[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CLARK UNIVERSITY, AND FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY]

D-Homosteroids. III. The Wagner–Meerwein Rearrangement of 20-Substituted Bisnorallocholanes[1,2]

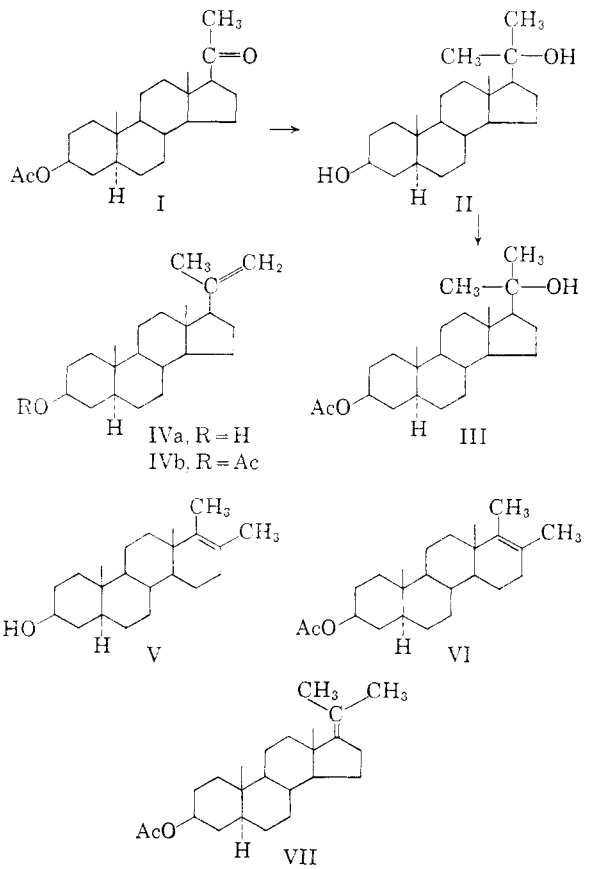
BY MILAN USKOKOVIĆ, MARCEL GUT AND R. I. DORFMAN

RECEIVED JULY 21, 1959

Bisnorallocholan-20-ol, 20-chlorobisnorallocholane and bisnorallochol-20-ene derivatives undergo a Wagner–Meerwein rearrangement to 17,17a-dimethyl-D-homoandrost-17(17a)-en derivatives. The structure of the rearranged product was finally substantiated by the reduction of 3β-acetoxy-17a,17a-dimethyl-D-homoandrostan-17-one, and a Wagner–Meerwein rearrangement of the 3β-acetoxy-17a,17a-dimethyl-D-homoandrostan-17β-ol to 17,17a-dimethyl-D-homoandrost-17(17a)-en-3β-ol 3β-acetate.

The general problem of stability of the steroid ring system is reflected, at least partially, in the D-homoannulation. In numerous reports it was shown that the steroid skeleton is not stable under the conditions of many common reactions, causing different types of saturated nucleophilic rearrangements yielding D-homosteroids. Thus, the 17-hydroxy-20-ketosteroids undergo D-homoannulation under conditions of Oppenauer oxidation,[3–5] Wolff–Kishner reduction,[6] when treated by Lewis acids,[3–6] bases,[6] sodium sulfite[7] or when heated above their melting point.[4] The 17-hydroxy-20-aminosteroids give D-homosteroids by nitrosation,[8] and the 17,20-dihydroxy-steroids rearrange when treated under acidic conditions.[9] These rearrangements, leading to D-homosteroids, have in common a nucleophilic substitution by the migrating C_{13-17} or C_{16-17} bond at carbon C_{20}.

The present paper describes the D-homoannulation of 17-desoxy steroids, which is observed in the series of 20-substituted bisnorallocholanes. We were concerned with the dehydration of the 20-hydroxybisnorcholane derivatives,[10] and searching the literature we found that variable quantities of unknown products were obtained in attempted dehydrations of bisnorallocholane-3β,20-diol (II) and its 3β-monoacetate III. Butenandt and Cobler[11] have refluxed a solution of II in acetic acid, and, after acetylation of the reaction product, they obtained as the main product bisnorallochol-17(20)-en-3β-ol acetate (VII) and in addition a small amount of bisnorallochol-20-en-3β-ol acetate (IVb) and also a small amount of the unknown substance VI, which had the same elemental analysis as VII and IVb. Koechlin and Reichstein[12] dehydrated bisnorallocholane-3β,20-diol 3β-acetate (III) by refluxing its acetic acid solution and showed that the main product (85%) was IVb, besides a small amount of VI (10%) and only a trace of VII. Dehydration with phosphorus oxychloride and pyridine furnished exclusively IVb, while phosphorus pentoxide in benzene solution rearranged III to VI, which remained unidentified.



On acetylation of bisnorallocholane-3β,20-diol (II) with acetic anhydride and pyridine the desired bisnorallocholane-3β,20-diol 3β-acetate (III) was obtained. However, the reaction product always contained more than 10% of bisnorallochol-20-

(1) D-Homosteroids. II, M. Uskoković, M. Gut and R. I. Dorfman, THIS JOURNAL, **82**, 958 (1960).

(2) Taken in part from a dissertation by Milan Uskoković in partial fulfillment of the requirements for the Ph.D. degree in Organic Chemistry, Clark University. Presented, in part, before the Division of Organic Chemistry, 136th National A.C.S. Meeting, Atlantic City, N. J., Sept., 1959. This investigation was supported, in part, by grants PSH-CY-2193 and PSH-C-321.

(3) R. B. Turner, THIS JOURNAL, **75**, 3484 (1953).

(4) D. K. Fukushima, S. Dobriner, M. S. Heffer, T. H. Kritchevsky, F. Herling and G. Roberts, *ibid.*, **77**, 6585 (1955).

(5) R. B. Turner, M. Perelman and K. T. Park, Jr., *ibid.*, **79**, 1108 (1957).

(6) C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta*, **26**, 185, 201 (1953).

(7) G. Cooley, B. Ellis, F. Hartley and V. Petrow, *J. Chem. Soc.*, 4377 (1955).

(8) M. W. Goldberg and R. Monnier, *Helv. Chim. Acta*, **23**, 376, 840 (1940).

(9) M. Uskoković, M. Gut and R. I. Dorfman, THIS JOURNAL, **81**, 4561 (1959).

(10) M. Uskoković, R. I. Dorfman and M. Gut, *J. Org. Chem.*, **23**, 1947 (1958).

(11) A. Butenandt and H. Cobler, *Z. physiol. Chem.*, **234**, 218 (1935).

(12) B. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944).

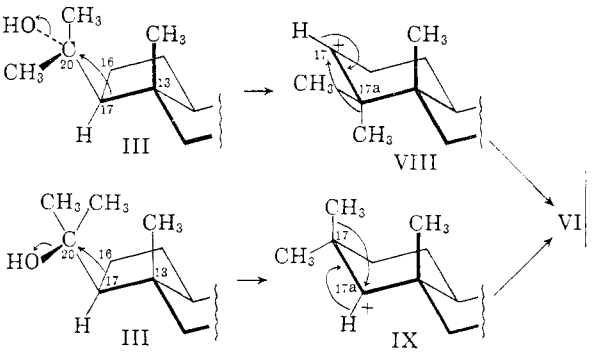
en-3β-ol 3β-acetate (IV). Previous publications,[11,12] and also our experience in the dehydration of 20-hydroxybisnorchol-4-en-3-one[10] with acetic anhydride and anhydrous sodium acetate (whereby bisnorchol-4,20-dien-3-one was obtained) suggests that IVb is obtained by initial attack of base on a hydrogen of the primary carbon C-21, which is more acidic and also less hindered than the alternative hydrogen at the tertiary carbon C-17. This is followed by a bimolecular elimination of the elements of water following Hoffmann's rule. A bimolecular elimination leading to the Δ^{17}-product VII would involve a transition state highly destabilized by the 21- and 22-methyl groups eclipsed with the C_{13}- and C_{16}-groups, which is probably the reason for the absence of VII. The transition state leading to a Δ^{20}-product will be free of such eclipsing effects.

Hence, the alternative mechanism of dehydration, namely, protonic attack on the 20-hydroxyl group, leads to a displacement giving bisnorallochol-17(20)-en-3β-ol 3β-acetate (VII) and the hitherto unidentified dehydration product VI. To prove this hypothesis the dehydration was carried out in super acidic solution.[13] The bisnorallocholane-3β,20-diol 3β-acetate (III) was refluxed for half an hour in glacial acetic acid containing a catalytic amount of elemental iodine, thereby yielding VI and VII in a ratio of 8:1. No IVb could be detected in the reaction product. When bisnorallocholane-3β,20-diol (II) was treated under the same conditions, or with acetic acid and a small amount of *p*-toluenesulfonic acid, there was obtained an unknown dehydration product V in nearly quantitative yield. The acetylation of V with acetic anhydride in pyridine gave VI, the latter being the acetate of V.

Koechlin and Reichstein[12] showed by hydrogenation that VI contains one double bond. They showed furthermore that upon ozonolysis the product did not lose carbon. We concluded, therefore, that the double bond could not be located in the side chain. In addition, infrared absorption data showed that this double bond was tetrasubstituted. Resting on this argumentation, we supposed VI to be 17,17a-dimethyl-D-homoandrost-17(17a)-en-3β-ol 3β-acetate and explained its formation by the mechanism in Chart II. A proton-catalyzed heterolysis of the 20-hydroxyl group, followed either by the migration of the C_{13-17}-bond or of the C_{16-17}-bond will give the intermediate 17a,17a-dimethyl-D-homo-17-carbonium ion VIII or 17,17-dimethyl-D-homo-17a-carbonium ion IX, respectively. This is followed by migration of a methyl group and successive formation of a double bond by the removal of a proton.

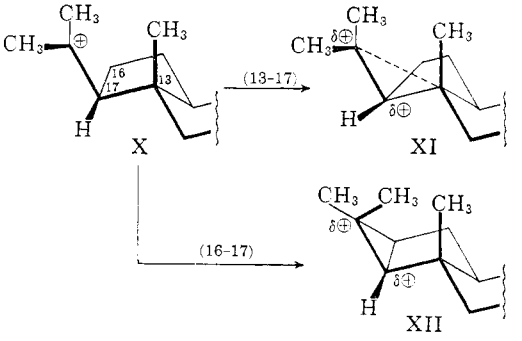
The proton-catalyzed heterolysis of the 20-hydroxyl group may proceed simultaneously with migration, in which case it will be anchimerically assisted by the migrating group. Alternatively, the heterolysis may proceed by an SN1 mechanism, giving the C_{20}-carbonium ion X, which is probably highly stabilized by methyl groups. This will make the whole rearrangement a stepwise process. More likely the rearrangement proceeds through the 20-

(13) J. B. Conant and N. F. Hall, THIS JOURNAL, **49**, 3062 (1927); S. Glasstone, "Textbook of Physical Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1946, p. 976.



carbonium ion X, an argument which is supported by the parallel formation of bisnorallochol-17(20)-en-3β-ol acetate (VII) and also by the following mechanistic consideration: If heterolysis of the 20-hydroxyl group and the migration proceed simultaneously, then such a rearrangement should be much faster when C_{20} is a secondary carbon atom due to much higher opportunity for anchimeric assistance (prim. > sec. > tert. carbon atom). But our experience shows that allopregnane-3β,20β-diol 3β-acetate is stable under the rearrangement conditions.

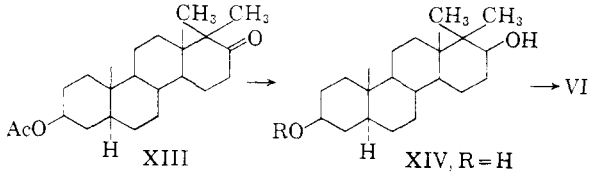
The preference of a C_{13-17}-bond to a C_{16-17}-bond migration can be evaluated from conformational analysis of the two corresponding transition states XI and XII.

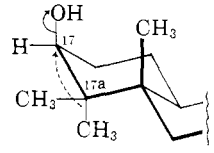


There are two factors which should be considered as contributory to conformational strain in the above transition states. The chair conformation will favor the transition state XII, *i.e.*, the migration of the C_{16-17}-bond. But steric effects of eclipsing groups (21-CH_3 *versus* C_{16} or C_{13}) will stimulate the migration of the C_{13-17} bond toward transition state XI. Furthermore, electronic effects favor XI also. That steric effects are predominant is experimentally shown in the pinacolic rearrangement of 17α,20-dihydroxybisnorcholanes[9] whereby only 17a,17a-dimethyl-17-keto-D-homo products were obtained, although in this last case the electronic effects were less in favor of C_{13-17}-bond migration.

The assignment of structure to 17,17a-dimethyl-D-homoandrost-17(17a)-en-3β-ol acetate (VI) rests on its formation from 3β-acetoxy-17a,17a-dimethyl-D-homoandrostan-17-one (XIII).[10] The reduction of XIII with potassium borohydride in methanol gave a mixture of 17a,17a-dimethyl-D-homoandrostane-3β,17β-diol (XIV) and its 3β-monoacetate XV, which could be separated by ab-

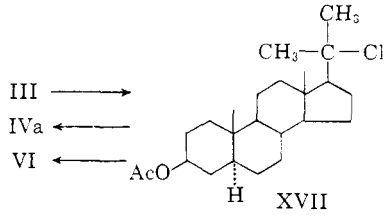
sorption chromatography. The Wagner–Meerwein rearrangement of XV, brought about by refluxing its acetic acid solution together with a catalytic amount of *p*-toluenesulfonic acid for 8 hours, gave VI in 85% yield.





The 17β (axial) conformation of the hydroxyl in XIV and XV is indicated by the greater mobility of XV, compared to XIII, on the silica gel column, and also by its transformation into VI, which can be brought about only when the relationship of the 17-hydroxyl and the 17a-methyl group is *trans* diaxial (XVI).

The 17,17a-dimethyl-D-homoandrost-17(17a)-en-3β-ol 3β-acetate (VI) also could be obtained by another method. In a previous publication[10] it was demonstrated that bisnorchol-5-ene-3β,20-diol 3β-acetate, upon treatment with hydrogen chloride in benzene solution, gave 20-chloro-bisnorchol-5-en-3β-ol 3β-acetate. The same procedure transformed III to 20-chlorobisnorallocholan-3β-ol 3β-acetate (XVII). The treatment of XVII with 5% potassium hydroxide in methanol furnished bisnorallochol-20-en-3β-ol (IVa).[14] Upon chromatography of XVII, a deep green color appeared where the substance contacted the silica gel, and the colored band gradually changed to violet during its movement to the bottom of the column. Elution from the column gave VI in quantitative yield. It is noteworthy that XVII is stable in benzene solution saturated with hydrogen chloride (a protonic acid), while a relatively weak acid such as silica gel brings about rearrangement. Probably chloride anions coördinate with outer unfilled orbitals on a silicon atom which would constitute a Lewis acid. That

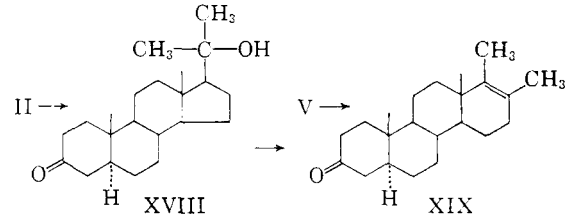


the rearrangement of XVII to VI involves a simultaneous migration with the heterolysis of the 20-chloro atom rests on the more quantitative yield and the absence of bisnorallochol-17(20)-en-3β-ol acetate (VII) in the product.

(14) F. Sondheimer and R. Mechoulam, THIS JOURNAL, **80**, 3087 (1958).

The fourth method by which VI was obtained involved the Wagner–Meerwein rearrangement of bisnorallochol-20-en-3β-ol acetate (IV). This process was catalyzed by *p*-toluenesulfonic acid in acetic solution, when the attack of a proton at C_{21} brings about the formation of a carbonium ion X, which was transformed to VI.

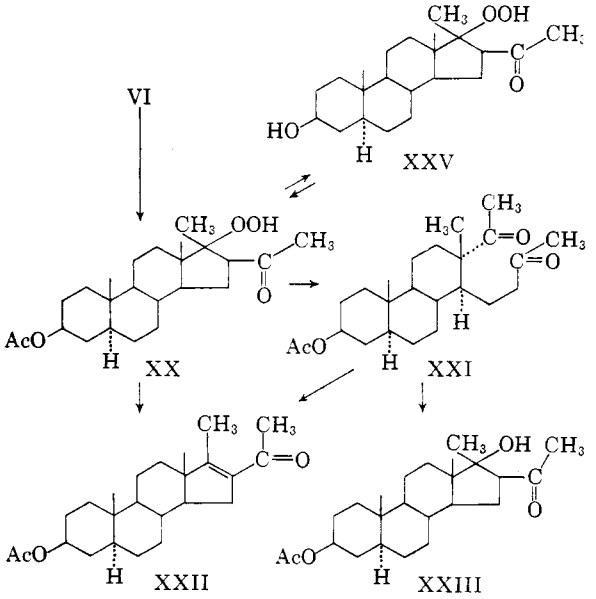
The Wagner–Meerwein rearrangement of 20-hydroxybisnorallocholan-3-one (XVIII) also was accomplished. The XVIII was obtained by chromic acid oxidation of the bisnorallocholane-3β,20-diol (II) and was rearranged to 17,17a-dimethyl-D-homoandrost-17(17a)-en-3-one (XIX) by refluxing its acetic acid solution containing a catalytic amount of *p*-toluenesulfonic acid. The XIX was also obtained from the 3β-hydroxy derivative V by oxidizing it with one equivalent of chromic acid in acetic acid–methylene chloride solution at room temperature.



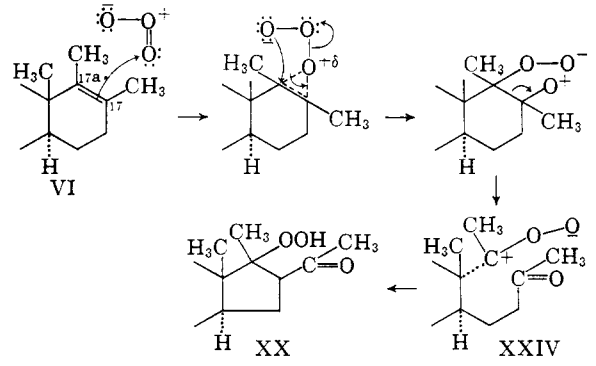
On repeating the ozonization of 17,17a-dimethyl-D-homoandrost-17(17a)-en-3β-ol acetate (VI), the reaction product XX was similar in melting point and rotation to the oxidation product obtained by Koechlin and Reichstein.[12] The infrared analysis revealed the presence of a carbonyl group at the frequency 1698 cm.$^{-1}$, fitting a hindered methyl ketone. The same frequency in the ketonic region was also found in the infrared spectrum of 3β-acetoxy-16-acetyl-17-methyl-16,17-seco-androstan-17-one (XXI). This compound XXI was obtained by Koechlin and Reichstein[12] from a transformation of XX on an aluminum oxide column, while in this work it was obtained by a sudden decomposition of XX at approximately 180° (0.01 mm.). The infrared absorption curves of XX was clearly distinct from that of XXI by having a maximum for a hydroxyl (3550 and 1040 cm.$^{-1}$) and an ether band (1123 cm.$^{-1}$) and finally by lacking an absorption maximum for a methylene group (1420 cm.$^{-1}$) in the α-position to a carbonyl. The data mentioned would support a hydroperoxide structure, as indicated for XX, which is also in agreement with its elemental analysis. Refluxing in 5% methanolic potassium hydroxide solution for 2 hours did not rearrange XX. However, the ester was hydrolyzed and unchanged starting material was regenerated by acetylation of the hydrolyzed product with acetic anhydride in pyridine. Refluxing of XX in acetic acid solution with catalytic amounts of *p*-toluenesulfonic acid gave a product which could not be crystallized and which might still be impure, but the ultraviolet absorption maximum at 249 mμ and infrared absorption maxima at 1667 and 1625 cm.$^{-1}$ account for a conjugated ketone, in agreement with the expected 16-acetyl-17-methylandrost-16-en-3β-ol 3β-acetate (XXII). A substance with identical absorption also was obtained by refluxing

XXI in acetic acid containing a trace of *p*-toluenesulfonic acid.

Koechlin and Reichstein[12] obtained XXI upon chromatography of XX on aluminum oxide and in addition a more polar substance, m.p. 202–205°, having the same elemental analysis. We have obtained a product of the same m.p. as that more polar substance upon chromatography of XXI on alumina. Its infrared analysis shows a carbonyl absorption (1700), a tertiary hydroxyl group (3550 and 1200) and an acetate group (1720 and 1260 cm.$^{-1}$). These data are in agreement with the structure of an aldol, 16-acetyl-17-methylandrostane-3β,17-diol 3β-acetate (XXIII).



The proposed hydroperoxide ozonolysis product XX can be formed by the mechanism advanced by Criegee.[15] The zwitterion XXIV, a primary prod-



uct of ozonolysis, can give the hydroperoxide XX by an intramolecular aldol-type condensation involving an α-methylene group of the ketone.

Experimental

All melting points were taken on a Kofler block. Rotations were taken in a 1-dm. tube in chloroform. Ultraviolet absorption spectra were determined in methanol by means of a Cary model 11 MS spectrophotometer. The infrared spectra were obtained from a pressed potassium bromide pellet taken on a Perkin–Elmer model 12C spectrometer. All chromatographic separations were made on Davison silica gel mesh 60–200, unless otherwise indicated. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

Bisnorallocholane-3β,20-diol (II)[11] from 3β-Acetoxyallopregnan-20-one (I).—To a cooled and stirred Grignard solution, prepared from 14.6 g. of magnesium and 38.3 ml. of methyl iodide in 500 ml. of anhydrous ether, was added dropwise a solution of 7.2 g. of 3β-acetoxyallopregnan-20-one (I) in 300 ml. of anhydrous ether. The reaction mixture was stirred overnight at room temperature, then hydrolyzed with an ice-cold saturated solution of ammonium chloride. The ether layer, containing suspended organic material, was washed with water and evaporated. The residue was extracted with hot benzene, the benzene evaporated and the residue crystallized from methanol to give crude II, m.p. 145–180°. Upon chromatography, the eluates with 25% ether-in-benzene furnished 6.2 g. of pure II, m.p. 182–184°, $[\alpha]^{20}D$ −1.8° (*c* 0.85); infrared absorption maxima 3600 and 1208 (−OH); 3500 and 1045 (−OH); 1390, 1375, 1365, 1170 and 950 cm.$^{-1}$ (isopropyl).

Anal. Calcd. for $C_{22}H_{38}O_2$: C, 78.98; H, 11.45. Found: C, 80.32; H, 11.52.

Bisnorallocholane-3β,20-diol 3-Monoacetate(III)[11] and Bisnorallochol-20-en-3β-ol 3β-Acetate (IVb).—The solution of 2.5 g. of crude II from the Grignard reaction (m.p. 145–180°) in 20 ml. of pyridine and 4 ml. of acetic anhydride was left standing for 24 hr. at room temperature. The excess acetic anhydride was decomposed with 2 ml. of water at 0° within 2 hr. and then the reaction mixture was poured into a large excess of water. The crystalline precipitate was filtered off, washed with water until all pyridine was removed and finally dried at 45°. Recrystallization from methanol gave 2.5 g. of III, m.p. 197.5–199°, $[\alpha]^{20}D$ −5.4° (*c* 1.4); infrared absorption maximum ν_{max} 3600 and 1205 (hydroxyl); 1720 and 1260 (acetate); 1390, 1381, 1369, 1180 and 950 cm.$^{-1}$ (isopropyl).

Anal. Calcd. for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.70; H, 10.56.

The methanolic mother liquors of III were evaporated to dryness and chromatographed. The benzene eluates furnished, after recrystallization from acetone, 300 mg. of IVb, m.p. 118°, $[\alpha]^{20}D$ + 1.5° (*c* 1.8); infrared absorption maxima ν_{max} 1730 and 1260 (acetate), 883 cm.$^{-1}$ (terminal double bond).

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.30; H, 10.97.

The acetylation of pure II gave also IVb in about a 10% yield.

17,17a-Dimethyl-D-homoandrost-17(17a)-en-3β-ol (V) from Bisnorallocholane-3β-20-diol (II).—A solution of 334.5 mg. of II and 6 mg. of iodine in 100 ml. of glacial acetic acid was refluxed for half an hour under nitrogen. After cooling, the iodine was reduced with a few drops of a saturated aqueous sodium hydrogen sulfite solution and a large amount of water was added. The resulting suspension was extracted with chloroform, the extract washed with water to neutrality, dried with sodium sulfate and evaporated. The sirupy residue was chromatographed, whereby the ether–benzene (1:99) eluates furnished, after recrystallization from methanol, V, m.p. 144.5–145.5°, with a better than 90% yield, $[\alpha]^{20}D$ −68° (*c* 1.16); infrared absorption maxima ν_{max} 3500 and 1040 (hydroxyl), 1650 (double bond), 1420 (allylic methylene), 1062 and 898 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{36}O$: C, 83.48; H, 11.47. Found: C, 83.49; H, 11.52.

On repeating this rearrangement on a larger scale, V could be obtained directly by crystallization in equally good yield.

A solution of 334.5 mg. of II and 10 mg. of *p*-toluenesulfonic acid in 100 ml. of 95% acetic acid was refluxed for 2 hours. After cooling, the reaction mixture was poured into a large excess of water and the resulting suspension extracted with chloroform, the extract washed with 2 *N* sodium hydroxide solution and water, dried over sodium sulfate and finally evaporated. The residue was chromatographed; the eluates with 2% ether in benzene gave, after recrystallization from methanol, 250 mg. of V, identical with the substance obtained above.

17,17a-Dimethyl-D-homoandrost-17(17a)-en-3β-ol Acetate (VI)[12] and Bisnorallochol-17(20)-en-3β-ol Acetate (VII)[11] from 3β-Acetoxybisnorallocholan-20-ol (III).—The solution of 376.5 mg. of III and 7 mg. of iodine in 100 ml. of glacial

(15) P. S. Bailey, *Chem. Revs.*, **58**, 925 (1958).

acetic acid was refluxed for half an hour. After cooling, the iodine was reduced with a few drops of a saturated aqueous solution of sodium hydrogen sulfite, followed by addition of a large excess of water. The resulting suspension was extracted with chloroform, the extract washed with water to neutrality, dried over sodium sulfate and evaporated to dryness *in vacuo*. The non-crystalline residue was chromatographed, whereby the eluates with 2 and 5% benzene in hexane gave an oily product, which was crystallized from methanol below 0°, to give 200 mg. of VI, m.p. 62–64°, $[\alpha]^{20}D$ −58° (*c* 1.38); infrared absorption maxima 1737 and 1243 (acetoxy), 1370 cm.$^{-1}$ (methyl groups).

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.22; H, 10.70.

The eluates with 25% benzene-in-hexane, after recrystallization from acetone, gave 25 mg. of VII, m.p. 145°; infrared absorption maxima ν_{max} 1732 and 1250 (acetoxy), 901 cm.$^{-1}$ (cyclopentane ring vibration).

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.21; H, 10.65.

17a,17a-Dimethyl-D-homoandrostane-3β,17β-diol (XIV) and its 3β-Monoacetate XV from 3β-Acetoxy-17a,17a-dimethyl-D-homoandrostan-17-one (XIII.)[9]—To the solution of 150 mg. of XIII in 50 ml. of methanol was added 200 mg. of potassium borohydride and the reaction mixture shaken at room temperature for 24 hours. The reaction mixture was diluted with benzene, and washed with 2 *N* hydrochloric acid, aqueous 2 *N* sodium hydroxide solution and water; after drying over sodium sulfate and evaporation, the crystalline residue was chromatographed. The eluates with 1% ether-in-benzene gave 85 mg. of XV which, after recrystallization from methanol, had m.p. 193–195° $[\alpha]^{20}D$ −13.9° (*c* 0.18); infrared absorption maxima ν_{max} 3600 and 1033 (hydroxyl), 1730 and 1255 cm.$^{-1}$ (acetoxy).

Anal. Calcd. for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.80; H, 10.86.

The eluates with 10% ether-in-benzene gave 35 mg. of XIV, recrystallized from methanol, m.p. 210–212°, $[\alpha]^{20}D$ −8.50° (*c* 0.293); infrared absorption maxima ν_{max} 3550 and 1028, 3450 and 1045 cm.$^{-1}$ (hydroxyls).

Anal. Calcd. for $C_{22}H_{38}O_2$: C, 78.98; H, 11.45. Found: C, 78.87; H, 11.46.

The saponification of XV with an equivalent amount of sodium hydroxide in methanol solution at room temperature gave XIV.

17,17a-Dimethyl-D-homoandrost-17(17a)-en-3β-ol Acetate (VI) from 17a,17a-Dimethyl-D-homoandrostane-3β,17β-diol 3-Monoacetate (XV).—The solution of 50 mg. of XV and 2 mg. of *p*-toluenesulfonic acid in 20 ml. of glacial acetic acid was refluxed for 8 hours. The reaction mixture was poured into a large excess of water, the mixture extracted with chloroform, the extract washed with 2 *N* aqueous sodium hydroxide solution and water, dried over sodium sulfate and evaporated *in vacuo*. The sirupy residue was chromatographed; the eluates with 50% benzene-in-hexane gave 42 mg. of VI, m.p. 63–65°. The hydrolysis of VI with sodium hydroxide in methanol at room temperature gave V, m.p. 140–141°. Both VI and V had melting points and infrared absorption spectra identical with the corresponding materials obtained previously.

20-Chlorobisnorallocholan-3β-ol Acetate (XVII) from Bisnorallocholane-3β,20-diol 3β-Acetate (III).—To the solution of 300 mg. of III in 40 ml. of anhydrous benzene was added 40 ml. of benzene saturated with gaseous hydrogen chloride, and the reaction mixture was shaken for one hour at room temperature. The solution was evaporated to dryness *in vacuo* at room temperature, and the crystalline residue recrystallized from acetone to give XXII in quantitative yield, m.p. 163–164°, $[\alpha]^{20}D$ −6.5° (*c* 1.39); infrared absorption maxima ν_{max} 1730 and 1265 (acetoxy), 1473 and 715 cm.$^{-1}$ (C–Cl).

Anal. Calcd. for $C_{24}H_{39}O_2Cl$: C, 72.97; H, 9.95; Cl, 8.98. Found: C, 73.07; H, 9.97; Cl, 6.97.

Bisnorallochol-20-en-3β-ol (IVa) from 20-Chlorobisnorallocholan-3β-ol Acetate (XVII).—The solution of 100 mg. of XVII in 20 ml. of 5% potassium hydroxide in methanol was shaken overnight. After addition of a large excess of water, the crystalline precipitate was filtered off, washed with water, dried at 45°, and recrystallized from methanol to give 70 mg. of IVa, m.p. 134–134.5°, $[\alpha]^{20}D$ + 7.5° (*c* 1.21) (literature[14] gives m.p. 143–147°, $[\alpha]D$ + 15°; infrared absorption maxima ν_{max} 3475 and 1043 (hydroxyl), 890 cm.$^{-1}$ (terminal double bond).

Anal. Calcd. for $C_{22}H_{36}O$: C, 83.48; H, 11.47. Found: C, 83.54; H, 11.63.

The acetylation of IVa with acetic anhydride in pyridine solution at room temperature gave IVb in a quantitative yield.

17,17a-Dimethyl-D-homoandrost-17(17a)-en-3β-ol Acetate (VI) from 20-Chlorobisnorallocholan-3β-ol Acetate (XVII).—The hexane solution of 150 mg. of XVII was put on a 30-g. column of silica gel whereby a deep-green color developed, which, on moving toward the end of the column, gradually changed to violet. The eluates with 5% benzene-in-hexane gave, after crystallization from methanol at low temperature, VI, m.p. 65–66°, in a quantitative yield.

17,17a-Dimethyl-D-homoandrost-17(17a)-en-3β-ol Acetate (VI) from 17,17a-Dimethyl-D-homoandrost-17(17a)-en-3β-ol (V).—To the solution of 100 mg. of V in 5 ml. of pyridine was added 1 ml. of acetic anhydride and the reaction mixture let stand overnight. After evaporation to dryness *in vacuo*, the sirupy residue was chromatographed. The eluates with 50% benzene-in-hexane gave, after recrystallization from methanol, VI, m.p. 63–65°, in a quantitative yield. The identification of VI with previously obtained material was obtained by mixed melting point and comparison of their infrared absorption spectra.

17,17a-Dimethyl-D-homoandrost-17(17a)-en-3β-ol Acetate (VI) from Bisnorallochol-20-en-3β-ol Acetate (IVb).—The solution of 300 mg. of IVb and 10 mg. of *p*-toluenesulfonic acid in 100 ml. of glacial acetic acid was refluxed for 2 hours. After cooling, the reaction mixture was poured into a large excess of water and the resulting suspension extracted with chloroform. The extract was washed with 2 *N* sodium hydroxide solution and water, dried over anhydrous sodium sulfate and finally evaporated. The residue crystallized after standing for 48 hours and was recrystallized from methanol to give 225 mg. of VI, m.p. 63–64°, which gave an infrared absorption spectrum identical with the sample previously obtained.

20-Hydroxybisnorallocholan-3-one (XVIII) from Bisnorallocholan-3β-20-diol (II).—To the solution of 1 g. of II in 100 ml. of methylene chloride was added 10 ml. of 2% chromium trioxide in 80% acetic acid and the two-phase system was shaken for 24 hours at room temperature. After addition of a few drops of saturated aqueous sodium sulfite solution, the methylene chloride layer was washed with 1 *N* aqueous sodium hydroxide solution and with water to neutrality, dried over sodium sulfate and evaporated to dryness. The crystalline residue was chromatographed, whereby the eluates with 5% ether-in-benzene, after recrystallization from methanol, gave 960 mg. of XVIII, m.p. 192–194°, $[\alpha]^{20}D$ +22.9 (*c* 1.2); infrared absorption maxima ν_{max} 3650 and 1208 (hydroxyl); 1710 (ketone); 1425 and 1410 (α-methylene groups to carbonyl); 1391, 1380, 1365, 1186, 950 cm.$^{-1}$ (isopropyl group).

Anal. Calcd. for $C_{22}H_{36}O$: C, 79.46; H, 10.92. Found: C, 79.29; H, 11.03.

17,17a-Dimethyl-D-homoandrost-17(17a)-en-3-one (XIX) from 20-Hydroxybisnorallocholan-3-one (XVIII).—The solution of 300 mg. of XVIII and 10 mg. of *p*-toluenesulfonic acid in 100 ml. of 95% acetic acid was refluxed for 2 hours. After cooling, the reaction mixture was poured into a large excess of water, and the resulting suspension extracted with chloroform. The extract was washed with a 2 *N* aqueous sodium hydroxide solution and water, dried over sodium sulfate and evaporated *in vacuo*. The sirupy residue was chromatographed; the eluates with 1% ethyl acetate in benzene gave 260 mg. of crystalline XIX, which on recrystallization from methanol had m.p. 107–108°, $[\alpha]^{20}D$ −39.1° (*c* 0.96); infrared absorption maxima ν_{max} 1708 (ketone), 1425 (α-methylene group to a carbonyl), 1390 and 1370 cm.$^{-1}$ (methyl groups).

Anal. Calcd. for $C_{22}H_{34}O$: C, 84.01; H, 10.90. Found: C, 84.28; H, 11.17.

17,17a-Dimethyl-D-homoandrost-17(17a)-en-3-one (XIX) from 17,17a-Dimethyl-D-homoandrost-17(17a)-en-3β-ol (V).—To the solution of 300 mg. of V in 50 ml. of methylene chloride was added 3.0 ml. of 2% chromium trioxide in 80% acetic acid, and the two-phase system shaken for 24 hours at room temperature. After the addition of a few

drops of saturated aqueous sodium sulfite solution, the methylene chloride layer was washed with aqueous sodium hydroxide solution and water to neutrality, then dried over sodium sulfate and evaporated to dryness. The crystalline residue was recrystallized from methanol to give XIX, m.p. 106–108°, in quantitative yield.

Ozonization of 17,17a-Dimethyl-D-homoandrost-17(17a)-en-3β-ol Acetate (VI) to XX.—The solution of 0.5 g. of VI in 100 ml. of ethyl acetate was cooled to −70° and an ozone–oxygen mixture was introduced for 45 minutes, or until the solution turned blue. The ethyl acetate was evaporated *in vacuo* at room temperature, the residue dissolved in 30 ml. of glacial acetic acid, followed by the addition of 1 ml. of 30% hydrogen peroxide. The reaction mixture was left overnight and then evaporated *in vacuo* at room temperature. The residue was taken up in benzene, the benzene solution washed with 2 *N* aqueous sodium carbonate and water, dried over sodium sulfate and evaporated to dryness *in vacuo*. The amorphous residue was chromatographed whereby the eluates with 5 and 10% ether in benzene gave, after several recrystallizations from methanol, XX, m.p. 183–184.5°, $[\alpha]^{20}D$ + 24° (*c* 1.02); infrared absorption maxima ν_{max} 3550 and 1440 (hydroxyl), 1737 and 1245 (acetoxy), 1698 (ketone) and 1123 cm.$^{-1}$ (ether). The result of the molecular weight determination (406) showed the product to be a monomer. The product oxidizes potassium iodide to iodine in boiling acetic acid solution.

Anal. Calcd. (for expected diketone XXI) $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Calcd. (for hydroperoxide) $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 71.19; H, 9.48.

To the solution of 100 mg. of XX in 50 ml. of methanol and 50 ml. of methylene chloride was added 2.5 ml. of 1 *N* aqueous sodium hydroxide solution and the reaction mixture allowed to stand for 24 hours. The excess base was neutralized quantitatively with 1 *N* aqueous hydrochloric acid solution, revealing that only one equivalent of sodium hydroxide had been used for the hydrolysis. The solution was evaporated, the residue extracted with methylene chloride, the extract washed with water, dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The amorphous residue was chromatographed whereby the eluates with 50% ethyl acetate in benzene gave, after recrystallization from methanol, XXIV, m.p. 187–188°, $[\alpha]^{20}D$ −89° (*c* 0.534); infrared absorption maxima ν_{max} 3475 and 1042 (hydroxyl), 1140 (ether) and 1695 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.02; H, 10.09.

The molecular weight indicated for substance XXV a value of 390. The acetylation of XXIV in pyridine solution with acetic anhydride at room temperature gave quantitatively XX, and left untouched the other hydroxyl group present in the molecule. The same hydrolysis product was also obtained when XX was refluxed with alkali and, here again, reacetylation furnished starting material.

3β-Acetoxy-16-acetyl-17-methyl-16,17-*seco*-androstan-17-one (XXI) from XX.—A molecular still, containing 300 mg. of XX was gradually heated to 180° at 0.01 mm., when suddenly a decomposition occurred, which transformed the product into a sirupy substance. It was first crystallized from methanol, then from ether–petroleum ether, giving XXI, m.p. 154–157°, $[\alpha]^{20}D$ + 18.6° (*c* 1.61); infrared absorption maxima ν_{max} 1733 and 1240 (acetoxy), 1698 (methyl ketone) and 1420 cm.$^{-1}$ (methylene group alpha to carbonyl).

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.44; H, 9.88.

Ten mg. of XXI was chromatographed on an aluminum oxide column, whereby the eluates with 5% ethyl acetate-in-benzene gave crystalline XXIII, recrystallized from ether, m.p. 202–203°; infrared absorption maxima ν_{max} 3550 and 1200 (tertiary hydroxyl), 1720 and 1260 (acetoxy) and 1700 cm.$^{-1}$ (methyl ketone).

16-Acetyl-17-methylandrost-16-en-3β-ol Acetate (XXII) from XX and XXI.—The solution of 50 mg. of XX or XXI and 5 mg. of *p*-toluenesulfonic acid in 25 ml. of glacial acetic acid was refluxed for 4 hours. After cooling, the reaction mixture was poured into a large excess of ethyl acetate, then washed with 1 *N* aqueous sodium hydroxide solution and water, dried over sodium sulfate and evaporated. The sirupy residue was chromatographed, whereby the eluates with 5% ethyl acetate-in-benzene gave XXII as a glassy colorless substance, λ_{max} 249 mμ[16]; infrared absorption maxima ν_{max} 1737 and 1245 (acetoxy), 1667 and 1625 cm.$^{-1}$ (conj. ketone).

(16) N. L. Wendler and D. Taub, *J. Org. Chem.*, **23**, 953 (1958).

WORCESTER, MASS.

[CONTRIBUTION FROM THE MEDICAL RESEARCH LABORATORY, DEPARTMENT OF MEDICINE, VETERANS ADMINISTRATION HOSPITAL, INDIANAPOLIS, IND.]

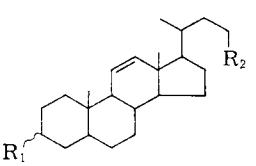
The Synthesis of 20-Methyl-5-pregnen-3β-ol

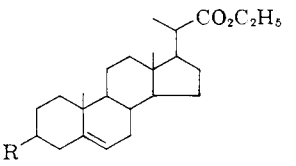
BY ROBERT T. BLICKENSTAFF

RECEIVED NOVEMBER 20, 1959

Ethyl 3β-hydroxy-5-bisnorcholenate was converted to 20-methyl-5-pregnen-3β-ol by two routes each involving stepwise reduction of carbethoxy to methyl. In one sequence the 3β-hydroxyl was converted to 3β-chloro, which was stable to the lithium aluminum hydride reductions. Alternatively the 3-hydroxyl function could be protected in the form of the trityl ether. 20-Methyl-5-pregnen-3β-ol was also synthesized from pregnenolone.

Ethyl 3β-chloro-11-cholenate (Ia) is one of a group of derivatives of bile acid esters that exhibit interesting seroflocculating properties.[1] Activity is retained when the ω-carbethoxy group is converted to methyl, as in 3β-chloro-11-cholene (Ib).[2] Other side-chain variations such as acetoxymethyl and chloromethyl (compare Ic with Id and Ie) also produced active compounds.[2] Of the derivatives of 3β-hydroxy-5-bisnorcholenic acid that have been screened as seroflocculants, ethyl 3β-chloro-5-bisnorcholenate (IIe) is highly active.[1] This paper reports the preparation of 20-methyl-5-pregnen-3β-ol (IVb) and 3β-chloro-20-methyl-5-pregnene (IIId), the reduced side chain analogs of 3β-hydroxy-5-bisnorcholenic acid and IIe, respectively, and of the 22-acetoxy (IIIb) and 22-chloro (IIIe) derivatives of IIId.





Ia, R_1 = β-Cl, R_2 = $CO_2C_2H_5$
b, R_1 = β-Cl, R_2 = CH_3
c, R_1 = α-AcO, R_2 = $CO_2C_2H_5$
d, R_1 = α-AcO, R_2 = CH_2OAc
e, R_1 = α-AcO, R_2 = CH_2Cl

IIa, R = HO
b, R = BzO
c, R = *p*-$C_7H_7SO_3$
d, R = $(C_6H_5)_3CO$
e, R = Cl

(1) F. C. Chang, *et al.*, THIS JOURNAL, **79**, 2161 (1957).
(2) R. T. Blickenstaff and F. C. Chang, *ibid.*, **81**, 2835 (1959).