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

MANASSE NUSSIM,[2] YEHUDA MAZUR, AND FRANZ SONDHEIMER

Daniel Sieff Research Institute, Weizmann Institute of Science, Rehovoth, Israel

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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-

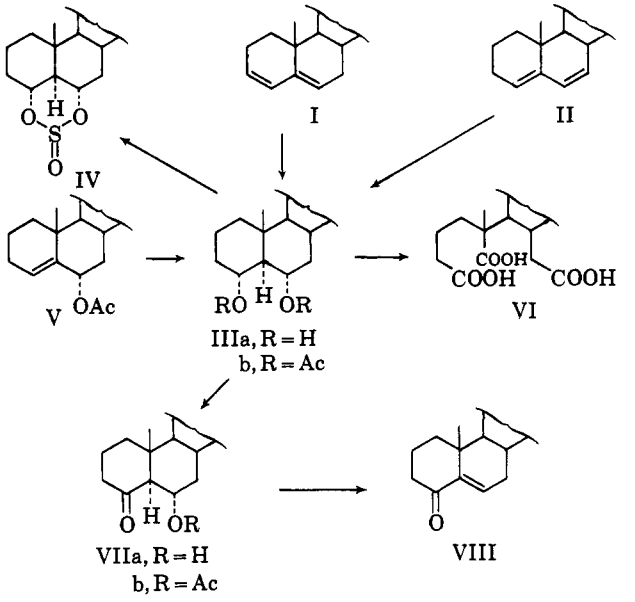
(1) Part I, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29**, 1120 (1964).

(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.

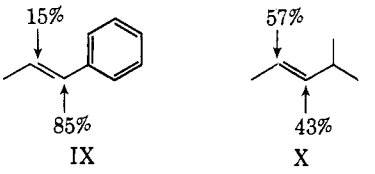
(4) Yields are given to the nearest 5%.

acetate (IIIb), indicating the presence of two secondary hydroxyl groups. The same diol was obtained from cholesta-4,6-diene (II) (following), and the hydroxyl groups must, therefore, be at C-4 and C-6. The diol IIIa readily yielded the cyclic sulfite IV on treatment with thionyl chloride and pyridine, indicating a *cis* relationship of the hydroxyl groups.[5] It was suspected that the hydroxyl groups are α oriented in view of the usual predominant attack of diborane from the α side of steroidal Δ^3 and Δ^5 double bonds[1]; confirmation was provided by a separate experiment, involving the hydration of 6α-acetoxycholest-4-ene (V) by method b, whereby the same diol IIIa was obtained (60% yield) after saponification. The 5α configuration assigned to IIIa follows from the usual over-all *cis* addition of water by the hydration reaction.[1,3]



The oxidation of the 4α,6α-diol IIIa under various conditions was studied, whereby further confirmation of structure was obtained. Oxidation with chromium trioxide in acetic acid gave rise to the amorphous triacid VI, presumably formed *via* 5α-cholestane-4,6-dione. The structure of VI is based on the fact that it required almost exactly 3 molar equiv. of sodium hydroxide for neutralization. On the other hand, oxidation of the 4α,6α-diol IIIa with chromium trioxide in pyridine[6] yielded 6α-hydroxy-5α-cholestan-4-one (VIIa) as sole crystalline material. The corresponding acetate VIIb on treatment with potassium bisulfate at 170° underwent β elimination to give the known cholest-5-en-4-one (VIII), identified by direct comparison with an authentic sample.[7] This transformation shows the ketol obtained by the chromium trioxide–pyridine oxidation of IIIa to possess the 6α-hydroxy-4-one structure VIIa rather than the alternative 4α-hydroxy-6-one structure.

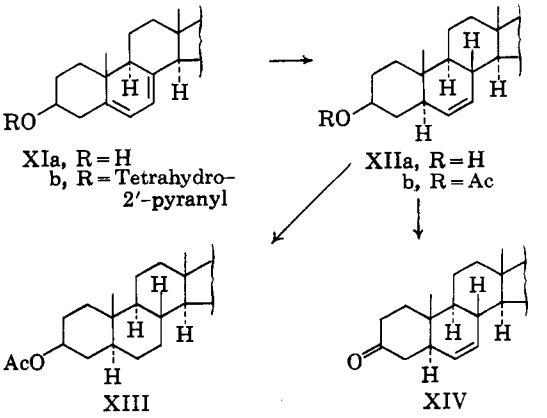
It has been observed previously that ethylenes conjugated with a phenyl group[3b] or with another double bond[3a] on hydroboration undergo addition of the boron atom to the carbon atom α to the conjugating group to a considerably greater extent than ethylenes with the same degree of substitution in which the conjugating group is absent. For instance, *trans*-1-phenylpropene (IX) is attacked at the α-position to the extent of 85%, while the nonconjugated *trans*-4-methyl-2-pentene (X) is attacked at the corresponding position



to the extent of only 43%.[3b,8] An explanation for this behavior of conjugated ethylenes in terms of electronic factors has been given.[3a,b] The result obtained on hydroboration of cholesta-3,5-diene (I) is completely in accord with the previously observed behavior of conjugated ethylenes. The disubstituted Δ^3 double bond is presumably attacked first, the presence of the conjugated Δ^5 bond causing boron to add predominantly at the 4-position; the equatorial α configuration is that expected from steric factors. The trisubstituted Δ^5 double bond is then attacked at C-6 in the usual anti-Markownikoff manner, addition again occurring from the less hindered α side.

The next diene investigated was cholesta-4,6-diene (II). This substance on hydration by method a yielded 35% of 5α-cholestane-4α,6α-diol (IIIa), identical with that obtained by the hydration of the $\Delta^{3,5}$-diene I. In addition *ca.* 10% of a more polar hydroxy compound was isolated, which was not further investigated. The conversion of cholesta-4,6-diene (II) to the 4α,6α-diol IIIa presumably involves attack first of the disubstituted Δ^6 double bond, the presence of the conjugated Δ^4 bond causing boron to add predominantly at the 6-position; the trisubstituted Δ^4 bond is then attacked in the expected anti-Markownikoff manner, both additions again occurring from the less hindered α side.

7-Dehydrocholesterol (cholesta-5,7-dien-3β-ol) (XIa)[9] by method a unexpectedly yielded 20% of 5α-cholest-6-en-3β-ol (XIIa) as the only crystalline substance to be



(5) *Inter alia*, see P. A. Plattner, A. Segré, and O. Ernst, *Helv. Chim. Acta*, **30**, 1432 (1947); P. B. D. de la Mare, W. Klyne, D. J. Millen, J. G. Pritchard, and D. Watson, *J. Chem. Soc.*, 1813 (1956).

(6) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(7) *Inter alia*, A. Butenandt and G. Rothenstroth Bauer, *Ber.*, **77**, 397 (1944).

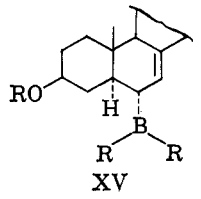
(8) For a similar result with the *p*-methoxy derivative of IX (anethole), see E. L. Allred, J. Sonnenberg, and S. Winstein, *J. Org. Chem.*, **25**, 26 (1960).

(9) Kindly provided by Dr. B. A. Hems, Glaxo Ltd., Greenford, Middlesex, England.

isolated.[10] That the product was a cholestenol followed from the elemental composition of the corresponding acetate XIIb, and the fact that the latter substance on catalytic hydrogenation smoothly furnished cholestanyl acetate (XIII) by uptake of 1 molar equiv. of hydrogen. The Δ^6 formulation XIIa was indicated on the basis of the good agreement of the physical properties of the alcohol XIIa, the acetate XIIb, and the ketone XIV (obtained by oxidation of XIIa with chromium trioxide in pyridine)[11] with those reported[12]; subsequently these three substances were identified by direct comparison with the respective authentic samples.

The formation of 5α-cholest-6-en-3β-ol (XIIa) presumably takes place prior to the alkaline hydrogen peroxide oxidation, and in fact about the same yield of this olefin was obtained when the oxidation step was omitted. Since this represents a useful synthetic route to the Δ^6-ene XIIa, the reaction was studied in more detail. It was found that the yield was improved when 7-dehydrocholesterol 3-(2′-tetrahydropyranyl) ether (XIb) was subjected to the lithium aluminum hydride–boron trifluoride reaction, whereby 5α-cholest-6-en-3β-ol acetate (XIIb) was obtained in 35% yield after acetylation of the product. None of the Δ^6 compound was obtained when 7-dehydrocholesterol was treated with lithium aluminum hydride and aluminum chloride[13] in ether.

The mechanism of the reaction leading from 7-dehydrocholesterol to 5α-cholest-6-en-3β-ol was not studied by us. However, it has been shown very recently by Caglioti, Cainelli, and Maina[14] that hydroboration of 7-dehydrocholesterol by passing in diborane gas gives rise to the expected Δ^7-6α-borane XV, which on acid treatment (acetic anhydride–



XV

acetic acid in boiling diglyme) undergoes hydrolysis with rearrangement to yield 5α-cholest-6-en-3β-ol in 35% over-all yield. The apparent direct formation of the Δ^6 compound from 7-dehydrocholesterol in our hands is, therefore, presumably due to the prior formation of the borane XV by means of the lithium aluminum hydride–boron trifluoride combination, hydrolysis with rearrangement occurring subsequently through the action of the fluoroboric acid which is generated from the excess boron trifluoride when water is added at the end of the reaction. It is known that allylic organoboranes are readily susceptible to hydrolysis.[15] This explanation also accounts for the apparent paradox that 5α-cholest-6-en-3β-ol had been formed in the presence of excess of lithium aluminum hydride–boron trifluoride, despite the fact that this combination is known to react readily with this olefin.[1]

Finally the hydration of several $\Delta^{7,9(11)}$-dienes was studied. Hydration of 5α,25D-spirosta-7,9(11)-dien-3β-ol acetate (XVIb) by method b, followed by acetylation, yielded 70% of a substance subsequently shown to be the previously unknown 5α,25D-spirost-7-ene-3β,11α-diol diacetate (XVIIb). In addition, *ca.* 10% of 5α,25D-spirost-7-en-3β-ol acetate (XVIII) was isolated, identified by direct comparison with an authentic sample.[16] This substance most probably had been present as an impurity in the starting $\Delta^{7,9(11)}$-diene XVIb (which had been prepared from the Δ^7-ene XVIII by mercuric acetate dehydrogenation according to Ruyle, *et al.*[17]), and, as found previously,[1] did not undergo hydroboration. It has been noted previously that $\Delta^{7,9(11)}$-dienes prepared by the mercuric acetate dehydrogenation of Δ^7-enes are contaminated with the latter.[17]

The formation of the 11α-acetoxy-Δ^7 compound XVIIb is in keeping with expectation, since Δ^7 steroids are unreactive and $\Delta^{9(11)}$ steroids yield the 11α-hydroxy derivatives in the hydroboration reaction.[1] The structure XVIIb follows from the following observations. Saponification led to the free diol XVIIa, which, though unaffected on treatment with manganese dioxide,[18] yielded the known 5α,25D-spirost-8-ene-3,7,11-trione (XIX)[19] on oxidation with chromium trioxide in pyridine.[6] These results indicated the presence of a β,γ-unsaturated alcohol grouping in XVIIa. Oxidation of the latter substance by the Oppenauer method resulted merely in attack at C-3 to give the hydroxy ketone XX, but oxidation of XVIIa with chromium trioxide in acetone–sulfuric acid[20] affected both hydroxyl groups and gave a mixture of the unconjugated Δ^7-3,11-dione XXI and the conjugated Δ^8-3,11-dione XXII. Isomerization of this mixture with sodium hydroxide at room temperature then yielded the pure Δ^8-3,11-dione XXII, the physical properties of which were in good agreement with those reported.[21] Final proof of the location of the new oxygen group was provided by reduction of Δ^8-3,11-dione XXII with lithium in ammonia containing methanol,[22] giving 5α,25D-spirostane-3β,11α-diol (XXIII), identified by direct comparison with an authentic sample.[19,22] The fact that the 11-hydroxyl group in the hydration product XVIIa is α oriented follows

(10) For preliminary communication, see Y. Mazur, M. Nussim, and F. Sondheimer, *Proc. Chem. Soc.*, 314 (1959).

(11) F. Sondheimer, Y. Klibansky, Y. M. Y. Haddad, G. H. R. Summers, and W. Klyne, *J. Chem. Soc.*, 767 (1961).

(12) *Inter alia*, (a) D. H. R. Barton and W. J. Rosenfelder, *ibid.*, 2459 (1949); (b) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **72**, 1923 (1950).

(13) See E. L. Eliel, *et al.*, *ibid.*, **82**, 1362, 1367 (1960); **84**, 2356, 2371, 2377 (1962).

(14) L. Caglioti, G. Cainelli, and G. Maina, *Tetrahedron*, **19**, 1057 (1963).

(15) B. M. Mikhailov and F. B. Tutorskaya, *Doklady Akad. Nauk SSSR*, **123**, 479 (1958) [*Chem. Abstr.*, **53**, 6990 (1959)]; D. Devaprabhakara and P. D. Gardner, *J. Am. Chem. Soc.*, **85**, 1458 (1963).

(16) *Inter alia*, G. Rosenkranz, J. Romo, E. Batres, and C. Djerassi, *J. Org. Chem.*, **16**, 298 (1951); W. V. Ruyle, E. M. Chamberlin, J. M. Chemerda, G. E. Sita, L. M. Aliminosa, and R. L. Erickson, *J. Am. Chem. Soc.*, **74**, 5929 (1952).

(17) W. V. Ruyle, T. A. Jacob, J. M. Chemerda, E. M. Chamberlin, D. W. Rosenburg, G. E. Sita, R. L. Erickson, L. M. Aliminosa, and M. Tishler, *ibid.*, **76**, 2604 (1953).

(18) See J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952); F. Sondheimer, C. Amendolla, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 5930 (1953).

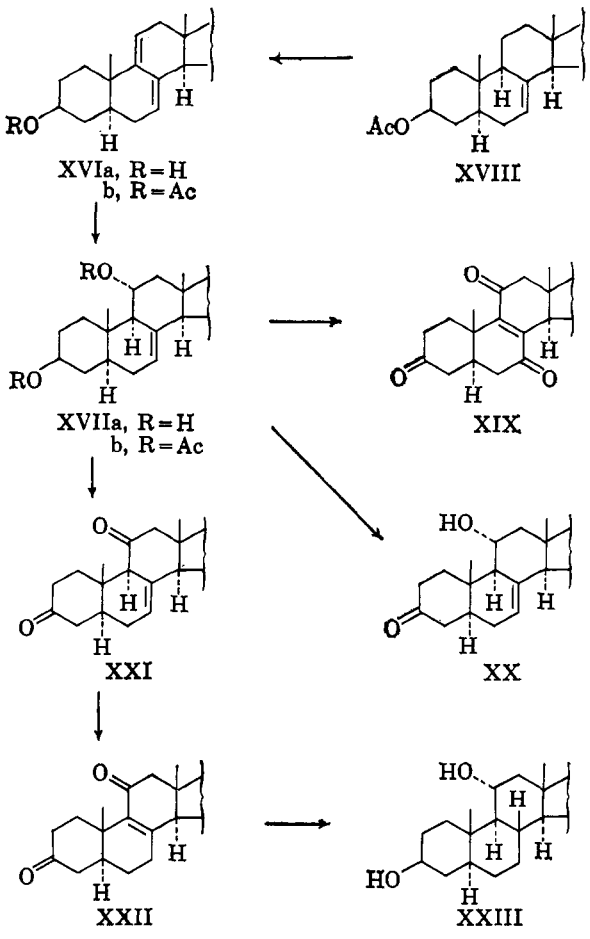
(19) C. Djerassi, E. Batres, M. Velasco, and G. Rosenkranz, *ibid.*, **74**, 1712 (1952).

(20) *Inter alia*, K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *ibid.*, 2402 (1951); R. G. Curtis, I. M. Heilbron, E. R. H. Jones, and G. F. Woods, *ibid.*, 457 (1953).

(21) A. J. Lemin and C. Djerassi, *J. Am. Chem. Soc.*, **76**, 5672 (1954).

(22) See F. Sondheimer, O. Mancera, G. Rosenkranz, and C. Djerassi, *ibid.*, **75**, 1282 (1953).

CHART I



from its ready acetylation with acetic anhydride in pyridine, while the 9α configuration is based on the usual over-all *cis* addition of water by the hydration reaction. (See Chart I.)

5α-Cholesta-7,9(11)-dien-3β-ol (type XVIa) on hydration by method a behaved similarly to the $\Delta^{7,9(11)}$-diene in the spirostane series. After acetylation, 60% of 5α-cholest-7-ene-3β,11α-diol diacetate (type XVIIb) was isolated, which on saponification yielded the corresponding diol (type XVIIa). The structures of these substances are based on analogy with the results obtained in the spirostane series. In addition, 10% of 5α-cholest-7-en-3β-ol acetate (type XVIII) was obtained, this substance (as the alcohol) presumably again having been present as an impurity in the $\Delta^{7,9(11)}$-diene.

In the same way, 5α-ergosta-7,9(11)-dien-3β-ol (type XVIa) by method a and subsequent acetylation led to 70% of 5α-ergost-7-ene-3β,11α-diol diacetate (type XVIIb, saponifiable to the corresponding diol XVIIa), as well as to *ca.* 10% of 5α-ergost-7-en-3β-ol acetate (type XVIII).

Experimental[23]

Hydration of Cholesta-3,5-diene (I).—Cholesta-3,5-diene (I) [m.p. 79–80°, $[\alpha]_D$ −123°; λ_{max} 228, 235, and 243 mμ (ϵ 19,000, 20,200, and 12,600)] was prepared from cholest-4-en-3-one by lithium aluminum hydride reduction to a mixture of cholest-4-en-3β-ol and cholest-4-en-3α-ol,[24] followed by dehydration with boiling ethanolic hydrochloric acid.[25] The diene I (1 g.) was hydrated by method a, and the product was chromatographed on 30 g. of alumina. Elution with ether and crystallization from acetone yielded 535 mg. (49%) of 5α-cholestane-4α,6α-diol (IIIa), m.p. 188–190°, as only crystalline material. The analytical sample showed m.p. 194–196°, $[\alpha]_D$ +21°.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96. Found: C, 80.38; H, 11.97.

Acetylation of the diol IIIa, followed by crystallization from acetone, led to the diacetate IIIb, m.p. 98–100°, $[\alpha]_D$ +65°.

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72; $COCH_3$ (2), 17.62. Found: C, 76.22; H, 10.85; $COCH_3$, 17.97.

Hydration of cholesta-3,5-diene by method b gave the 4α,6α-diol IIIa, m.p. 187–189°, in 42% yield.

5α-Cholestane-4α,6α-diol Cyclic Sulfite (IV).—Dry pyridine (0.5 cc.) and then thionyl chloride (0.4 cc.) were added to an ice-cold solution of 80 mg. of the 4α,6α-diol IIIa in 5 cc. of dry chloroform. The solution was allowed to stand for 40 hr., and ice was then added. The product was isolated with ether and chromatographed on 3 g. of alumina. Elution with pentane–benzene (4:1) yielded 78 mg. of the cyclic sulfite IV, m.p. 98–100°, which on crystallization from methanol showed m.p. 103–104°, $[\alpha]_D$ +25°, no hydroxyl bands in the infrared.

Anal. Calcd. for $C_{27}H_{46}O_3S$: C, 71.96; H, 10.29; S, 7.10. Found: C, 71.75; H, 10.25; S, 6.75.

The cyclic nature of the sulfite IV was confirmed by the fact that it was recovered unchanged on treatment with acetic anhydride in pyridine at room temperature.

Oxidation of 5α-Cholestane-4α,6α-diol (IIIa). a. With Chromium Trioxide in Acetic Acid.—A solution containing 100 mg. of the diol IIIa and 100 mg. of chromium trioxide in 20 cc. of 95% acetic acid was allowed to stand at room temperature for 16 hr. Isolation with ether and separation into neutral and acidic products gave rise to 85 mg. of an acidic amorphous material (after evaporation of acetic acid) which appears to be the crude triacid VI. Titration of 13.3 mg. of this substance in 20 cc. of ethanol against 0.01 *N* aqueous sodium hydroxide required 8.6 cc. for neutralization; the theoretical amount needed for the triacid VI is 8.55 cc.

b. With Chromium Trioxide in Pyridine.—A solution of 200 mg. of the 4α,6α-diol IIIa in 5 cc. of pyridine was added to a mixture of 260 mg. of chromium trioxide and 2 cc. of pyridine, and the mixture was shaken for 4 days. Saturated aqueous sodium sulfite was added, and shaking was continued for 4 hr. Water was then added, and the product was isolated with ether. Crystallization from methanol afforded 32 mg. of 6α-hydroxy-5α-cholestan-4-one (VIIa), m.p. 128–130°, infrared bands at 1703 cm.$^{-1}$ (4-one) and hydroxyl band.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52; active H (1), 0.25. Found: C, 80.35; H, 11.45; active H, 0.26.

Acetylation of the hydroxy ketone VIIa led to 6α-acetoxy-5α-cholestan-4-one (VIIb), which on crystallization from methanol showed m.p. 156–158°, $[\alpha]_D$ +81°; infrared bands at 1721 and 1236 (acetate) and 1706 cm.$^{-1}$ (4-one), no hydroxyl band.

Converstion of 6α-Acetoxy-5α-cholestan-4-one (VIIb) to Cholest-5-en-4-one (VIII).—The acetoxy ketone VIIb (10 mg.) and freshly fused anhydrous potassium bisulfate (100 mg.) were finely ground together and then heated at 170° under reduced pressure (*ca.* 2 mm.) for 30 min. The mixture was cooled, water was added, and the product was isolated with ether. Chromatography on 2 g. of alumina and crystallization from acetone yielded 4 mg. of cholest-5-en-4-one (VIII), m.p. 108–110°, λ_{max} 240 mμ (ϵ 7400); lit.[7] m.p. 111–112°, λ_{max} 241 mμ (ϵ 7200). The substance proved to be identical with an authentic sample (prepared from 2-bromo-5α-cholestan-3-one, according to Butenandt, *et al.*[7]) through infrared comparison and nondepression of the melting point on admixture.

Hydration of 6α-Acetoxycholest-4-ene (V).—6α-Acetoxycholest-4-ene (V) was prepared from cholest-5-ene as described by Jones, *et al.*[26] The acetate V (250 mg.) was hydrated by method b; the product was saponified by means of boiling methanolic potassium hydroxide and then chromatographed on 8 g. of alumina.

(23) For general experimental conditions, as well as details of methods a and b, see the preceding paper.[1]

(24) *Inter alia*, see W. G. Dauben, R. A. Micheli, and J. F. Eastham, *J. Am. Chem. Soc.*, **74**, 3852 (1952).

(25) See (a) R. Schoenheimer and E. A. Evans, *J. Biol. Chem.*, **114**, 567 (1936); (b) J. C. Eck, R. L. Van Peursem, and E. W. Hollingsworth, *J. Am. Chem. Soc.*, **61**, 171 (1939).

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

Penzene eluted 55 mg. (24%) of unchanged cholest-4-en-6α-ol, m.p. 136–138°, while ether eluted 145 mg. (61%) of 5α-cholestane-4α,6α-diol (IIIa), m.p. 186–188°. Crystallization of this diol from acetone yielded a sample, m.p. 193–196°, $[\alpha]_D$ +23°, which was identical with the diol obtained from cholesta-3,5-diene through infrared comparison and nondepression of the melting point on admixture.

Cholesta-4,6-diene (II).—Cholest-5-en-7-one was prepared in three steps from cholesteryl acetate, essentially as described by Nickon and Bagli.[27] The unsaturated ketone (2.5 g.) was reduced with 1 g. of lithium aluminum hydride in 200 cc. of ether (2-hr. boiling), and the total reduction product, consisting mainly of cholest-5-en-7β-ol,[28] was dehydrated directly with boiling alcoholic hydrochloric acid as described by Eck, *et al.*[25b,29] The product was isolated with ether and chromatographed on 500 g. of Alcoa activated alumina (grade F-20). Elution with pentane and crystallization from acetone yielded 1.55 g. of cholesta-4,6-diene (II), m.p. 91–92°, $[\alpha]_D$ +7°, λ_{max} 230, 238, and 245 mμ (ε 21,500, 25,800, and 14,500); lit.[27] m.p. 92–92.5°, $[\alpha]_D$ +13° (lit.[30] $[\alpha]_D$ +9°), λ_{max} 230, 238, and 246 mμ (ε 22,300, 26,100, and 15,200).

Hydration of Cholesta-4,6-diene (II).—Cholesta-4,6-diene (500 mg.) was hydrated by method a, and the product was chromatographed on 15 g. of alumina. Elution with ether furnished 195 mg. (36%) of 5α-cholestane-4α,6α-diol (IIIa), m.p. 184–188°, which after crystallization from acetone showed m.p. 192–194°, $[\alpha]_D$ +20°; it was identical with the diol obtained from cholesta-3,5-diene by infrared comparison and nondepression of the melting point on admixture. Elution with chloroform yielded 55 mg. of crystalline material, m.p. 115–120°, which was not further investigated.

Conversion of 7-Dehydrocholesterol (XIa) to 5α-Cholest-6-en-3β-ol (XIIa).—7-Dehydrocholesterol (XIa)[9] (1 g.) was hydrated by method a, and the product was chromatographed on 30 g. of alumina. The only crystalline material was eluted with benzene. Crystallization from ether–methanol yielded 205 mg. (20%) of 5α-cholest-6-en-3β-ol (XIIa), m.p. 116–117°, $[\alpha]_D$ −86°; lit.[12a] m.p. 114–115°, $[\alpha]_D$ −92°; lit.[12b] m.p. 114–119°, $[\alpha]_D$ −81°. Essentially identical results were obtained when the alkaline hydrogen peroxide step was omitted.

Acetylation of XIIa led to the acetate XIIb, which after crystallization from methanol showed m.p. 104–105°, $[\alpha]_D$ −88°; lit.[12a] m.p. 103.5–104.5°, $[\alpha]_D$ −89°; lit.[12b] m.p. 104–106°, $[\alpha]_D$ −88°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.22; H, 11.40.

Full hydrogenation of the acetate XIIb in acetic acid over a platinum catalyst resulted in the uptake of 1.02 molar equiv. of hydrogen and yielded 5α-cholestan-3β-yl acetate (XIIII), m.p. and m.m.p. 109–110°.

Oxidation of the alcohol XIIa with chromium trioxide in pyridine (see Sondheimer, *et al.*[11]), followed by crystallization from methanol, yielded 5α-cholest-6-en-3-one (XIV), m.p. 120–121°, $[\alpha]_D$ −73°; lit.[11] m.p. 121–122°, $[\alpha]_D$ −75°.

Subsequent to the appearance of the preliminary communication describing this work,[10] authentic samples of the alcohol XIIa, the acetate XIIb, and the ketone XIV became available, and identity with the respective compounds derived from 7-dehydrocholesterol was established by infrared comparison and mixture melting point determination.

Conversion of 7-Dehydrocholesterol 3-(2′-Tetrahydropyranyl) Ether (XIb) to 5α-Cholest-6-en-3β-ol Acetate (XIIb).—The ether XIb was prepared in 90% yield from 7-dehydrocholesterol,[9] 2,3-dihydropyran, and phosphorus oxychloride in chloroform, as described for cholesterol by Greenhalgh, *et al.*[31] After crystallization from acetone it showed m.p. 139–141°, $[\alpha]_D$ −58°; λ_{max} 272, 282, and 293 mμ (ε 11,400, 11,900, and 6,700).

Anal. Calcd. for $C_{32}H_{52}O_2$: C, 81.99; H, 11.18. Found: C, 81.65; H, 11.09.

Boron trifluoride etherate (20 g.) was added to a solution of 2 g. of the ether XIb in 80 cc. of ether, the solution was cooled in ice–water, and a solution of 1.2 g. of lithium aluminum hydride in 60 cc. of ether was then added dropwise during 1 hr., with stirring and continued ice–water cooling, under nitrogen. The ice bath was removed, and the mixture was stirred for 1 hr. at room temperature. Water (50 cc.) was added, and the mixture was stirred for a further 10 min. to complete cleavage of the ether. Ether and more water were added; the ether solution was washed with water, dilute sulfuric acid, sodium bicarbonate solution, and water, and was then dried and evaporated. The residue was acetylated directly and was then chromatographed on 60 g. of alumina. Elution with pentane–benzene (9:1), followed by crystallization from methanol, yielded 650 mg. (36%) of 5α-cholest-6-en-3β-ol acetate (XIIb), m.p. 102–104°. Further crystallization gave a sample, m.p.104–105°, $[\alpha]_D$ −89°, identical with the compound obtained by the hydroboration of free 7-dehydrocholesterol.

Hydration of 5α,25D-Spirosta-7,9(11)-dien-3β-ol Acetate (XVIb).—This diene [m.p. 208–212°, $[\alpha]_D$ −15°; λ_{max} 236, 242, and 251 mμ (ε 13,500, 14,400, and 9500)] was prepared by dehydrogenation of 5α,25D-spirost-7-en-3β-ol acetate (XVIII)[16] with mercuric acetate, as described by Ruyle, *et al.*[17] The diene (1 g.) was hydrated by method b; the product was acetylated and then chromatographed on 35 g. of alumina. Elution with pentane–benzene (1:3) yielded 80 mg. (8%) of 5α,25D-spirost-7-en-3β-ol acetate (XVIII), m.p. 228–231°, identified by direct comparison with an authentic sample.[16] Elution with benzene furnished 790 mg. (70%) of 5α,25D-spirost-7-en-3β,11α-diol diacetate (XVIIb), m.p. 183–185°, which after crystallization from acetone–methanol exhibited m.p. 187–188°, $[\alpha]_D$ −96°. The compound gave a yellow color with tetranitromethane, and a positive Fieser selenium dioxide test (in keeping with the 5α-Δ⁷ formulation).[32]

Anal. Calcd. for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01. Found: C, 72.46; H, 9.13.

Saponification of the diacetate XVIIb with methanolic potassium hydroxide (1-hr. boiling), followed by crystallization from acetone, afforded 5α,25D-spirost-7-ene-3β,11α-diol (XVIIa), m.p. 190–192°, $[\alpha]_D$ −86°.

Oxidation of 5α,25D-Spirost-7-ene-3β,11α-diol (XVIIa). a. With Chromium Trioxide in Pyridine.—A solution of 100 mg. of the diol XVIIa in 2 cc. of pyridine was added to 130 mg. of chromium trioxide in 1.5 cc. of pyridine, and the mixture was shaken for 48 hr. Methanol was added, the solvents were evaporated under reduced pressure, and the residue was extracted with hot benzene. Evaporation of the solvent, followed by crystallization from methylene chloride–acetone afforded 32 mg. of the yellow 5α,25D-spirost-8-ene-3,7,11-trione (XIX), m.p. 238–242°, $[\alpha]_D$ 0°, λ_{max} 268 mμ (ε 8900); lit.[19] m.p. 243–245°, $[\alpha]_D$ −3°, λ_{max} 268 mμ (ε 8900).

b. With Aluminum Isopropoxide.—A solution of 50 mg. of the diol XVIIa in 5 cc. of toluene and 1 cc. of cyclohexanone was distilled until *ca.* 1 cc. had passed over, in order to remove moisture. Aluminum isopropoxide (100 mg.) was then added, and the solution was boiled under reflux for 1 hr. Ether and water were added, and the organic layer was washed with dilute hydrochloric acid and water. Steam distillation, followed by extraction with ether and crystallization from acetone, furnished 28 mg. of 11α-hydroxy-5α-25D-spirost-7-en-3-one (XX), m.p. 258–262° dec., $[\alpha]_D$ −68°, infrared bands (potassium bromide) at 1710 cm.$^{-1}$ (3-one) and free hydroxyl band. The compound was unchanged on treatment with sodium hydroxide, showing the absence of the Δ⁷-11-one grouping.

Anal. Calcd. for $C_{27}H_{46}O$: C, 75.66; H, 9.41. Found: C, 75.38; H, 9.31.

c. With Chromium Trioxide in Acetone–Sulfuric Acid.—An 8 *N* chromium trioxide solution in aqueous sulfuric acid[20] was added dropwise to a solution of 50 mg. of the diol XVIIa in 10 cc. of acetone until the orange color persisted. After being shaken at room temperature for 5 min., the mixture was diluted with water and extracted with ether. The resulting product, consisting of a mixture of the unconjugated Δ⁷-3,11-dione XXI and the conjugated Δ⁸-3,11-dione XXII, showed a strong infrared band at 1705 (3-one and Δ⁷-11-one) as well as a weak band at 1675 cm.$^{-1}$ (Δ⁸-11-one), but no hydroxyl band. This material was isomerized through being allowed to stand for 10 min. in 10 cc. of methanol with 3 drops of 10% aqueous sodium hydroxide. Water was then added, and the product was isolated with ether. Crystallization from acetone yielded 5α,25D-spirost-8-ene-3,11-dione (XXII), m.p. 209–212°, λ_{max} 253 mμ (ε 9200), infrared bands

(27) A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, **83**, 1498 (1961).

(28) See ref. 27; L. F. Fieser, M. Fieser, and R. N. Chakravarti, *ibid.*, **71**, 2226 (1949).

(29) J. C. Eck and E. W. Hollingsworth, *ibid.*, **63**, 107 (1941).

(30) C. W. Shoppee, G. H. R. Summers, and R. J. W. Williams, *J. Chem. Soc.*, 1893 (1956); G. J. Kent and E. S. Wallis, *J. Org. Chem.*, **24**, 1235 (1959).

(31) C. W. Greenhalgh, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951).

(32) See L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4395 (1953).

(potassium bromide) at 1712 (3-one) and 1675 cm.$^{-1}$ (Δ^8-11-one), no hydroxyl band; lit.[21] m.p. 210–212°, λ_{max} 253 mμ (ε 9300).

Lithium–Ammonia Reduction of 5α,25D-Spirost-8-ene-3,11-dione (XXII).—A solution of 30 mg. of the diketone XXII in 10 cc. of ether was added to a stirred solution of 1 cc. of methanol in 30 cc. of liquid ammonia. Lithium (60 mg.) was added in small pieces, and the mixture was stirred for 10 min. Ammonium chloride (1 g.) was then added, the ammonia was allowed to evaporate, water was added to the residue, and the product was isolated with chloroform. Chromatography on 2 g. of alumina and crystallization from methanol yielded 9 mg. of 5α,25D-spirostane-3β,11α-diol (XXIII), m.p. 216–218°. This compound was identical with an authentic sample (m.p. 217–219°)[19,22] through infrared comparison and nondepression of the m.p. on admixture.

Hydration of 5α-Cholesta-7,9(11)-dien-3β-ol (XVIa).—5α-Cholesta-7,9(11)-dien-3β-ol [m.p. 110–112°, $[\alpha]_D$ +40°; λ_{max} 235, 243, and 251 mμ (ε 13,500, 15,600, and 10,100)] was prepared by dehydrogenation of 5α-cholest-7-en-3β-ol with mercuric acetate, as described by Fieser and Herz.[33] The diene (500 mg.) was hydrated by method a; the product was acetylated and then chromatographed on 20 g. of alumina. Elution with pentane–benzene (9:1) yielded 55 mg. (10%) of 5α-cholest-7-en-3β-ol acetate (XVIII), m.p. 116–118°, identified by direct comparison with an authentic sample. Elution with pentane–benzene (1:1) afforded 375 mg. (59%) of 5α-cholest-7-ene-3β,11α-diol diacetate (XVIIb), m.p. 146–148°, which after crystallization from ether–methanol showed m.p. 150–151°, $[\alpha]_D$ −20°. The compound gave a yellow color with tetranitromethane and a positive Fieser selenium dioxide test.[32]

Anal. Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.17; H, 10.39.

(33) L. F. Fieser and J. E. Herz, *J. Am. Chem. Soc.*, **75**, 121 (1953).

Saponification of the diacetate XVIIb with methanolic potassium hydroxide (1-hr. boiling), followed by crystallization from ether–methanol, yielded 5α-cholest-7-ene-3β,11α-diol (XVIIa), m.p. 161–162°, $[\alpha]_D$ +3°.

Hydration of 5α-Ergosta-7,9(11)-dien-3β-ol (XVIa).—5α-Ergosta-7,9(11)-dien-3β-ol [m.p. 142–144°, $[\alpha]_D$ +32°; λ_{max} 236, 243, and 252 mμ (ε 13,200, 14,900, and 9600)] was prepared by dehydrogenation of 5α-ergost-7-en-3β-ol with mercuric acetate, as described by Fieser and Herz[33] for 5α-cholest-7-en-3β-ol. The diene (500 mg.) was hydrated by method a; the product was acetylated and then chromatographed on 20 g. of alumina. Elution with pentane–benzene (4:1) furnished 65 mg. (12%) of 5α-ergost-7-en-3β-ol acetate (XVIII), m.p. 155–157°, identified by direct comparison with an authentic sample. Elution with pentane–benzene (4:1) yielded 425 mg. (68%) of 5α-ergost-7-ene-3β,11α-diol diacetate (XVIIb), m.p. 137–140°, which after crystallization from ether–methanol showed m.p. 143–145°, $[\alpha]_D$ −17°. The substance gave a yellow color with tetranitromethane and a positive Fieser selenium dioxide test.[32]

Saponification of the diacetate XVIIb through 1-hr. boiling with methanolic potassium hydroxide and subsequent crystallization from ether–methanol led to 5α-ergost-7-ene-3β,11α-diol (XVIIa), m.p. 171–173°, $[\alpha]_D$ +2°.

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.35; H, 11.56.

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Nuclear Magnetic Resonance Studies on Steroids. III.[1] Steroidal Epoxides and Episulfides

KAZUO TORI, TAICHIRO KOMENO, AND TOSHIO NAKAGAWA

Shionogi Research Laboratory, Shionogi and Company, Ltd., Fukushima-ku, Osaka, Japan

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Proton magnetic resonance spectra of steroidal epoxides and episulfides were investigated to evaluate chemical shifts of the angular methyls and of the epoxidic or episulfidic protons due to the orientation of α and β isomers. The epoxidic or episulfidic proton signal of α isomers is generally found at a higher field than that of β isomers, and their patterns are characteristic of the locations and configurations. Even though the coupling constants obtained from those signals by first-order approximation were considerably smaller than the values calculated from the Karplus equation with the dihedral angles measured in Dreiding models, they allowed the estimation of a $\cos^2$ dependence of the coupling constants on dihedral angles in the epoxide or episulfide systems. A revised Karplus equation is proposed for the 1,2-epoxycyclohexane system. Furthermore, the relationship between the magnitudes of the coupling constants and electronegativities is discussed briefly.

In regard to the proton magnetic resonance (n.m.r.) spectra of steroidal epoxides, Zürcher[2] has reported the chemical shift of the 19-methyl group in several compounds. More recently, Cross[3] has published the n.m.r. spectra of many steroidal 5,6-epoxides, with a discussion on the signal of the epoxidic and 19-methyl protons. On the other hand, the n.m.r. spectra of ethylene oxide, ethylene sulfide,[4] and their monosubstituted derivatives[5–7] have been reported in detail.

This paper presents the n.m.r. spectra of 33 steroidal epoxides and episulfides, and the relationships of the angular methyl and epoxidic (episulfidic) proton signals to the location and configuration of the epoxy (epithio) group. Further, correlation of the coupling constant of the epoxidic (episulfidic) proton with the dihedral angle is discussed in connection with the electronegativities of the participating atoms.

Results and Discussion

Table I lists the n.m.r. spectral data obtained, and Fig. 1 shows typical examples of the signal patterns of epoxidic and episulfidic protons.

Recent studies have shown that geminal and vicinal proton spin-coupling constants are of the opposite sign in various systems.[6,8] In a series of ethylene oxides, geminal couplings (J_{gem}) and vicinal couplings (J_{trans}

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(7) J. I. Musher and R. G. Gordon, *ibid.*, **36**, 3097 (1962).

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