evident. After stirring for 2.5 hr. at room temperature, the precipitate of tetramethylammonium bromide was removed, the acetone evaporated and the residue taken up in ether. The ether was washed with water and saturated sodium chloride solution and dried over anhydrous sodium sulfate. On evaporation of the solvent 0.37 g. of a white powder remained which gave a positive Beilstein test. This material was chromatographed on 10 g. of Merck acid-washed alumina. Elution with petroleum ether and with 10% benzene in petroleum ether gave 0.069 g. (19% yield) of Δ^4-cholestene-3-one, m.p. 78–80.5°, undepressed on admixture with authentic material. The infrared spectra of the two specimens were identical. Further elution with 30% benzene in petroleum ether gave 0.019 g. (4% yield) of material which was recrystallized once from 95% ethanol to give colorless flat blades, m.p. 144–147°, depressed on admixture with 4α-acetoxycholestane-3-one but not with the complex of 2α- and 4α-acetoxycholestane-3-one. The infrared spectra of the complex and the 144–147° sample were identical.

In another experiment, 0.251 g. of 4α-bromocholestane-3-one, m.p. 150.5–151.1°, was treated with 0.13 g. of dry tetramethylammonium acetate in 25 ml. of anhydrous acetone at ice bath temperature, with stirring. During the next 24 hr., the reaction mixture was allowed to warm to room temperature and the product was isolated as described above to give 0.210 g. of oil, $\lambda_{max}^{95\% C_2H_5OH}$ 242 mμ (ε 6930) which corresponds to 28% of Δ^4-cholestane-3-one.[31] The aqueous washes on treatment with silver nitrate gave 90% of the theoretical amount of silver bromide.

Reaction of 2α-acetoxycholestane-3-one (XI) *with tetramethylammonium acetate.* A mixture of 18.8 mg. of 2α-acetoxycholestane-3-one (XI), m.p. 122–123°, and 20.0 mg. of dry tetramethylammonium acetate in 1 ml. of acetone (distilled from Drierite) was stirred magnetically for 72 hr. at room temperature and then refluxed for 2.5 hr. The reaction mixture was diluted with ether, washed with water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Evaporation of the ether gave a quantitative yield of a light yellow oil that spontaneously crystallized, m.p. 130–143°. One recrystallization from 95% ethanol resulted in long blades, m.p. 145.5–146°, undepressed on admixture with authentic 3β-acetoxycholestane-2-one (IV).

Hydrolysis of 2α-acetoxycholestane-3-one (XI). A procedure for hydrolysis of the complex 2α- and 4α-acetoxy 3-ketones was used.[5]

To 42.3 mg. of 2α-acetoxycholestane-3-one (XI), m.p. 123.5–124.5°, in 1.0 ml. of benzene was added 1.7 ml. of a freshly prepared solution of 312 mg. of potassium carbonate dissolved in 5 ml. of water and 80 ml. of methanol. After standing overnight at room temperature, the solution was poured into 10 ml. of ice water, acidified with 2*N* sulfuric acid to a phenolphthalein end point, and extracted with five 10-ml. portions of ether. The ether extracts were washed with ice cold potassium carbonate solution, water, saturated sodium chloride solution, and were dried over anhydrous sodium sulfate. Removal of the ether gave 38.1 mg. (99.5%) of small colorless granules, m.p. (hot stage) 120–128°. Recrystallization from absolute methanol gave 21.1 mg., m.p. 126.2–129°. Recrystallization afforded 17.2 mg., m.p. 126.5–128.5°, reported,[4] 125–127°.

Acetylation of 2α-hydroxycholestane-3-one. 2α-Hydroxycholestane-3-one, m.p. 126.5–128.5°, was treated by the procedure of Sheehan and Erman[4] with acetic anhydride in pyridine to give a 60% yield of needles, m.p. 121–123.5°. Recrystallization from 95% ethanol gave colorless plates, m.p. 116–116.5°, which resolidified to needles, m.p. 126–126.5°, undepressed on admixture with authentic 2α-acetoxycholestane-3-one (see above). The infrared spectra of the two specimens were identical.

Acknowledgment. We wish to express our thanks to Professor J. C. Sheehan for furnishing specimens of his products for comparison purposes. We also thank the National Science Foundation, the U. S. Public Health Service, and the Allied Chemical Corp. for providing support for this study.

(31) R. D. H. Heard and P. Ziegler, *J. Am. Chem. Soc.*, 73, 4036 (1951) report $\lambda_{max}^{95\% C_2H_5OH}$ 242 mμ (ε 18,000).

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[CONTRIBUTION FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

Ring D α-Halo Ketones of 14β-Steroids[1,2]

TOSHIO NAMBARA[3] AND JACK FISHMAN

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The preparation of epimeric 16-bromo- and 16-chloro-3β-acetoxy-5α,14β-androstane-17-ones is described. The conformation and chemistry of the *cis* linked ring D is discussed in terms of the data obtained.

The infrared, ultraviolet, and optical rotatory dispersion spectra of the various α-bromo 16-keto and 17-keto compounds have been useful in the study of the conformation of ring D.[4] This work has so far been limited to the more common 14 α C/D *trans* series. The 14β C/D *cis* series was of interest because of the influence of the *cis* linkage on the conformation and chemistry of ring D. A suitable start to the problem was the preparation

(1) A portion of this work has been published in a preliminary note, J. Fishman and T. Nambara, *Chem. & Ind.* 79 (1961).

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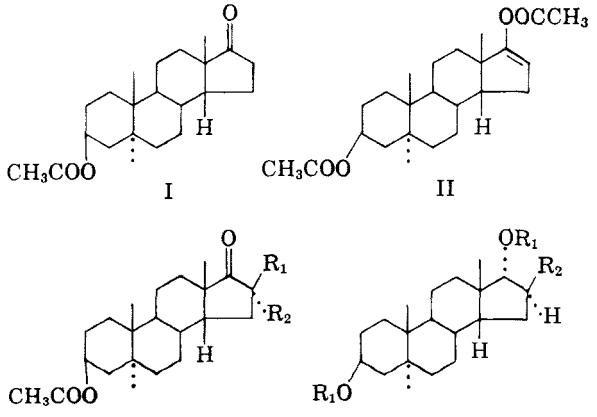
(3) Visiting Postdoctoral Research Fellow from the University of Tokyo, Japan.

(4)(a) F. V. Brutcher, T. Roberts, J. J. Barr, and N. Pearson, *J. Am. Chem. Soc.*, 81, 4915 (1959). (b) J. Fishman and C. Djerassi, *Experientia*, 16, 138 (1960). (c) J. Fajkos and J. Joska, *Chem. & Ind.*, 1162 (1960). (d) J. Fishman, *Chem. & Ind.*, 1961 *in press.*

and study of 16-halo-17-ketoandrostanes with the 14β-stereochemistry.

The starting material 3β-acetoxy-5α,14β-androstane-17-one (I) was prepared by the method of St. Andre *et al.*[5] Treatment of I with isopropenyl acetate and an acid catalyst gave the enol diacetate II m.p 94–95° in excellent yield. Reaction of II with bromine in carbon tetrachloride under non-enolizing conditions gave a single α-bromo ketone, m.p. 110–111°. The structure of the new compound was shown to be 3β-acetoxy-16β-bromo 5α,14β-androstane-17-one (IIIa) by the standard procedure of Fieser and Ettore.[6] Reduction of the bromo ketone IIIa with lithium aluminum hydride led to the 16β-bromo 17α-hydroxy *trans*-bromohydrin IVb, m.p. 168–169°. The orientation of the hydroxyl group in IVb was established by reductive debromination with hydrogen to give the known 3β,17α-diol IVa.[5] The *trans* nature of the bromohydrin IVb followed from the formation of the 16α, 17α-oxide Va, m.p. 137–139°, on treatment with base. The structure of the oxide Va was further confirmed by reduction with lithium aluminum hydride to yield to 3β,17α-diol IVa. The latter result is of some interest in that the reductive cleavage of the oxide takes the same course as that found in the 14α series.[7] It is doubtful if the rule of preference for axial alcohols as products of such openings[8] is applicable in this instance. Apparently the steric effect of the C-13 methyl group on the β side of C-17[7] is still effective in the *cis* C/D structure and results in preferential attack of the reagent at C-16.



IIIa. R_1 = Br, R_2 = H
b. R_1 = H, R_2 = Br
c. R_1 = R_2 = Br
d. R_1 = Cl, R_2 = H
e. R_1 = H, R_2 = Cl
f. R_1 = R_2 = Cl

IVa. R_1 = R_2 = H
b. R_1 = H, R_2 = Br
c. R_1 = CH_3CO, R_2 = Br
d. R_1 = H, R_2 = Cl
e. R_1 = CH_3CO, R_2 = Cl

The 16β-bromo 17-ketone IIIa was epimerized readily with hydrogen bromide in glacial acetic acid to yield an equilibrium mixture from which the 16α-bromo isomer IIIb, m.p. 163–165° (184–185°) could be isolated by fractional crystallization. The composition of the equilibrium mixture attained from either one of the isomers IIIa and IIIb was measured both by optical rotation and infrared spectrometry. In the latter case use was made of a digital computer attached to the spectrophotometer[9] which yielded results with an accuracy of $\pm 2\%$. The results from both methods agreed well and gave an equilibrium value corresponding to 45% β and 55% α.

The reduction of the 16α-bromo 17-ketone IIIb with lithium aluminum hydride proceeded in an abnormal manner in that bromine was lost and the product obtained was the 3β,17α-diol IVa. Despite varying the conditions and the reducing reagents, bromine could not be retained in the product. This result is clearly a consequence of the *cis* C/D linkage since in the 14α series no difficulty is encountered in the preparation of both the *cis* and *trans* bromohydrins from the 16α-bromo 17-ketone.[7,10] The geometry of *cis* joined rings C/D is such as to constitute a cage like structure, similar to that resulting from a ring A/B *cis* linkage.[11] In this case the reduction of the 17-ketone group will proceed from the less hindered β side to give the 16α-bromo-17α-hydroxy complex. The steric strain of these two adjacent groups on the concave side of the C/D cage is not significantly relieved by staggering and results in elimination of hydrogen bromide to yield the 17-ketone. This in turn is further reduced by the excess reagent to give as the final product the 3β,17α-diol IVa. In one experiment where a limited amount of reducing reagent was used, the 17-ketone could be isolated. That a dehydrobromination can be effected under certain circumstances without the presence of base has been shown by the direct formation of oxides upon lithium aluminum hydride reduction of 5α-bromo 6-ketones and 12α-bromo 11-ketones.[12] In those instances the reaction proceeds due to the extremely favorable geometrical alignment of the reaction centers.[13]

The 16-*gem*-dibromo compound IIIc, m.p. 154–155°, was prepared from either IIIa or IIIb by

(5) A. F. St. Andre, H. B. MacPhillamy, J. A. Nelson, A. Shabica, and C. R. Scholz, *J. Am. Chem. Soc.*, **74**, 5506 (1952).

(6) L. F. Fieser and R. Ettore, *J. Am. Chem. Soc.*, **75**, 1700 (1953).

(7) J. Fajkos, *Chem. Listy*, **48**, 1300 (1954); *Coll. Chech. Chem. Comm.*, **20**, 312 (1955).

(8) A. Furst and A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949); A. Furst and R. Scotoni, *Helv. Chim. Acta*, **36**, 1332 (1953).

(9) Spectro-Analyzer, I. T. & T. Laboratories, Nutley, N. J.

(10) J. Fishman and W. R. Biggerstaff, *J. Org. Chem.*, **23**, 1190 (1958).

(11) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(12) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596 (1957).

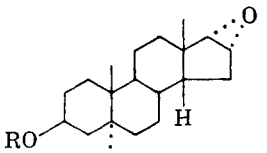
(13) Similar instances of the loss of bromine were noted without comment in the case of 9-bromo 11-keto and 8-bromo 7-keto steroids; H. B. Henbest, E. R. H. Jones, A. A. Wagland, and T. I. Wrigley, *J. Chem. Soc.*, 2477 (1955); E. R. H. Jones and D. J. Wluka, *J. Chem. Soc.*, 907, 911 (1959).

TABLE I

	CCl_4 I.R. ν_{max} ($cm.^{-1}$)	$\Delta\nu$ ($cm.^{-1}$)	C_2H_5OH U.V. λ_{max} ($m\mu$)	$\Delta\lambda$	R. D. First Extremum ($m\mu$)	R. D. First Extremum CH_3OH [α]	R.D. $\Delta\lambda$ ($m\mu$)
17-Ketone I	1739		290		301	+992	
16β-Bromo-17-one IIIa	1746	+7	319	+29	342	+1195	+41
16α-Bromo-17-one IIIb	1753	+14	308	+18	312	+942	+11
16,16-Dibromo-17-one IIIc	1759	+20	315	+25	337	+1382	+36
16β-Chloro-17-one IIId	1753	+14	310	+20			
16α-Chloro-17-one IIIe	1758	+19	303	+13			
16,16-Dichloro-17-one IIIf	1770	+31	307	+17			

bromination in acetic acid in the presence of hydrogen bromide.

In view of the steric effects operative in the *cis* linked ring D it was of interest to us to prepare the corresponding α-chloro compounds to observe the effect of the somewhat smaller size of this halogen. The 16β-chloro 17-ketone IIId was produced by chlorination of the enol diacetate II but could not be obtained crystalline. It did, however, behave homogeneously on silica chromatography, showed the expected carbonyl shift in the infrared and on reduction with lithium aluminum hydride gave 16β-chloro 17α-hydroxychlorohydrin IVd, m.p. 168–170°. The structure of IVd was confirmed by its reaction with base to yield the 16α, 17α-epoxide Va. The non-crystalline β-chloro compound IIId



Va. R = H
b. R = CH_3CO

was epimerized readily to the crystalline 16α-chloro 17-ketone IIIe, m.p. 188–190°. This isomer IIIe, like the 16α-bromo ketone IIIb, was reduced with lithium aluminum hydride with loss of chlorine to give the 3β,17α-diol IVa. The 16-*gem*-dichloro 17-ketone IIIf, m.p. 134–135° was obtained from either IIId or IIIe with excess chlorine in acetic acid in the presence of hydrogen chloride.

The equilibrium between the 16α- and 16β-chloro compounds favors the 16α to a much greater extent than in the bromo series. Thus the 16α-chloro 17-ketone IIIe was recovered essentially unchanged from acetic acid containing hydrogen chloride, while the 16β-chloro was largely epimerized. Our inability to obtain the 16β-chloro compound crystalline prevented a more quantitative estimation of the equilibrium composition.

The infrared, ultraviolet and optical rotatory dispersion curves of the α-halo ketones are of particular interest. The pertinent carbonyl absorptions and the shifts from the unsubstituted 17-ketone are listed in Table I. It is apparent from these shifts that unlike the 14α series the two 16 positions in the 14β series are not bisectional and equivalent. Indeed the nature of the displacements is such as to assign to the 16β bond quasiaxial and to the 16α bond quasiequatorial character. Thus, the infrared shifts of the 16β-halo ketones are smaller than those of the corresponding 16α epimers,[14] while the ultraviolet displacements show the expected reverse relationship.[15] The rotatory dispersion curves[16] support these conformational assignments in that the quasiaxial 16β epimer exhibits the much larger bathochromic shift of the first extremum.[17] Furthermore the magnitude of the shifts is quite comparable to those found in the epimeric 17-bromo[4c] and 15-bromo 16-ketones[4d] of the 14α series. The *gem*-dihalo compounds IIIc and IIIf are unexceptional in that the values of their infrared shifts are additive while the ultraviolet shifts are typical of α-*gem*-dihalo ketones being only about half the additive value.[15] It is difficult to reconcile these findings with molecular models of these structures which have shown themselves to be reasonably accurate in the 14α series. These reveal no significant conformational differences in the 16 position between the 14α and 14β series. In either series ring D with a ketone at C-17 appears to be in a half-envelope form[4a,18] with carbons 13, 15, 16 and 17 in one plane. Carbon 14 is below that plane in the 14α structure and above it in the 14β isomer. It is conceivable that steric pressure on the 16α substituent, occasioned by the cage-like *cis* structure, would result in distortion bringing it more into the plane of the 17-carbonyl. Indeed, in 16-chloro ketones, where this effect should be reduced, the infrared and ultraviolet show smaller differences between the two eipmers than in the bromo ketones. However, this argument fails to account satisfactorily for the quasiaxial conformation of the 16β-substituent. An alternative and attractive explanation is that the conformation of ring C is altered by the 14β stereochemistry and in turn results in a D ring

(14) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).

(15) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(16) The authors are grateful to Professor Carl Djerassi, Stanford University, for the rotatory dispersion data.

(17) C. Djerassi and W. Klyne, *J. Am. Chem. Soc.*, **79**, 1506 (1957); C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 1216 (1958).

(18) J. Fishman, *J. Am. Chem. Soc.*, **82**, 6143 (1960).

conformation which would account for the above results. We are at present exploring this possibility by preparing the two epimeric 11-bromo-12-keto-14β steroids. The infrared and ultraviolet spectra and in particular the optical rotatory dispersion of these compounds should permit the detection of any conformational changes in ring C as compared to the 14α structures.

In view of the quasiequatorial nature of the 16α bromine the equilibrium would be expected to favor it over the 16β to a greater extent than that actually found. It must, however, be emphasized that the terms quasiequatorial and quasiaxial are in reference only to the C-17 ketone and the plane of ring D and do not reflect the stability criteria usually associated with them. In actuality the *cis* C/D junction produces a situation where the α side is hindered in contrast to the β side. Therefore, the stereochemistry of ketonization[19] would favor the 16α-bromo ketone, while the 16β bromine being less hindered would be preferred on thermodynamic grounds. The equilibrium mixture may then represent a compromise between these two opposing forces. In the case of the chlorine and its smaller size the stereochemistry of ketonization may become dominant and result in the observed greater preference for the 16α-chloro 17-ketone.

EXPERIMENTAL[20]

5α,14β-Δ^{16}-Androstene-3β,17-diol diacetate (II). To a solution containing 650 mg. of 3β-acetoxy-5α,14β-androstane-17-one (I) in 10 ml. of isopropenyl acetate was added 16 drops of catalyst solution (5 ml. of isopropenyl acetate and 0.1 ml. of concd. sulfuric acid). Approximately 5 ml. of the solvent was distilled over a period of 2 hr. An additional 5 ml. of isopropenyl acetate containing 8 drops of catalyst solution was added and the reaction mixture was concentrated to one-half of its volume by slow distillation over another 2 hr. The solution was then cooled and diluted with ether. The ether was washed with cold 5% sodium bicarbonate solution and with water, dried, and the solvent was evaporated. The residue was dissolved in petroleum ether and filtered through 2.5 g. of alumina. Upon concentration of the filtrate the product crystallized. Recrystallization from dilute methanol gave 562 mg. of II, m.p. 92–93° as white needles. The mother liquor yielded 120 mg. of crude product which on further recrystallization gave 60 mg. of the enol diacetate, 91–92°. The analytical sample melted at 94–95°, $[\alpha]_D^{26}$ + 51°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76, H, 9.15. Found: C, 74.01; H, 9.01.

3β-Acetoxy-16β-bromo-5α,14β-androstane-17-one (IIIa). To a solution of 560 mg. of II in 50 ml. of carbon tetrachloride 0.5 g. of anhydrous potassium carbonate was added. To this mixture the calculated amount of bromine dissolved in carbon tetrachloride was added dropwise with stirring at 0°, and then the reaction mixture was washed with sodium bisulfite solution and with water, dried, and the solvent was evaporated. The oily residue solidified on scratching and on recrystallization from dilute methanol gave 440 mg. of IIIa, m.p. 106–109° as white plates. The mother liquor yielded an additional 85 mg. of the product. The analytical sample melted at 110–111°, $[\alpha]_D^{26}$ + 104°.

Anal. Calcd. for $C_{21}H_{31}BrO_3$ C, 61.31; H, 7.59; Br, 19.43. Found: C, 61.39; H, 7.40; Br, 19.71.

3β-Acetoxy-16α-bromo-5α,14β-androstane-17-one (IIIb). To a solution of 550 mg. of IIIa dissolved in 4 ml. of glacial acetic acid was added 1 ml. of acetic acid saturated with hydrogen bromide and the solution was allowed to stand at room temperature for 48 hr. The mixture was then poured into ice water and the white precipitate was filtered, and washed well with water. Recrystallization from dilute methanol gave 255 mg. of IIIb, m.p. 162–165° as white needles. The analytical sample melted at 163–165° (isomorphic form m.p. 184–185°), $[\alpha]_D^{28}$ + 52°.

Anal. Calcd. for $C_{21}H_{31}BrO_3$ C, 61.31; H, 7.59; Br, 19.43. Found: C, 61.70; H, 7.25; Br, 19.21.

Equilibration of epimeric 16-bromo 17-ketones (IIIa *and* IIIb). To a solution of 15 mg. of each epimer in 4 ml. of glacial acetic acid was added 1 ml. of acetic acid saturated with hydrogen bromide. The solutions were allowed to stand overnight and were then poured into ice water. The precipitates were filtered off, washed with water and dried. The rotation and infrared spectra were obtained on each sample.

From 16β-bromo 17-ketone IIIa: Mixture $[\alpha]_D^{28}$ +75.4, IIIa 45.1%, IIIb 54.9%, infrared analysis gave IIIa 46.4%, IIIb 53.6%.

From 16α-bromo 17-ketone IIIb: Mixture $[\alpha]_D^{26}$ +75.1, IIIa 44.5%, IIIb, 55.5%; Infrared analysis gave IIIa 46.1%, IIIb 53.9%.

3β-Acetoxy-16,16-dibromo-5α,14β-androstane-17-one (IIIc). To a solution of 50 mg. of IIIa in 4 ml. of glacial acetic acid containing 0.1 g. of bromine was added 1 ml. of acetic acid saturated with hydrobromic acid and the solution was allowed to stand at room temperature for 48 hr. The mixture was then poured into ice water containing a small amount of sodium bisulfite and the white precipitate was filtered and washed with water. Recrystallization from dilute methanol gave 49 mg. of IIIc, m.p. 151–154° as white plates. The analytical sample melted at 154–155°, $[\alpha]_D^{28}$ + 104°.

Anal. Calcd. for $C_{21}H_{30}Br_2O_3$: C, 51.44; H, 6.17; Br, 32.60. Found: C, 51.26; H, 6.27; Br, 32.31.

The same compound was similarly obtained from the 16α-bromo epimer IIIb.

3β-Acetoxy-16β-chloro-5α,14β-androstane-17-one (IIId). To a solution of 200 mg. of the enol diacetate II dissolved in 20 ml. of carbon tetrachloride 0.5 g. of anhydrous potassium carbonate was added. To this mixture a solution of chlorine in carbon tetrachloride was added dropwise with stirring at 0°. Filtration and evaporation of solvent gave an oily material which showed carbonyl absorption in the infrared at 1753 cm.$^{-1}$ Chromatography of crude product on 10 g. of silica gel and elution with 7:3 benzene-petroleum ether gave 184 mg. of IIId as a colorless oil. Examination of the infrared spectrum still showed the carbonyl absorption at 1753 cm.$^{-1}$

3β-Acetoxy-16α-chloro-5α,14β-androstane-17-one (IIIe). The crude 16β-chloro 17-ketone IIId, which was obtained starting from 195 mg. of enol acetate II in same manner as described above, was dissolved in petroleum ether and absorbed on 10 g. of acid-washed alumina and allowed to stand overnight. Elution with increasing percentage of benzene in petroleum ether yielded 87 mg. of semicrystalline material. Recrystallization from dilute methanol gave 33 mg. of IIIe, m.p. 187–188° (isomorphic form m.p. 160–161°) as white needles. The analytical sample melted at 188–190°, $[\alpha]_D^{28}$ +67°.

Anal. Calcd. for $C_{21}H_{31}ClO_3$: C, 68.74; H, 8.52; Cl, 9.66. Found: C, 68.95; H, 8.72; Cl, 9.98.

(19) H. E. Zimmerman, *J. Am. Chem. Soc.*, 79, 6554 (1957).

(20) Melting points were obtained on a Kofler hot stage and are corrected. Rotations were determined in chloroform. Infrared measurements were obtained on a calibrated Perkin-Elmer 21 instrument using a calcium fluoride prism. Ultraviolet measurements were obtained on a Cary recording spectrophotometer Analyses were performed by Spang Microanalytical Laboratories.

The same compound was also obtained by allowing a sample of IIId to stand in glacial acetic acid containing hydrogen chloride for 24 hr., pouring into ice water, filtering off the precipitate, drying, and crystallizing from dilute methanol.

Attempted epimerization of IIIe. To a solution of 20 mg. of IIIe in 1 ml. of acetic acid was added 1 ml. of acetic acid saturated with hydrogen chloride and the solution was allowed to stand at room temperature overnight. The reaction mixture was poured into ice water to give a white precipitate (m.p. 182–185°), undepressed on mixture melting point with starting material.

3β-Acetoxy-16,16-dichloro-5α,14β-androstane-17-one (IIIf). IIIe (58 mg.) was dissolved in 4 ml. of glacial acetic acid containing excess chlorine and hydrogen chloride and the solution was allowed to stand at room temperature overnight. The reaction mixture was then poured into ice water and the white precipitate was filtered and washed with water. Recrystallization from dilute methanol gave 60 mg. of IIIf, m.p. 133–135° as white plates. The analytical sample melted at 134–135°, $[\alpha]_D^{25}$ +90°.

Anal. Calcd. for $C_{21}H_{30}Cl_2O_3$: C, 62.84; H, 7.53; Cl, 17.67. Found: C, 62.73; H, 7.48; Cl, 17.67.

The same compound was also obtained from IIId in an identical manner but poorer yield.

16β-Bromo-5α,14β-androstane-3β,17α-diol (IVb). To a solution of 780 mg. of IIIa in 100 ml. of dry ether was added an excess amount of lithium aluminum hydride under cooling in ice water; the solution was allowed to stand at 0° for 2 hr. with occasional shaking. The excess reagent was then decomposed by the addition of ice-water, acidified with dilute sulfuric acid, and the ethereal layer was washed with 5% sodium bicarbonate solution, water, and dried. Upon evaporation of solvent, an oily residue was obtained. The crude product was dissolved in benzene and chromatographed on 25 g. of acid washed alumina. Elution with increasing concentration of ether in benzene yielded 260 mg. of crystalline material. Recrystallization from acetone–petroleum ether gave 202 mg. of IVb, m.p. 162–163.5° as white leaflets. The analytical sample melted at 168–169°, $[\alpha]_D^{28}$ +33°.

Anal. Calcd. for $C_{19}H_{31}O_2Br \cdot 0.5H_2O$: C, 59.99; H, 8.48; Br, 21.01. Found: C, 59.85; H, 8.47; Br, 20.96.

The 3β,17α-diacetate (IVc) was obtained in the usual manner, with pyridine and acetic anhydride. Recrystallization from dilute methanol gave white prisms, m.p. 124–126°, $[\alpha]_D^{26}$ +45°.

Anal. Calcd. for $C_{23}H_{35}BrO_4$: C, 60.65; H, 7.75; Br, 17.55. Found: C, 60.81; H, 7.68; Br, 17.62.

16β-Chloro-5α,14β-androstane-3β,17α-diol (IVd). IIId (150 mg.) was treated with excess amount of lithium aluminum hydride in 30 ml. of ether in a same manner as described above. The isolated crude product was dissolved in benzene chromatographed on 8 g. of acid washed alumina. Elution with increasing concentrations of ether in benzene yielded 72 mg. of crystalline material. Recrystallization from acetone–petroleum ether gave IVd, m.p. 163–167° as white leaflets. The analytical sample melted at 168–170°, $[\alpha]_D^{23}$ +36°.

Anal. Calcd. for $C_{19}H_{31}ClO_2 \cdot H_2O$: C, 66.16; H, 9.64; Cl, 10.28. Found: C, 66.47; H, 9.75; Cl, 10.48.

The 3β,17α-diacetate IVe was obtained in the usual manner with acetic anhydride and pyridine. Recrystallization from dilute methanol gave white prisms, m.p. 138–139°, $[\alpha]_D^{28}$ +60°.

Anal. Calcd. for $C_{23}H_{35}ClO_4$: C, 67.21; H, 8.59; Cl, 8.63. Found: C, 66.94; H, 8.45; Cl, 8.57.

16α,17α-Epoxy-5α,14β-androstane-3β-ol (Va). A. *From* IVb. IVb (20 mg.) was boiled under reflux in 5 ml. of 5% methanolic potassium hydroxide for 4 hr. The solution was concentrated almost to dryness under reduced pressure, water was added, and the aqueous mixture was extracted twice with ether. The ethereal extract was washed with water, dried, and evaporated. The oily residue was dissolved in petroleum ether and chromatographed on 2 g. of acid washed alumina. Elution with increasing concentration of benzene in petroleum ether yielded 10 mg. of crystalline material. Recrystallization from petroleum ether gave 8 mg. of Va, m.p. 135–137° as white needles. The analytical sample melted at 137–139°, $[\alpha]_D^{28}$ +45°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.94; H, 10.19.

B. *From* IVd. IVd (12 mg.) was treated exactly as above and the product was also obtained in the same manner. Recrystallization gave 6 mg. of Va, m.p. 137–138°. Melting point of the mixture with the product from IVb showed no depression, and the infrared spectra were identical in all respects.

The acetate Vb was obtained in the usual manner with acetic anhydride and pyridine. Recrystallization from methanol gave needles, m.p. 121–122°. The analytical sample melted at 122–123°, $[\alpha]_D^{25}$ +35°.

Anal. Calcd. For: $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.61; H, 9.49.

5α,14β-Androstane-3β,17α-diol (IVa). A. *By Debromination of* IVb. Bromohydrin IVb (25 mg.) was dissolved in 50 ml. of ethanol and was shaken in a hydrogen atmosphere with 150 mg. of 25% palladium on calcium carbonate for 20 hr. The reaction mixture was diluted with ether and filtered. Evaporation of solvent left an oily product, which solidified trituration with ether. Recrystallization from dilute methanol gave 17 mg. of IVa, m.p. 187–188° as white leaflets. The melting point of the mixture with an authentic sample[5] showed no depression, and the infrared spectra of the two samples were identical.

B. *By hydride reductions of* IIIb. 1) To a solution of 80 mg. of IIIb in 50 ml. of dry ether was added an excess amount of lithium aluminum hydride portionwise with cooling in ice. The reaction mixture was allowed to stand at 0° for 2 hr. with occasional shaking. The excess reagent was decomposed by the addition of ice water, acidified with dilute sulfuric acid and the ethereal layer was washed with 5% sodium bicarbonate solution, water, and dried. Upon evaporation of solvent an oily residue was obtained. Recrystallization from dilute methanol gave 52 mg. of crude IVa, m.p. 176–183°. One more recrystallization gave white leaflets, m.p. 183–185°. The melting point of a mixture with an authentic sample[5] showed no depression, and the infrared spectra of two samples were identical.

2) Reduction of IIIb with lithium aluminum tri-*t*-butoxy hydride in tetrahydrofuran, and hydrolysis of the acetate group also resulted in IVa, m.p. 183–185°.

3) Reduction of 100 mg. of IIIb with an equal weight of sodium borohydride in ethanol gave a crude product which showed the presence of the 17-ketone in the infrared. Hydrolysis of the acetate with 5% ethanolic sulfuric acid and chromatography gave 15 mg. of 3β-hydroxy-5α,14β-androstane-17-one, m.p. 156–158° and 50 mg. of the 3β,17α-diol IVa.

C. *By lithium aluminum hydride reduction of* IIIe. Chloroketone IIIe (50 mg.) was reduced with excess lithium aluminum hydride in the same manner as above and 40 mg. of crude product was obtained. Recrystallization from dilute methanol gave 17 mg. of IVa, m.p. 180–185° as white leaflets. The mixed melting point of the mixture with authentic sample[5] showed no depression, and the infrared spectra of two samples were also identical.

D. *By lithium aluminum hydride reduction of the oxide* Va. 16α,17α-epoxide Va (23 mg.) was treated with excess lithium aluminum hydride in the same manner as above. The crude product weighed 21 mg. and on recrystallization from acetone–petroleum ether gave 13 mg. of IVa, m.p. 180–183°. This was identical with the authentic sample by mixed melting point and infrared.

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The Synthesis of 16α-Methoxyhydrocortisone Acetate and Congeners

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Alkylation of 3,20-bisethylenedioxy-16α,17α-dihydroxy-5-pregnene (V), and 3,20-bisethylenedioxy-16α,17α-dihydroxy-5-pregnene-11-one (VII) with methyl iodide gave the corresponding 16α-methoxy derivatives. Use of this reaction in conjunction with known procedures furnished the 16α-methoxy analogs of 17α-hydroxyprogesterone, Reichstein's Substance S, 4-androstene-3,17-dione, 21-deoxycortisone, 21-deoxyhydrocortisone, cortisone acetate, hydrocortisone acetate, prednisone acetate, prednisolone acetate, 21-deoxy-9α-fluorohydrocortisone, 9α-fluorohydrocortisone acetate, and 9α-fluoroprednisolone acetate.

Since 1956 several laboratories have studied the effects on corticoid activity brought about by the substitution of certain groups in the C-16 position of hydrocortisone and its congeners. Initially, Bernstein and his co-workers[2] found that 9α-fluoro-16α-hydroxyprednisolone is a potent glucocorticoid lacking the salt-retaining properties of the 9α-fluorocorticoids. Subsequently, Fried and his collaborators[3] reported on the marked potentiation of the glucocorticoid activity of this compound by 16,17-acetal and -ketal formation. The introduction of a methyl group in either the α- or β-orientation at C-16,[4] as well as the 16α-fluoro atom,[5] also has a favorable effect on the corticoid activity of the parent hormones. In contrast to the above results, substitution of 16β-hydroxy,[6] 16β-fluoro,[7] 16β-methoxy,[8] and 16,16-*gem*-dimethyl[9] groupings in hydrocortisone and related hormones has a detrimental effect on the activity of these compounds. It may be noted that modified hormones bearing the 16α-hydroxy, 16α,17α-isopropylidenedioxy, 16α-methyl and 16β-methyl groups are of proved value as anti-inflammatory agents in human therapy.[10]

Because the masking of the glycol grouping in 9α-fluoro-16α-hydroxyprednisolone by ketal or acetal formation has an advantageous effect on its activity, it appeared desirable to prepare an analog of this compound in which one of the glycol hydroxyl groups was masked. Etherification was chosen as the method for effecting this modification, and in view of the frequency of success with various substituents at C-16 the preparation of 16α-methoxy analogs of hydrocortisone and its congeners was undertaken.[11]

16α-Methoxypregnane derivatives (*B*) may be conveniently prepared by the 1,4-addition of methanol to a 16-dehydro-20-ketone (*A*).[12] However, this procedure was considered unsatisfactory for our purposes, since the subsequent introduction of the 17α-hydroxy group would require treatment

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