-diacetate XXXIIIb.

Saponification of 200 mg. of the 3β,6α-diacetate XIIIb through 2-hr. boiling with 3% methanolic potassium hydroxide, followed by crystallization from ether–methanol, led to 130 mg. of 5α-cholestane-3β,6α-diol (XIIIa), m.p. 215–217°, $[\alpha]_D$ +38°; lit.[18a] m.p. 213–215°, $[\alpha]_D$ +38°. Oxidation of 100 mg. of this diol with chromium trioxide in acetic acid for 18 hr. at room temperature and subsequent crystallization from methanol afforded 65 mg. of 5α-cholestane-3,6-dione (XIV), m.p. 171–173°, $[\alpha]_D$ +8°, identical with the previously described sample obtained from 5α-cholest-6-en-3β-ol acetate (XII); lit.[20b] m.p. 171–172°, $[\alpha]_D$ +8°.

Similarly, saponification of 100 mg. of the 3β,6β-diol diacetate XXXIIIb and crystallization from ether–methanol yielded 75 mg. of the free 3β,6β-diol XXXIIIa, m.p. 197–199°, $[\alpha]_D$ +23°;

(60) The lithium–ammonia reduction of ergosta-4,22-dien-3-one to 5α-ergost-22-en-3-one has been reported previously by D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 903 (1954).

(61) (a) D. H. R. Barton, J. D. Cox, and N. Y. Holness, *J. Chem. Soc.*, 1771 (1949); (b) D. H. R. Barton and C. H. Robinson, *ibid.*, 3045 (1954); (c) R. Budziarek, F. Johnson, and F. S. Spring, *ibid.*, 534 (1953).

(62) L. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

(63) H. Hauptmann, *ibid.*, **69**, 562 (1947).

(64) J. Broome, B. R. Brown, A. Roberts, and A. M. S. White, *J. Chem. Soc.*, 1406 (1960).

(65) P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *ibid.*, 2402 (1951).

(66) O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1431 (1958); J. Fajkos, *Collection Czech. Chem. Commun.*, **24**, 2284 (1959).

(67) R. E. Ireland, T. Y. Wrigley, and W. G. Young, *J. Am. Chem. Soc.*, **80**, 4604 (1958).

lit.[29] m.p. 198–200°, $[\alpha]_D$ +24°. Oxidation of 50 mg. of this diol with chromium trioxide in acetic acid and crystallization from methanol furnished 25 mg. of 5β-cholestane-3,6-dione (XXXIV), m.p. 178–180°, $[\alpha]_D$ −72°; lit.[29] m.p. 170–174°, $[\alpha]_D$ −57°; lit.[68] m.p. 175–179°, $[\alpha]_D$ −79°, −82°.

5β-Cholestane-3,6-dione (10 mg.), dissolved in 2 cc. of benzene, was adsorbed on a column of 2 g. of Alcoa activated alumina (grade F-20) and allowed to stand overnight. Elution with benzene and crystallization from methanol yielded 7 mg. of 5α-cholestane-3,6-dione, m.p. 168–170°, $[\alpha]_D$ +7°, identified by direct comparison with the previously described sample.

Hydration of Cholesterol 3-(2′-Tetrahydropyranyl) Ether (XXXV).—The ether XXXV (m.p. 154–156°, $[\alpha]_D$ −24°) was prepared from cholesterol, 2,3-dihydropyran, and phosphorus oxychloride, as described by Greenhalgh, *et al.*[69] This ether (1 g.) was hydrated by method a, the oxidation being carried out as described for the hydration of cholest-4-ene (XXV). The product, dissolved in 95% ethanol containing *p*-toluenesulfonic acid, was boiled for 1 hr. Acetylation, followed by chromatography on 40 g. of alumina, yielded 470 mg. (45%) of the 3β,6α-diacetate XIIIb, m.p. 101–103°, and 350 mg. (34%) of the 3β, 6β-diacetate XXXIIIb, m.p. 131–134°. Each of these substances was identical with the corresponding one obtained from the direct hydration of cholesterol. In addition, 95 mg. of an oil was obtained which was not investigated further.

Hydration of 3-Cycloethylenedioxycholest-5-ene (XXXVI).—The ketal XXXVI (m.p. 134–135.5°) was prepared from cholest-4-en-3-one and ethylene glycol, as described by Antonucci, *et al.*[70] This ketal (1.7 g.) was hydrated by method b, the oxidation being carried out as described for the hydration of cholest-4-ene (XXV). The product was acetylated and then chromatographed on 60 g. of alumina. Elution with benzene afforded 1.82 g. (94%) of *ca.* a 1:2 mixture of 3-cycloethylenedioxy-5α-cholestan-6α-ol acetate (XXXVII) and 3-cycloethylenedioxy-5β-cholestan-6β-ol acetate (XXXVIII), m.p. 116–119°; crystallization from methanol gave a sample, m.p. 123–125° (unchanged by further crystallization), $[\alpha]_D$ +21°.

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72. Found: C, 75.93; H, 10.79.

A solution of 1.78 g. of the mixed acetoxy ketals XXXVII and XXXVIII in 50 cc. of 90% acetic acid was boiled under reflux for 15 hr. The solution was diluted with water; the product was isolated with ether and chromatographed on 50 g. of alumina. Elution with benzene furnished 510 mg. (30% over-all from XXXVI), of 6α-acetoxy-5α-cholestan-3-one (XXXIX), m.p. 126–128°, which after crystallization from ether–methanol showed m.p. 132–133°, $[\alpha]_D$ +62°.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.37; H, 10.81.

Elution with benzene–ether (9:1) yielded 1.05 g. (61% over-all from XXXVI) of 6β-acetoxy-5β-cholestan-3-one (XL), m.p. 105–108°, which after crystallization from ether–methanol exhibited m.p. 112–114°, $[\alpha]_D$ +22°; lit.[31] m.p. 113–115°, $[\alpha]_D$ +20°.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.57; H, 10.94.

Reduction of 100 mg. of the 6α-acetoxy-3-one XXXIX with 200 mg. of lithium aluminum hydride in 20 cc. of ether (1-hr. reflux), followed by crystallization from ether–methanol, led to 5α-cholestane-3β,6α-diol (XIIIa), m.p. 212–214°. The corresponding diacetate XIIIb showed m.p. 105–107°, $[\alpha]_D$ +40°. Both these substances were identical with the corresponding ones obtained by the hydration of cholesterol.

Reduction of 150 mg. of the 6β-acetoxy-3-one XL with 300 mg. of lithium aluminum hydride in 30 cc. of ether (1-hr. reflux), followed by crystallization from ether–methanol, yielded 5β-cholestane-3β,6β-diol (XXXIIIa), m.p. 196–197°, $[\alpha]_D$ +23°. The corresponding diacetate XXXIIIb showed m.p. 135–137°, $[\alpha]_D$ +14°. Both of these compounds were found to be identical with the corresponding ones obtained by the hydration of cholesterol.

5α-Androst-9(11)-ene (XLIIa).—5α-Androstan-11-one (XLIV) was prepared according to Sondheimer, *et al.*[35] This ketone (1.2 g.) was reduced with 1 g. of lithium aluminum hydride in 50 cc. of dry tetrahydrofuran (6-hr. boiling). Isolation with ether and crystallization from pentane yielded 1.05 g. (87%) of 5α-androstan-11β-ol, m.p. 92–93°, $[\alpha]_D$ +19°, no carbonyl band in the infrared.

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.81; H, 11.51.

5α-Androstan-11β-ol (1.0 g.) dissolved in 10 cc. of dry pyridine was dehydrated by addition of 3 cc. of freshly distilled phosphorus oxychloride at 0°. The mixture was allowed to stand overnight at room temperature and the product was then isolated with ether. Chromatography on 30 g. of alumina, elution with pentane, and crystallization from ether–methanol gave 0.65 g. (70%) of 5α-androst-9(11)-ene (XLIIa), m.p. 41–42°. The analytical sample showed m.p. 43–44°, $[\alpha]_D$ +15°.

Anal. Calcd. for $C_{19}H_{30}$: C, 88.30; H, 11.70. Found: C, 88.08; H, 11.70.

Hydration of 5α-Androst-9(11)-ene (XLIIa).—5α-Androst-9-(11)-ene (250 mg.) was hydrated by method a, and the product was chromatographed on 10 g. of alumina. Elution with benzene yielded 245 mg. (92%) of 5α-androstan-11α-ol (XLIIIa) as a colorless oil which could not be crystallized. Acetylation led to the 11α-acetate XLIIIb (strong infrared bands at 1726 and 1243 cm.$^{-1}$), which also was not crystalline. Oxidation of the 11α-ol XLIIIa (100 mg.) with chromium trioxide in acetic acid for 16 hr. at room temperature afforded 62 mg. of 5α-androstan-11-one (XLIV), m.p. 47–49°, $[\alpha]_D$ +64°, which was identified by direct comparison with an authentic sample (lit.[35] m.p. 49–50°, $[\alpha]_D$ +65°).

Hydration of 5α-androst-9(11)-ene (100 mg.) by method b, followed by chromatography, gave 41 mg. (41%) of unchanged starting material as well as 58 mg. (54%) of 5α-androstan-11α ol.

5β-Androst-9(11)-ene (XLIIb).—This olefin was obtained from 5β-androstan-11-one[35] (1 g.) by reduction with lithium aluminum hydride and subsequent dehydration with phosphorus oxychloride, exactly as described in the 5α-series. Chromatography of the product on 30 g. of alumina and elution with pentane gave 0.68 g. (72% over-all) of 5β-androst-9(11)-ene, m.p. 66–68°. Crystallization from ether led to the analytical specimen, m.p. 69–70°, $[\alpha]_D$ +32°.

Anal. Calcd. for $C_{19}H_{30}$: C, 88.30; H, 11.70. Found: C, 88.23; H, 11.65.

Attempted hydration of 5β-androst-9(11)-ene by method a or b led to the recovery of unchanged starting material in over 95% yield.

3,20-Biscycloethylenedioxy-5α-pregn-9(11)-ene (XLVa).—A solution of 10 g. of pregn-4-ene-3,11,20-trione (11-ketoprogesterone) in 500 cc. of dioxane was shaken in hydrogen over 1.4 g. of a 10% palladium–charcoal catalyst for 24 hr. at room temperature and a pressure of 45 p.s.i.[71] The mixture was then heated, the catalyst was removed, and the filtrate was evaporated. Crystallization from ethyl acetate yielded 7.0 g. (70%) of 5α-pregnane-3,11,20-trione, m.p. 209–212°, $[\alpha]_D$ +135° (ethanol), no selective absorption in the ultraviolet; lit.[37b] m.p. 211–213°, $[\alpha]_D$ +129° (ethanol).

5α-Pregnane-3,11,20-trione (6 g.) in 150 cc. of benzene containing 14 cc. of ethylene glycol was slowly distilled until 30 cc. were removed, in order to remove moisture. *p*-Toluenesulfonic acid (300 mg.) was added and the mixture was boiled for 15 hr., water being removed during this time by means of a Dean–Stark tube. Aqueous sodium bicarbonate was then added, and the organic layer was washed with water, dried, and evaporated. Crystallization from ethyl acetate yielded 6.35 g. (84%) of 3,20-biscycloethylenedioxy-5α-pregnan-11-one, m.p. 210–212°. The analytical sample showed m.p. 213–214°, $[\alpha]_D$ +47°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.70; H, 9.05.

The keto diketal (2.5 g.) was reduced with 2.5 g. of lithium aluminum hydride in 150 cc. of tetrahydrofuran (15-hr. reflux). The excess reagent was decomposed by the addition of ethyl acetate, followed by a saturated sodium sulfate solution. Solid sodium sulfate was then added, the mixture was filtered, and the filtrate was evaporated. Crystallization from isopropyl alcohol yielded 2.05 g. (82%) of 3,20-biscycloethylenedioxy-5α-pregnan-11β-ol, m.p. 164–166°. Further crystallization gave the analytical sample, m.p. 167–169°, $[\alpha]_D$ +38°.

Anal. Calcd. for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.81; H, 9.61.

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(70) R. Antonucci, S. Bernstein, R. Littel, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(71) For a similar hydrogenation of 11-ketoprogesterone, see J. Pataki, G. Rosenkranz, and C. Djerassi, *J. Biol. Chem.*, **195**, 751 (1952).

The hydroxy diketal (1.8 g.) dissolved in 20 cc. of dry pyridine was dehydrated by addition of 5 cc. of freshly distilled phosphorus oxychloride at 0°. The mixture was set aside overnight at room temperature, and the product was then isolated with ether. Crystallization from ether–methanol afforded 1.45 g. (84%) of 3,20-biscycloethylenedioxy-5α-pregn-9(11)-ene (XLVa), m.p. 155–157°. A further purified sample showed m.p. 161–162°, $[\alpha]_D$ +33°.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.39; H, 9.57.

Hydration of 3,20-Biscycloethylenedioxy-5α-pregn-9(11)-ene (XLVa).—The unsaturated diketal XLVa (500 mg.) was hydrated by method b, and the product was chromatographed on 15 g. of alumina. Elution with pentane–benzene (1:1) furnished 160 mg. (32%) of unchanged starting material. Elution with benzene–ether (4:1) yielded 325 mg. (62%) of 3,20-biscycloethylenedioxy-5α-pregnan-11α-ol (XLVI) as an amorphous substance which could not be crystallized. The product dissolved in 12 cc. of acetone was boiled under reflux for 1 hr. with 4 cc. of water containing 1 drop of concentrated sulfuric acid. The solution was evaporated to small volume and diluted with water. Isolation with ether and crystallization from acetone–hexane yielded 225 mg. (88%) of 11α-hydroxy-5α-pregnane-3,20-dione (XLVIIa), m.p. 193–195°, $[\alpha]_D$ +84°; lit.[36] m.p. 193–195°, $[\alpha]_D$ +83°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.47; H, 9.71.

The corresponding acetate XLVIIb after crystallization from acetone–hexane showed m.p. 175–177°, $[\alpha]_D$ +64°; lit.[36] m.p. 177–179°, $[\alpha]_D$ +66°.

Oxidation of the hydroxydione XLVIIa with chromium trioxide in acetic acid (16 hr. at room temperature) and crystallization from ethyl acetate yielded 5α-pregnane-3,11,20-trione, m.p. 210–213°; the melting point was undepressed on admixture with the previously described sample (m.p. 209–212°) obtained by the hydrogenation of 11-ketoprogesterone, and the infrared spectra were identical.

Hydration of 5α,25D-Spirost-9(11)-en-3β-ol Acetate (XLVIII). This olefin (500 mg., m.p. 205–206°, $[\alpha]_D$ −64°)[38] was hydrated by method b. The product was acetylated and then chromatographed on 15 g. of alumina. Elution with pentane–benzene (1:1) yielded 155 mg. (31%) of unchanged starting material. Elution with benzene furnished 335 mg. (59%) of 5α,25D-spirostane-3β,11α-diol diacetate (ILb), m.p. 167–169°, which after crystallization from acetone–hexane showed m.p. 173–175°, $[\alpha]_D$ −82°; lit.[21a] m.p. 175–177°, $[\alpha]_D$ −84°. The corresponding free diol, obtained by 1-hr. boiling with 3% methanolic potassium hydroxide, after crystallization from acetone exhibited m.p. 217–219°, $[\alpha]_D$ −68°; lit.[21a] m.p. 217–218°, $[\alpha]_D$ −69°. The diacetate ILb and the corresponding diol proved to be identical with the corresponding substances (XVIIIb and XVIIIa) obtained by the hydration of 5α-25D-spirost-11-en-3β-ol acetate (XVII).

In another experiment, 250 mg. of the $\Delta^{9(11)}$-ene XLVIII was hydrated by method b, as before, and the total product was then oxidized with 150 mg. of chromium trioxide in 50 cc. of 95% acetic acid for 16 hr. at room temperature. Isolation with ether yielded material, which was chromatographed on 20 g. of alumina. Elution with pentane–benzene (3:7) furnished 90 mg. (36%) of unchanged starting material. Elution with benzene then gave 126 mg. (49%) of 3β-acetoxy-5α-25D-spirostan-11-one (L), m.p. 216–218°, which after crystallization from acetone exhibited m.p. 223–225°, $[\alpha]_D$ −37°; lit.[21a] m.p. 222–223°, $[\alpha]_D$ −32°; lit.[72] m.p. 223–227°, $[\alpha]_D$ −41°. The substance was identified by direct comparison with an authentic specimen.

5α-Cholest-14-en-3β-ol (LIa).—This substance was obtained by isomerization of 5α-cholest-7-en-3β-ol (XLIa) under conditions based on those described by Cornforth, *et al.*,[73] involving the passage of a stream of hydrogen chloride through a chloroform solution of the Δ^7 compound at −30° for 2 hr. The chloroform solution was then poured into 3% sodium bicarbonate solution and ether was added. After 30 min. shaking, the organic layer was separated, washed with water, dried, and evaporated. Chromatography on alumina, elution with benzene, and crystallization from methanol gave 55% of the Δ^{14} compound LIa, m.p. 129–131°, $[\alpha]_D$ +36°; lit.[74] m.p. 130–131°, $[\alpha]_D$ +34°.

Hydration of 5α-Cholest-14-en-3β-ol (LIa).—The Δ^{14} compound LIa (200 mg.) was hydrated by method a, and the product was chromatographed on 6 g. of alumina. Elution with benzene–ether (1:1) gave 155 mg. (74%) of 5α-cholestane-3β,15α-diol (LIIa), which after crystallization from acetone showed m.p. 191–193°, $[\alpha]_D$ +60°; the substance appears to contain one molecule of acetone of crystallization.

Anal. Calcd. for $C_{27}H_{48}O_2 \cdot C_3H_6O$: C, 77.86; H, 11.76. Found: C, 77.70; H, 11.88.

The corresponding diacetate LIIb after crystallization from ether–methanol exhibited m.p. 144–146°, $[\alpha]_D$ +45°; for a substance believed to have this structure, lit.[39] m.p. 145–147°, $[\alpha]_D$ +50°.

Hydration of 5α-Androst-14-ene-3β,17β-diol (LIb).—This olefin, obtained in 80% yield from 3β-acetoxy-5α-androst-14-en-17-one[75] by reduction with lithium aluminum hydride in boiling ether, showed m.p. 141–143°, $[\alpha]_D$ +35°; by St. André, *et al.*, who carried out this reduction in *ca.* 50% yield with sodium borohydride, lit.[75a] m.p. 140–141°, $[\alpha]_D$ +36°. The Δ^{14}-ene LIb (100 mg. in 25 cc. of tetrahydrofuran) was hydrated by method a, and the product was chromatographed on 3 g. of alumina. Elution with chloroform–methanol (9:1) yielded 73 mg. (69%) of 5α-androstane-3β,15α,17β-triol (LIIc), m.p. 255–262°, which after crystallization from choloroform–methanol exhibited m.p. 263–265°, $[\alpha_D]$ +49° (pyridine).

5α-Pregn-16-ene-3β,20α-diol (LIII).—This substance was prepared by the lithium aluminum hydride reduction of 3β-acetoxy-5α-pregn-16-en-20-one (a degradation product of tigogenin)[76]; it has been shown that this type of reduction of Δ^{16}-20-ones leads to the Δ^{16}-20α-ols.[77] A solution of 1 g. of the Δ^{16}-20-one and 0.5 g. of lithium aluminum hydride in 100 cc. of ether was boiled under reflux for 30 min. Ethyl acetate was added to destroy excess reagent and then dilute sulfuric acid. Isolation with ether and crystallization from acetone yielded 0.75 g. (84%) of 5α-pregn-16-ene-3β,20α-diol (LIII), m.p. 178–180°. The analytical sample exhibited m.p. 181–182°, $[\alpha]_D$ −14°, no high-intensity absorption in the ultraviolet.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.06; H, 10.80.

The 20α stereochemistry in LIII was confirmed by hydrogenation in ethyl acetate over a 10% palladium–charcoal catalyst. Crystallization from acetone then yielded 5α-pregnane-3β,20α-diol, m.p. 217–218°, $[\alpha]_D$ +25°; for this diol, lit.[78] m.p. 218–219°, $[\alpha]_D$ +23°; for 5α-pregnane-3β,20β-diol, lit.[79] m.p. 194.5–195.5, $[\alpha]_D$ +4°.

Hydration of 5α-Pregn-16-ene-3β,20α-diol (LIII).—The Δ^{16} compound LIII (0.5 g. in 40 cc. of tetrahydrofuran) was hydrated by method a, and the product was chromatographed on 15 g. of alumina. Crystallization from acetone yielded 0.42 g. (80%) of 5α-pregnane-3β,16α,20α-triol (LIVa), m.p. 255–258°, $[\alpha]_D$ −5° (ethanol); lit.[44a] m.p. 251–253°; lit.[45b] m.p. 254–256°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.65; H, 10.78.

The corresponding triacetate LIVb after crystallization from ether–methanol showed m.p. 174–176°, $[\alpha]_D$ −50° (ethanol); lit.[44a] m.p. 177–179°, $[\alpha]_D$ −58° (ethanol); lit.[44b] m.p. 177–180°, $[\alpha]_D$ +(?)54° (ethanol).

19-Norpregna-1,3,5(10),16-tetraene-3,20α-diol (LV).—3-Hydroxy-19-norpregna-1,3,5(10),16-tetraen-20-one[80] (2 g.) was reduced through 2-hr. boiling with 1 g. of lithium aluminum hydride in 150 cc. of tetrahydrofuran. Ethyl acetate was added, followed by dilute sulfuric acid. Isolation with ethyl acetate and crystallization from acetone furnished 1.52 g. (76%) of 19-norpregna-1,3,5(10),16-tetraene-3,20α-diol (LV),[81] m.p. 201–202°, $[\alpha]_D$ +82° (ethanol), λ_{max}^{EtOH} 280 mμ (ε 2400).

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Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.17; H, 8.70.

Hydration of 19-Norpregna-1,3,5(10),16-tetraene-3,20α-diol (LV).—The diol LV (0.5 g. in 40 cc. of tetrahydrofuran) was hydrated by method a, and the product was chromatographed on 15 g. of alumina. Elution with chloroform–methanol (4:1) furnished 0.47 g. (89%) of 19-norpregna-1,3,5(10)-triene-3,16α,-20α-triol (LVIa), m.p. 202–204°, which after crystallization from acetone–hexane showed m.p. 206–208°, $[\alpha]D$ +49° (ethanol). The corresponding triacetate LVIb after crystallization from ether exhibited m.p. 178–180°, $[\alpha]D$ −20°.

Anal. Calcd. for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.39; H, 7.84.

2-Methyl-2-butene (LVIII).—Dehydration of *t*-amyl alcohol with 15% aqueous sulfuric acid according to Whitmore, *et al.*,[47] afforded in 85% yield a mixture consisting of 87% of 2-methyl-2-butene and 13% of 2-methyl-1-butene (determined by gas–liquid chromatography). A solution of 14 g. (0.2 mole) of this olefin mixture and 3 g. (0.079 mole) of sodium borohydride in 50 cc. of diglyme was cooled in an ice bath and 15 g. (0.106 mole) of boron trifluoride etherate was added during 30 min., with stirring and continued cooling. The reaction mixture was allowed to stand for 1 hr. at 0°, and a further 35 g. (0.5 mole) of the olefin mixture was then added during 5 min., with stirring and cooling. The reaction was allowed to proceed for 2 hr. at room temperature, and the remaining olefin was then distilled through a column. The resulting 2-methyl-2-butene (23.5 g.) showed b.p. 38–38.5° and, on gas–liquid chromatographic analysis, proved to be uncontaminated with 2-methyl-1-butene.

Hydroboration of 5α-Cholest-1-ene (I) with Disiamylborane.—A solution of 0.50 g. (13.2 mmoles) of lithium aluminum hydride in 30 cc. of dry ether was added dropwise during 20 min. to a stirred solution containing 2.47 g. (35.3 mmoles) of 2-methyl-2-butene and 2.50 g. (17.6 mmoles) of boron trifluoride etherate in 40 cc. of ether, with ice cooling under nitrogen. After an additional hour at 0°, a solution of 0.50 g. (1.35 mmoles) of 5α-cholest-1-ene[49] in 30 cc. of ether was added during 5 min. at 0°, and the mixture was allowed to stand for 4 hr. without further cooling. It was then treated with a saturated sodium sulfate solution and solid sodium sulfate, and then filtered and evaporated. The residue was oxidized in tetrahydrofuran with alkaline hydrogen peroxide, in the usual way. Chromatography on 15 g. of alumina led to 0.39 g. (74%) of cholestan-2α-ol, m.p. 178–180°, $[\alpha]D$ +27°, identical with a previously obtained sample; no cholestan-1α-ol could be detected.

Essentially identical results were obtained when the hydroboration of 5α-cholest-1-ene was carried out with disiamylborane prepared from 2-methyl-2-butene by reaction with sodium borohydride and boron trifluoride etherate in diglyme at 0°, according to Brown and Zweifel.[45]

Hydroboration of 5α-Cholest-2-ene (IV) with Disiamylborane.—5α-Cholest-2-ene[50] (500 mg.) was allowed to react with disiamylborane (prepared from 2-methyl-2-butene, lithium aluminum hydride, and boron trifluoride in ether) exactly as described previously for the Δ^1 isomer, and the product was oxidized with alkaline hydrogen peroxide in the usual way. Chromatography on 15 g. of alumina then yielded 229 mg. (44%) of 5α-cholestan-3α-ol, m.p. 185–187°, and 185 mg. (35%) of 5α-cholestan-2α-ol, m.p. 180–181°. Each of these alcohols was identical with a previously obtained sample.

Hydroboration of 5α-Cholest-3-ene (VII) with Disiamylborane.—The experiment was carried out with 170 mg. of 5α-cholest-3-ene exactly as described before for the Δ^1 and Δ^2 olefins. Chromatography on alumina then yielded 79 mg. (44%) of 5α-cholestan-3α-ol, m.p. 186–188°, and 63 mg. (35%) of 5α-cholestan-4α-ol, m.p. 187–189°. Each of these alcohols was identical with a previously obtained sample.

The Hydration of Unsaturated Steroids by the Brown Hydroboration Reaction. II.[1] Steroidal Conjugated Dienes

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The hydration of a number of steroidal conjugated dienes, through hydroboration and subsequent oxidation with alkaline hydrogen peroxide, was studied. Both cholesta-3,5-diene (I) and cholesta-4,6-diene (II) gave rise to 5α-cholestane-4α,6α-diol (IIIa), the structure of which was established by various transformations as well as through its formation by hydration of 6α-acetoxycholest-4-ene (V). Attempted hydration of 7-dehydrocholesterol (XIa) unexpectedly yielded 5α-cholest-6-en-3β-ol (XIIa), this substance presumably being formed by hydrolysis with rearrangement of the intermediate Δ^7-6α-borane XV. Hydration of several steroidal $\Delta^{7,9(11)}$-dienes (XVIa,b) was found to result only in attack of the $\Delta^{9(11)}$ double bond, and yielded the Δ^7-11α-ols XVIIa in high yield.

In the preceding paper[1] the hydration of a number of monounsaturated steroids was reported, through hydroboration and subsequent oxidation with alkaline hydrogen peroxide. We now describe the results obtained when steroidal conjugated dienes were subjected to the hydration reaction. Acyclic and simple cyclic dienes previously had been hydrated by this method, whereby unsaturated monools as well as saturated diols were formed.[3a]

As previously,[1] the hydroboration was carried out by adding an ethereal solution of lithium aluminum hydride to an ethereal solution of the diene and boron trifluoride (method a) or alternatively by passing diborane gas through a solution of the diene in tetrahydrofuran (method b). An excess of reagent was always used, and the preferential hydroboration of one of the two double bonds was not studied. Unless otherwise stated, the product, without further investigation, was oxidized directly in tetrahydrofuran solution through addition of 10% aqueous sodium hydroxide; followed by 30% aqueous hydrogen peroxide. The resulting alcohols were then isolated by chromatography on alumina, either directly or after acetylation.

Cholesta-3,5-diene (I), a heteroannular diene, on hydration by method a or b, gave rise to *ca.* 45%[4] of the hitherto unknown 5α-cholestane-4α,6α-diol (IIIa) as sole crystalline material isolated. The structure and stereochemistry assigned to this diol follow from the following facts. Acetylation with acetic anhydride in pyridine at room temperature afforded a di-

(1) Part I, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29**, 1120 (1964).

(2) Taken in part from a Ph.D. thesis presented by M. Nussim to the Hebrew University, Jerusalem, April, 1961.

(3) For a survey, see H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962: (a) Chapter 15; (b) Chapter 7.

(4) Yields are given to the nearest 5%.