An analytical sample of *3β-hydroxy-17a-oxa*-D-*homo-5α-androstane* (XIIa), prepared by saponifying the corresponding acetate derivative, recrystallized from methanol-water as colorless needles melting at 181–183°; $[\alpha]^{20}_{D}$ 0.0°, ν^{KBr}_{max} 3401, 1120, 1090, 1060, 1046, and 1026 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{32}O_2$(292): C, 78.03; H, 11.03; O, 10.94; active H, 0.34. Found: C, 77.54; H, 10.82; O, 11.56; active H, 0.28; mol. wt. (Rast), 297.

Treating alcohol XIIb, in pyridine solution, with benzoyl chloride (1 hr., steam bath) led to 3β-benzoyloxy-17a-oxa-D-homo-5α-androstane (XIIc); colorless needles from methanol, m.p. 162–164°, ν^{KBr}_{max} 1712, 1120, and 1098 cm.$^{-1}$

Anal. Calcd. for $C_{26}H_{36}O_3$: C, 78.71; H, 9.15; O, 12.10. Found: C, 78.36; H, 9.07; O, 12.17.

ORONO, ME.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN AND OF STANFORD UNIVERSITY]

Ring-A α-Acetoxy Ketones in the Cholestane Series

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The unambiguous synthesis of six isomeric keto acetates, 2α-, 2β-, 4α-, and 4β-acetoxycholestane-3-one and 3α- and 3β-acetoxycholestane-2-one, was undertaken in order to clarify a number of erroneous structural assignments in the literature as well as to prove the structures of the compounds produced by the action of potassium acetate and by tetramethylammonium acetate on 2α-bromocholestane-3-one.

α-Acetoxy ketones of known configuration and conformation were desired for NMR spectroscopy studies.[1] In exploring the availability of such substances in the cholestane series, we discovered that the situation as reported in the literature was confused; we therefore attempted to clarify matters. A compound, m.p. 148–149°, which is an inseparable mixture of 2α-acetoxycholestane-3-one (XI) and 4α-acetoxycholestane-3-one (XVI), has been shown[2] to be produced by the displacement of bromine from 2α-bromocholestane-3-one by potassium or sodium acetate in refluxing acetic acid. In an effort to prepare pure 2α-acetoxycholestane-3-one (XI) we tried the reaction of 2α-bromocholestane-3-one with tetramethylammonium acetate in refluxing acetone.[3] The product was shown to be identical with a substance prepared *via* the acyloin condensation of 2,3-secocholestane-2,3-dioic acid dimethyl ester and assigned the structure 3β-acetoxycholestane-2-one.[4] From the same acyloin reaction which produced 3β-hydroxycholestane-2-one, Sheehan and Erman isolated a compound which was assigned the structure 2-hydroxycholestane-3-one. The properties of the acetate of this ketol,[4] however, corresponded to those reported[2] for the complex of 2α- and 4α-acetoxycholestane-3-one. This complex, moreover, had been reduced and hydrolyzed by Ruzicka, Plattner, and Furrer,[5] who did not realize that they were dealing with a mixture. Unlikely structural assignments were made to a number of the resulting bewildering array of products.

In order to try to clarify the confusion and to ascertain the exact composition of the complex of 2α- and 4α-acetoxycholestane-3-one, the unequivocal synthesis of six keto acetates was undertaken: 2α-, 2β-, 4α-, and 4β-acetoxycholestane-3-one and 3α- and 3β-acetoxycholestane-2-one.

Synthesis of the keto acetates. An unambiguous method was employed. Diaxial hydroxy acetates were obtained by acetolysis of the appropriate epoxides. Oxidation by Jones' reagent[6] gave the axial α-acetoxy ketones which could be converted to their equatorial epimers by acid-catalyzed epimerization.

2α-Bromocholestane-3-one[7] was reduced to a mixture of bromohydrins,[8,9] one of which was converted to 2β,3β-oxidocholestane[9] (I) by the action of potassium hydroxide in isopropyl alcohol. This epoxide was cleaved with acetic acid to 2β-hydroxy-3α-acetoxycholestane (II), m.p. (dimorphic) 111–112.5° and 138.7–139.2°, $[\alpha]_D$ +42.2°, according to the procedure which Furst and Plattner[10] used to convert 2α,3α-oxidocholestane to 2β-acetoxy-3α-hydroxycholestane. Acetylation pro-

(1) See K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc., in press.*

(2) L. F. Fieser and M. A. Romero, *J. Am. Chem. Soc.*, **75**, 4716 (1953).

(3) See *inter alia* A. Streitwieser, Jr., and J. R. Wolfe, Jr., *J. Am. Chem. Soc.*, **79**, 903 (1957); H. L. Goering, T. D. Nevitt, and E. F. Silversmith, *J. Am. Chem. Soc.*, **77**, 4042 (1955); and J. Steigman and L. P. Hammett, *J. Am. Chem. Soc.*, **59**, 2536 (1937).

(4) J. C. Sheehan and W. F. Erman, *J. Am. Chem. Soc.*, **79**, 6050 (1957).

(5) L. Ruzicka, Pl. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, **27**, 727 (1944).

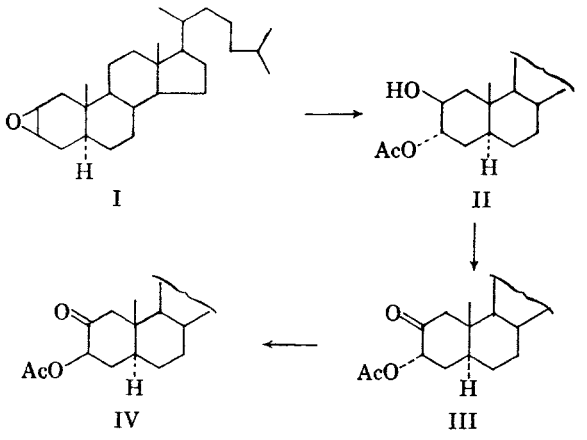
(6) (a) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953); (b) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953); (c) T. G. Halsall, R. Hodges, and E. R. H. Jones, *J. Chem. Soc.*, 3019 (1953); (d) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(7) A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935).

(8) L. F. Fieser and W. Y. Huang, *J. Am. Chem. Soc.*, **75**, 4837 (1953).

(9) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 4832 (1954).

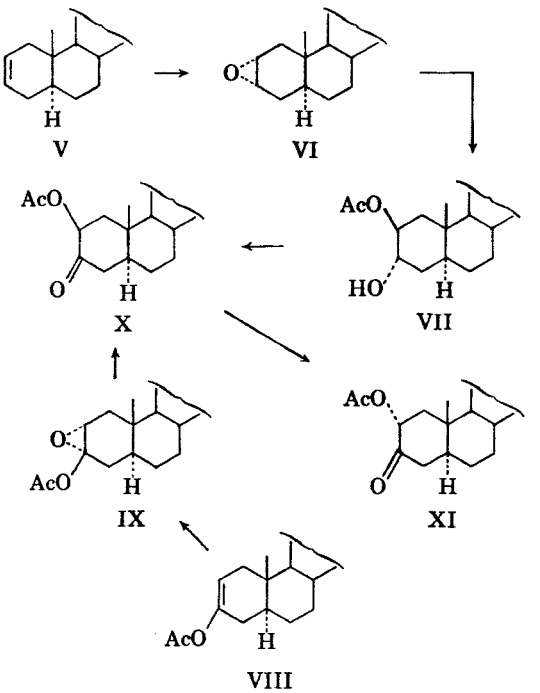
(10) A. Furst and Pl. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).



duced the known[10-12] 2β,3α-diacetoxycholestane, m.p. 141.2–142°, $[\alpha]_D$ +53.9°. 3α-Acetoxycholestane-2-one (III), m.p. 149–149.5° after purification, was prepared in quantitative yield by oxidation of the hydroxy acetate II with Jones' reagent.[6] Treatment of this axial α-acetoxy ketone with hydrobromic acid in acetic acid gave in only 50% yield 3β-acetoxycholestane-2-one (IV), m.p. 145.5–146°, $[\alpha]_D$ +75.5°, after purification. Either these conditions were not vigorous enough to effect complete isomerization or else equilibrium does not favor completely the equatorial isomer. This behavior is in marked contrast with that of the axial keto acetates X and XV which, because of 1,3-diaxial interactions with the C-19-methyl group, are much more susceptible to epimerization (see below). This authentic sample of 3β-acetoxycholestane-2-one (IV) was identical with the compound produced by treatment of 2α-bromocholestane-3-one with tetramethylammonium acetate (see below) as well as with the compound assigned this structure by Sheehan.[4]

Δ^2-Cholestene[13] (V), prepared by zinc–acetic acid reduction of the mixture of bromohydrins, on treatment with perbenzoic acid gave 2α,3α-oxidocholestane[10] (VI) which was cleaved to 2β-acetoxy-3α-hydroxycholestane[10] (VII) with acetic acid. Oxidation of this hydroxy acetate with Jones' reagent gave in only 17% yield 2β-acetoxycholestane-3-one (X), m.p. 145.3–146.3°, $[\alpha]_D$ +86.9°, after purification. The major product, obtained in 60% yield, was shown to be 2α-acetoxycholestane-3-one (XI), $[\alpha]_D$ +51.5°, m.p. 124.7–125.2°, after purification. Identical material was obtained in 67.5% yield by the isomerization of the 2β-isomer (X).

An alternative and more facile synthesis of this easily isomerized 2β-acetoxycholestane-3-one was realized by thermal rearrangement of the epoxy



acetate. Cholestanone enol acetate[14] (VIII) on treatment with perbenzoic acid gave, in 80% yield, 2α,3α-oxido-3β-acetoxycholestane (IX), m.p. 133–134.5°, $[\alpha]_D$ +16.5°, after purification. The α-orientation of the epoxide follows by analogy with other epoxidations of steroid olefins, attack occurring from the unhindered back side of the molecule. The epoxyacetate was smoothly rearranged to the axial acetoxy ketone by simply heating to 160° for five minutes. 2β-Acetoxycholestane-3-one, m.p. 147–148°, was thus obtained in 85% yield. The identity of this specimen with authentic material (see above) was established by mixed melting point and infrared spectral comparisons.[15]

The remaining pair of acetoxy ketones was prepared from Δ^3-cholestene (XII) which was ob-

(11) C. W. Shoppee, D. N. Jones, and G. H. R. Summers, *J. Chem. Soc.*, 3100 (1957).

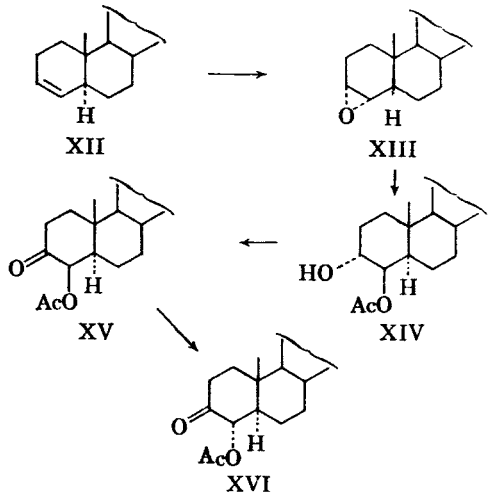
(12) R. E. Marker and L. Plambeck, Jr., *J. Am. Chem. Soc.*, 61, 1332 (1939).

(13) G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 4284 (1954).

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

(15) This case appears to constitute the first clear evidence of the stereospecificity of the thermal rearrangement of an epoxy acetate in a cyclic system. Some other examples of this type of reaction have been recorded. A. H. Soloway, W. J. Considine, D. K. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, 76, 2941 (1954), obtained 3β,17β-diacetoxyallopregnane-20-one in 81.5% yield by heating 17α,20β-epoxyallopregnane-3β,20α-diol diacetate at 235° for ten minutes. H. J. Shine and G. E. Hunt, *J. Am. Chem. Soc.*, 80, 2434 (1958), showed that the epoxide of cyclohexanone enol acetate rearranged to 2-acetoxycyclohexanone; and H. J. Shine and W. J. Heilman, Abstracts of Papers presented at Cleveland, Ohio, April 1960 meeting of the American Chemical Society, p. 18-O, demonstrated that 1-acetoxy-1,2-epoxy-4-methylcyclohexane rearranged, on heating to just 90°, to 2-acetoxy-4-methylcyclohexane of undefined stereochemistry. N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, 76, 2943 (1954), obtained 3β,16α-diacetoxyandrostane-17-one on heating 16α,17α-epoxyandrostane-3β,17β-diol diacetate at 200° for ten minutes. In this last case the conditions must have been severe enough to isomerize the 16β- to the 16α-isomer.

tained by zinc-acetic acid reduction of Δ^4-cholestene-3-one.[16] Perbenzoic acid oxidation of the olefin afforded 3α,4α-oxidocholestane[17] (XIII), which was cleaved to the diaxial hydroxy acetate[17] (XIV).



The latter substance was oxidized in 87% yield to 4β-acetoxycholestane-3-one (XV), m.p. 133.7–134.4, $[\alpha]_D$ +57°, after purification. Epimerization of this axial acetoxy ketone with hydrobromic acid in acetic acid gave an 89% yield of 4α-acetoxycholestane-3-one (XVI), m.p. 144–145°, $[\alpha]_D$ −3.7°, after purification.

Consideration of previous work and further related studies. Treatment of 2α-bromocholestane-3-one with potassium acetate in refluxing acetic acid has been reported[18] to give a 73% yield of an acetoxy ketone, m.p. 146°, $[\alpha]_D$ +27°. Later workers[2] obtained this product in 40% yield and showed it to be a complex of 2α- and 4α-acetoxycholestane-3-one.[2] In the present work a 46% yield of this product was realized. The remainder of the reaction mixture was fractionally crystallized, but no additional pure product could be isolated. The infrared spectrum of one fraction, m.p. 107–122°, obtained in 6% yield, strongly resembled that of pure 2α-acetoxycholestane-3-one (XI), m.p. 124.2–124.7°, the expected product from normal displacement of bromine. It should be pointed out that all combinations of the six isomeric acetoxy ketones, except that noted below, gave very large (20–30°) depressions of the melting points on admixture. That the 147–148°-compound is indeed a complex mixture of 2α- and 4α-acetoxycholestane-3-one was proved by mixing exactly equal quantities of the isomer (XI), m.p. 124.7–125.2°, and the 4α-isomer (XVI), m.p. 144–145°. Crystallization of the mixture from ethanol gave a quantitative yield of the complex acetoxy ketone, m.p. 149.0–149.3°, $[\alpha]_D$ +27°. That the complex is formed from equal parts of its components follows from its synthesis, the average of the optical rotations for the components (4α = −3.7°, 2α = +52°, av. = +27.8°; found + 27°) and integration of the area under certain parts of the NMR spectrum.[1] Fieser and Romero[2] reported that this 1:1 complex could not be separated by chromatography on alumina. In the present work, paper chromatography employing a phenoxyethanol-petroleum ether system also failed to effect any separation.

4α-Acetoxycholestane-3-one may be formed by S_N2' attack by acetate on the enolic form of 2α-bromocholestane-3-one. This product in combination with the product of normal displacement gives the easily isolated complex keto acetate, which is less soluble in ethanol than are its component parts. It is to be noted that pure 2α-acetoxycholestane-3-one was recovered unchanged after treatment with potassium acetate.

In view of the results obtained by displacement of bromine from 2α-bromocholestane-3-one with potassium acetate, it was of interest to study the displacement with tetramethylammonium acetate.[3] In refluxing acetone this reaction gave a 97% yield of a mixture of acetoxy ketones from which 3β-acetoxycholestane-2-one (IV), m.p. 141–145°, was isolated as the only crystalline product. Although the yield of pure crystalline material was only 12%, the oily residue gave a negative Beilstein test and its infrared spectrum strongly resembled that of the crystalline product, except for a band a 8.8 μ which might be attributed to contamination by 2α-acetoxycholestane-3-one. This unexpected behavior could be rationalized by envisaging initial attack of acetate at the carbonyl group with displacement of bromine to form 2β,3β-oxido-3α-acetoxycholestane followed by rearrangement to the observed product[19]; however, treatment of pure 2α-acetoxycholestane-3-one (XI) with tetramethylammonium acetate readily effected isomerization to the 3β-acetoxy-2-one (IV). The reaction of the bromo ketone thus may involve normal displacement by acetate followed by rearrangement, also presumably *via* the epoxy acetate.

The unexpected behavior noted above with tetramethylammonium acetate prompted us to examine its action in another case, namely with 4α-bromocholestane-3-one. This compound has been prepared[20] in 20% yield by chromous acetate reduction of 2,4-dibromocholestane-3-one.[21] In the present work it was discovered that a large excess of reductant acting for a short period of time gave a marked improvement in yield. Thus the dibromo

(16) J. McKenna, J. K. Norymberski, and R. D. Stubbs, *J. Chem. Soc.*, 2502 (1959).

(17) A. Furst and R. Scotoni, Jr., *Helv. Chim. Acta*, **36**, 1332 (1953).

(18) L. Ruzicka, Pl. A. Plattner, and R. Aeschbacher, *Helv. Chim. Acta*, **21**, 866 (1938).

(19) *Cf.* R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.*, 352 (1955).

(20) R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephenson, T. Walker, and B. M. Wilson, *J. Chem. Soc.*, 4356 (1956).

(21) A. L. Wilds and C. Djerassi, *J. Am. Chem. Soc.*, **68**, 1712 (1946).

compound when treated for ten minutes with freshly prepared (*in situ*) chromous acetate in acetic acid gave a 97% yield of 4α-bromocholestane-3-one, m.p. 139–149°. Recrystallization afforded in 78% yield material, m.p. 146–147.5° (reported[20] 144–146°). Chromatography of this material revealed a very slight contamination with cholestanone; a pure sample melted at 154.8–155.3°.

Treatment of 4α-bromocholestane-3-one with tetramethylammonium acetate in acetone at room temperature gave, in addition to some starting material, a 20% yield of Δ^4-cholestene-3-one, m.p. 78–80.5°, and a 4% yield of an acetoxy ketone, m.p. 144–147°, which was shown to be the 1:1 complex mentioned above. 4α-Acetoxycholestane-3-one was recovered unchanged after treatment with tetramethylammonium acetate.

Further consideration of the products described by previous workers follows. From the acyloin condensation of 2,3-secocholestane-2,3-dioic acid dimethyl ester, Sheehan and Erman[4] isolated, in 82% yield, an isomer to which they assigned the structure 3β-hydroxycholestane-2-one. This structure was confirmed by mixed melting point and infrared spectra comparisons of the acetate of their ketol with the authentic material prepared in the present work (see above). The second isomeric ketol, m.p. 120–125°, isolated by Sheehan and Erman in 5% yield and presumed to be the 2-hydroxy-3-keto compound, on acetylation afforded an acetoxy ketone which was shown by mixed melting point and infrared comparisons to be identical with the sharp melting 1:1 complex mixture of 2α- and 4α-acetoxycholestane-3-one obtained in the present work (see above). The possibility that rearrangement occurred during the acetylation of the ketol was ruled out by hydrolyzing the authentic 2α-acetoxy-3-keto compound (see above) to the ketol, m.p. 126.5–128.5°. Reacetylation by the procedure of Sheehan and Erman gave 2α-acetoxycholestane-3-one. None of the complex acetate was isolated. In order to rationalize the results of Sheehan and Erman, it may be assumed that the impure 2-hydroxy ketone, m.p. 120–125°, obtained from the acyloin condensation was contaminated with 4α-hydroxycholestane-3-one which could have arisen in the acyloin condensation from contaminating 3,4-secodiacid. Acetylation of this mixture of ketols then could have given the easily isolated complex acetate.

In 1944, Ruzicka[5] reduced and hydrolyzed the complex acetate in the belief that he was working with pure 2-acetoxycholestane-3-one. Catalytic hydrogenation of this compound could give a total of four hydroxy acetates: 2α-acetoxy-3α- and 3β-hydroxycholestane and 4α-acetoxy-3α- and 3β-hydroxycholestane. Ruzicka apparently isolated three of these, only one of which was crystalline and designated by him as compound "A." This substance on oxidation gave a keto acetate, m.p. 144–146°, $[\alpha]_D$ +1°, whose properties correspond most closely to those of 4α-acetoxycholestane-3-one (XVI), m.p. 144–145°, $[\alpha]_D$ −3.7°, prepared in the present work. Fieser and Stevenson[22] prepared 3β,4α-diacetoxycholestane, the properties of which, m.p. 162°, $[\alpha]_D$ +30°, are in good agreement with those of Ruzicka's diacetate, m.p. 161–162°, $[\alpha]_D$ +33°, made from hydroxy acetate "A." Compound "A" is therefore probably 3β-hydroxy-4α-acetoxycholestane. There is insufficient evidence to make structural assignments for the diols, m.p. 196–197° and 213–218°, resulting from hydrolysis of the other two noncrystalline hydroxyacetates, as well as the acetoxycholestanols "B" and "C" produced by catalytic reduction of the complex acetate (R-I)[23] under different conditions.

Wolff-Kishner reduction of the complex acetate gave the expected products, 2α- and 4α-cholestanol plus cholestane and "1-cholestanol" (R-II). The acetate of "1-cholestanol" (R-IIa) was isolated on catalytic hydrogenation of the complex acetate (R-I). Oxidation of this alcohol gave in 90% yield the ketone R-III, m.p. 120–120.5°, which could be reduced to cholestane. As the properties of this ketone did not agree with the then known 2-, 3- or 4-ketones, Ruzicka considered it to be cholestane-1-one. In the meantime, however, authentic cholestane-1-one, m.p. 85.5–86.5°, $[\alpha]_D$ +112°, was unambiguously synthesized,[24] and its properties obviously do not agree with those of R-III. It has been suggested[2,25] that R-II and R-III are 1:1 complexes of the 2- and 4-alcohols and ketones respectively. This is further borne out by the optical rotation data (2α-ol, +27°; 4α-ol, +4°; av., +15.5°; reported for "cholestane-1-ol" (R-II), +14°; 2-one, +50°; 4-one, +30°; av., +40°; reported for "cholestane-1-one (R-III), +41°).

Hydrolysis of the 1:1 complex (R-I) with methanolic potassium hydroxide afforded R-X which was characterized as an enediol because it gave a positive tetranitromethane test. On acetylation this "enediol" gave a 12% yield of an acetoxy ketone (R-VIIIa), m.p. 143.5–144°. Hydrolysis of the complex acetate R-I under milder conditions employing aqueous potassium carbonate gave a ketol R-VIII, m.p. 173–175°, which on acetylation also gave R-VIIIa. The 144° compound was assigned the 3-acetoxy-4-keto structure, but now it appears more likely to be 4α-acetoxycholestane-3-one (XVI), m.p. 144–145°, $[\alpha]_D$ −3.7°. Authentic

(22) L. F. Fieser and R. Stevenson, *J. Am. Chem. Soc.*, **76**, 1728 (1954).

(23) An R preceding a Roman numeral indicates the numbering employed in Ruzicka's article (ref. 5).

(24) P. Streibel and Ch. Tamm, *Helv. Chim. Acta*, **37**, 1094 (1954).

(25) Editor of Elsevier's *Encyclopedia of Organic Chemistry*, Series III, Vol. 14, supplement, Springer-Verlag, Berlin, 1959, p. 2417s.

3β-acetoxycholestane-4-one has a m.p. of 117–118.5°, $[\alpha]_D$ −22.9° ±4°.[26]

EXPERIMENTAL[27]

2β-Hydroxy-3α-acetoxycholestane (II). 2β,3β-Oxidocholestane[9] (2.0 g.), m.p. 90.4–91.1°, in 28 ml. of freshly distilled acetic acid was heated on the steam bath for 3 hr. following the procedure of Furst and Plattner[10] for preparing 2β-acetoxy-3α-hydroxycholestane. The acetic acid was removed under reduced pressure, and the resulting oil crystallized from 95% ethanol to give 0.75 g. of fine needles, m.p. (dimorphic) 111–112° and 138.7–139°, and 0.61 g. (second crop), m.p. 112–112.5° and 137.2–138.5°. Recrystallization from 95% ethanol gave colorless needles, m.p. 138.7–139.2°, $[\alpha]_D$ +42.2° (1.72 chf.). The lower melting point is not easily detected on pure samples.

Anal. Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 78.0; H, 11.2.

2β,3α-Diacetoxycholestane. 2β-Hydroxy-3α-acetoxycholestane (II), m.p. 138.7–139°, was acetylated with acetic anhydride in pyridine at room temperature to give the diacetate, m.p. 141.2–142°, in 89% yield. One recrystallization from acetone-methanol gave colorless thick elongated prisms, m.p. 141.5–142.1°, $[\alpha]_D$ +53.9° (1.87 chf.). The reported properties are m.p. 133–135°, $[\alpha]_D$ +56°[11]; m.p. 133–135° [12]; and m.p. 135°, $[\alpha]_D$ +57.4°.[10]

In a similar manner, 2β-acetoxy-3α-hydroxycholestane (VII), m.p. 113–114° (see below), was quantitatively acetylated to give material, m.p. 140–141°, which on recrystallization as above gave a compound, m.p. 140.3–141.5°, undepressed on admixture with the diacetate described above.

3α-Acetoxycholestane-2-one (III). This compound was prepared according to a procedure for the oxidation of Δ^5-pregnene-3β-ol-20-one to the dione.[6d]

To 0.30 g. of 2β-hydroxy-3α-acetoxycholestane (II), m.p. 138.7–139°, dissolved in 30 ml. of acetone (distilled from a mixture of Drierite and potassium permanganate) was added dropwise 0.19 ml. of standard chromic acid solution[28] over a 1-min. period with rapid swirling. After an additional 1 min. the reaction was quenched in 5% aqueous potassium carbonate solution and extracted with ether. The combined ether extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to give a quantitative yield of colorless elongated prisms, m.p. 149–149.5°. Two recrystallizations from acetone-methanol gave material m.p. 150.2–150.9°, $[\alpha]_D$ +53.7° (1.60 chloroform).

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.5; H, 10.9.

3β-Acetoxycholestane-2-one (IV). (*a*) *By isomerization of the 3α-isomer.* A solution of 0.30 g. of 3α-acetoxycholestane-2-one (III), m.p. 149–149.5°, in 30 ml. of acetic acid containing 1 drop of 48% hydrobromic acid was allowed to stand at room temperature for 24 hr. The solvent was removed at reduced pressure, the crystalline residue was taken up in absolute ethanol, and the slight yellow color was removed with Darco; water was added to the cloud point and crystallization allowed to proceed slowly overnight. There was deposited 0.22 g. of a mixture of elongated prisms and clusters of needles, m.p. 122–134°. Since isomerization was apparently incomplete, the 0.22 g. was dissolved in 3 ml. of acetic acid containing 0.1 ml. of 48% hydrobromic acid and heated on the steam bath for 15 min., then allowed to stand at room temperature overnight. The solvents were removed and the residue crystallized as before to afford 0.16 g. (50% yield), m.p. 140–143°. Recrystallization from 95% ethanol gave 0.10 g., m.p. 144.7–146.0°. Another recrystallization gave 0.09 g., m.p. 145.5–146.1°, $[\alpha]_D$ +75.5° (1.57 chloroform).

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.1; H, 10.85.

(*b*) *From 2α-bromocholestane-3-one.* A solution of 1.97 g. of 2α-bromocholestane-3-one, m.p. 168.3–168.4°, in 100 ml. of acetone (freshly distilled from Drierite) was stirred for 48 hr. with 2.0 g. of dry, powdered tetramethylammonium acetate.[29] The solution was refluxed for 2 hr., concentrated to 20 ml., diluted with water, and extracted with ether. The combined ether extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to give 1.80 g. of a thick yellow oil which slowly crystallized. Chromatography of this material on 70 g. of Florisil gave, in the fraction eluted with 70% benzene in petroleum ether, an 80% recovery of crystalline material, m.p. 111–133°. Three recrystallizations from 95% ethanol gave 0.22 g. (12%) of rectangular plates, m.p. 141–145°, undepressed on admixture with authentic 3β-acetoxycholestane-2-one (IV) prepared as described above. The infrared spectra of the crude reaction mixture and the final product were very similar except for a band at 8.8 μ which appeared in the former and might be attributed to some contaminating 2α-acetoxycholestane-3-one, the expected product.

2β-Acetoxy-3α-hydroxycholestane (VII) was prepared according to the procedure of Furst and Plattner[10] by acetic acid cleavage of the α-epoxide. The product obtained in 70% yield after chromatography on Florisil, had m.p. 110–114°. Furst and Plattner[10] report a 35% yield, m.p. 95°, which after four more crystallizations melted at 113°.

2β-Acetoxycholestane-3-one (X). *By oxidation of the hydroxyacetate.* 2α,3α,-Oxidocholestane[10] (VI) (1.50 g.) was cleaved with acetic acid as described above to the hydroxy acetate which without purification was oxidized to the ketone by treatment with 1.12 ml. of chromic acid solution as described above for 3α-acetoxycholestane-2-one. The resulting clear yellow glass (1.68 g.) was taken up in absolute methanol, decolorized with Darco, and cooled slowly to deposit 0.29 g. (17%) of fine needles, m.p. 141–145°. This material was recrystallized twice from 95% ethanol to give colorless needles, m.p. 145.3–146.3°, $[\alpha]_D$ + 86.9° (1.79 chloroform). On admixture with IV, m.p. 145–146°, the melting point was depressed below 136°.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.2; H, 10.8.

The mother liquors from the preceding experiment were chromatographed on 70 g. of Florisil. Elution with benzene and with 95% benzene in ether gave 1.03 g. (60%) of *2α-acetoxycholestane-3-one* (XI) as colorless plates which, after one recrystallization from 95% ethanol, melted at 122–124°. A sample recrystallized twice more from 95% ethanol had m.p. 124.7–125.2°, $[\alpha]_D$ +51.55° (1.67 chloroform).

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.1; H, 10.7.

Isomerization of 2β-acetoxycholestane-3-one (X). To 93.4 mg. of 2β-acetoxycholestane-3-one (X), m.p. 147–148°, in 2 ml. of glacial acetic acid was added 1 small drop of 48% hydrobromic acid. After 38 hr. at room temperature the solvent was evaporated at reduced pressure and the resulting pale yellow crystals were recrystallized from absolute ethanol to give 63 mg. (67.5% yield) of small, irregular colorless plates, m.p. 124.2–124.7°, undepressed on admixture with

(26) S. Lieberman and D. K. Fukushima, *J. Am. Chem. Soc.*, **72**, 5211 (1950).

(27) Melting points are corrected for stem exposure. Infrared measurements were made on a Baird double-beam spectrophotometer (chloroform solvent). The petroleum ether referred to is the fraction with b.p. 60–68°.

(28) The standard chromic acid solution was prepared by dissolving 13.45 g. of anhydrous chromium trioxide in 11.5 ml. of concd. sulfuric acid and diluting to 50 ml. with water.

(29) Tetramethylammonium acetate was prepared by acidifying a 10% solution of tetramethylammonium hydroxide (Eastman White Label) with acetic acid to a litmus paper end point and then evaporating to dryness at 0.3 mm The dry, flaky foam was used without further purification.

the analytical specimen of the 2α-isomer described above. The infrared spectra of the two specimens were identical. A second crop, amounting to 10 mg., m.p. 121.5–122.5°, was obtained from the mother liquors.

2α,3α-Oxido-3β-acetoxycholestane (IX). To 1.82 g. of cholestanone enol acetate,[14] m.p. 89–90°, dissolved in 10 ml. of chloroform and cooled to −5°, was added 0.011 mole of perbenzoic acid in 20 ml. of chloroform, also cooled to −5°. After 42 hr. at −12°, iodometric titration revealed that 0.0044 mole of peracid had been consumed. The reaction mixture was poured into cold saturated sodium bicarbonate solution, shaken for 5 min., and extracted with ether. The ether extracts were combined, washed with water, dried over anhydrous sodium sulfate, and evaporated to give 2.07 g. of crystalline product, which was recrystallized from ether to give 1.28 g. of fine colorless prisms, m.p. 134–136.5°, unchanged after two further recrystallizations. A second crop of 0.23 g., m.p. 130–134.5°, brought the total yield to 1.51 g. (80%). A sample, after three recrystallizations from ether, was obtained as colorless prisms, m.p. 133–134.5° (at a rate of heating of 2° per min.), $[\alpha]_D$ +16.5° (1.60 chloroform).

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 78.32; H, 10.88. Found: C, 78.1; H, 10.8.

2β-Acetoxycholestane-3-one (X). *By isomerization of the oxido acetate* (IX). A 0.33-g. sample of 2α,3α-oxido-3β-acetoxycholestane, m.p. 131.5–134°, was placed in a 15-ml. centrifuge tube which was immersed for 5 min. in an oil bath maintained at 160°. On cooling, the product spontaneously crystallized. Recrystallization from absolute ethanol gave 0.25 g. (first crop), m.p. 147–148.0°, and 0.03 g. (second crop), m.p. 144.5–147°, for a total of 0.28 g. (85% yield). A sample, recrystallized twice from 95% ethanol, was obtained as colorless prisms, m.p. 147.5–147.9°, undepressed on admixture with the acetoxy ketone prepared by the oxidation of the hydroxy acetate (see above). The infrared spectra of these two specimens were identical.

4β-Acetoxycholestane-3-one (XV) was prepared in the same manner as described above for 3α-acetoxycholestane-2-one (III).

Jones' reagent (0.24 ml.) was added to an acetone solution of 0.385 g. of 3α-hydroxy-4β-acetoxycholestane[17] (XIV), m.p. 157.7–158.7°, and processed as described above to give clusters of short needles from 95% ethanol: first crop, 0.113 g., m.p. 133.7–134.4°, $[\alpha]_D$ +57° (1.16 chloroform); second crop, 0.067 g., m.p. 128–132°; third crop, 0.152 g., m.p. 127–131.5°. The total yield thus was 0.331 g. (86.5%). The first crop material was analyzed.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.6; H, 10.9.

4α-Acetoxycholestane-3-one (XVI). To 18 mg. of 4β-acetoxycholestane-3-one, m.p. 133–134°, in 0.5 ml. of glacial acetic acid was added a trace of 48% hydrobromic acid and the solution was allowed to stand at room temperature overnight. The crystalline residue, obtained on removal of the solvent, was recrystallized from 95% ethanol to give 16 mg. (89% yield) of long colorless needles, m.p. 144–145°, $[\alpha]_D$ −3.7° (1.08 chloroform). Recrystallization did not raise the melting point. On admixture with 2α- and 4α-acetoxycholestane-3-one complex, the m.p. was 135–140.5°.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.3; H, 10.9.

The 2α- and 4α-acetoxycholestane-3-one complex from the pure components. In a drop of hot absolute ethanol were dissolved 2.1 mg. of 2α-acetoxycholestane-3-one (XI), m.p. 124.7–125.2°, and 2.1 mg. of 4α-acetoxycholestane-3-one (XVI), m.p. 144–145°. On cooling, long needles, m.p. 149.0–149.3°, $[\alpha]_D$ +27°, were deposited in quantitative yield. The melting point was undepressed on admixture with the product, m.p. 147–148.4°, prepared by the action of potassium acetate on 2α-bromocholestane-3-one,[2,18] and the infrared spectra of the two specimens were identical.

The complex was chromatographed by the technique of Neher and Wettstein[30] on Whatman No. 1 paper impregnated with 50:50 methanol-phenoxyethanol. Petroleum ether (b.p. 90–100°) was employed as the mobile phase. The complex appeared (after development with Zimmerman reagent) as a single unresolved spot with an R_f value of 0.160.

4α-Bromocholestane-3-one. A modification of the procedure of Evans and co-workers[20] was employed.

One side neck of a 500-ml. three-necked flask was fitted with a nitrogen inlet and an outlet tube, and the other side neck was fitted with a Y tube, one branch of which was connected to a Jones' reductor and the other to a 50-ml. dropping funnel. The center neck of the flask was fitted with a medium porosity sintered glass filter stick which could be raised and lowered through a rubber stopper. The top of the filter stick was connected by a rubber tube to a disposal flask.

The flask was thoroughly flushed with dry nitrogen and the Jones' reductor (a 2-cm. diameter chromatography column filled to a height of 40 cm. with Baker's AR 20 mesh zinc which had been amalgamated with mercuric chloride) was filled with 1*N* sulfuric acid. A solution of 3.28 g. (0.0207 mole) of Baker's AR chromic chloride in 4.4 ml. of water containing 1.1 ml. of 2*N* sulfuric acid was run through the Jones reductor, followed by water in such a way that the liquid level never dropped below the top surface of the zinc. As soon as all the bright blue solution of chromous chloride had passed into the flask, the reductor was turned off and a solution of 9.2 g. (0.091 mole) of anhydrous sodium acetate in 18 ml. of deoxygenated water was introduced into the flask from the dropping funnel without stirring, which resulted in the formation of fairly large crystals of deep red chromous acetate. After 5 min., the solution was stirred by a magnetic stirring bar, the filter stick was lowered, the gas outlet tube closed, and nitrogen pressure applied to force the filtrate through the filter stick, leaving a dark red precipitate. In the same manner this precipitate was washed with two 50-ml. portions and one 25-ml. portion of water; then with 50 ml. of 95% ethanol and two 25-ml. portions of ether. Finally nitrogen was passed through the flask until the brick red chromous acetate was dry. To this dry powder was added, with stirring, 1.89 g. of 2α,4α-dibromocholestane-3-one, m.p. 190–191°, dissolved in 16 ml. of chloroform (AR grade) and 38 ml. of acetic acid. With a rapid stream of nitrogen passing through the flask, stirring was continued for 10 min., which caused some evaporation of chloroform and precipitation of the product. Air was then blown through the filter stick to oxidize excess chromous ion. The dark slurry was taken up in 150 ml. of ether and washed with water, dilute sodium bicarbonate solution, water, and saturated sodium chloride solution. After drying over anhydrous sodium sulfate, the ether was removed to give 1.57 g. (97% yield) of colorless needles, m.p. 139–149°. Recrystallization from ethyl acetate–95% ethanol gave 1.26 g. (76% yield), m.p. 146–147.5°, and 0.258 g. (second crop), m.p. 137–140°. A sample exhibited the following melting points on successive recrystallizations: 146.7–148.2°, 151–153.3°, 153.3–154.3°, and 154.8–155.3° Evans and co-workers[20] reported a 20% yield of material melting at 144–146°. The infrared and NMR spectra[1] of the 146–147.5° material indicated that it was homogeneous, but careful chromatography and repeated crystallization suggested that it was slightly contaminated with cholestanone.

Reaction of 4α-bromocholestane-3-one with tetramethylammonium acetate. A mixture of 0.50 g. of 4α-bromocholestane-3-one, m.p. 144–145.5°, and 0.50 g. of tetramethylammonium acetate (see above) was rigorously dried at 80°/0.05 mm. and added with stirring to 25 ml. of anhydrous acetone in a flame-dried flask under a dry nitrogen atmosphere. There was an immediate cloudiness in the solution and soon white flakes of tetramethylammonium bromide were

(30) R. Neher and A. Wettstein, *Helv. Chim. Acta*, 35, 276 (1952).

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.

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(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]

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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

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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.*