All three showed absorption characteristic of *p*-nitrobenzylidene acetals. The third fraction crystallized on standing and was recrystallized twice from hexane. The large yellow crystals of **2-(1-hydroxy-*n*-butyl)cyclohexanol *p*-nitrobenzylidene acetal** melted at 62–63°.

Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59. Found: C, 67.03; H, 7.57.

The crude benzylidene acetals derived from 2-(1-hydroxy-*n*-butyl)cyclohexanol (**13**) and perhydro(4a,β,8aβ)naphthalene-1β,8α-diol (**9**), as well as the *p*-nitrobenzylidene acetal of the latter, obtained by this general procedure, showed infrared absorption characteristic of these acetals but could not be obtained crystalline, even after chromatographic fractionation on alumina.

2-(*n*-Butyryl)cyclohexanone (**14a**).—The copper salt of the diketone was prepared in 55% yield, m.p. 135–140°, by the Jones oxidation[2] of 2-(1-hydroxy-*n*-butyl)cyclohexanone. This was recrystallized once from hexane, m.p. 151–152°,[33] and then decomposed by stirring for several hours with a mixture of methylene chloride and 4 *N* sulfuric acid. The product **14a**, collected at 131–132° (20 mm.), $n^{32}D$ 1.4928–1.4932, was obtained in 79% yield (from recrystallized copper salt). In the infrared spectrum of the neat liquid, absorption peaks were evident at 3.20 (w, shoulder), 3.79 (w), 5.82 (m, shoulder), 5.86 (m), 6.25 (s, broad), 7.06 (m), and 9.38 μ (m). The n.m.r. spectrum exhibited a singlet at 16.28 p.p.m. (OH), a multiplet centered at 2.38 p.p.m. (allylic protons and hydrogens on the carbons adjacent to the carbonyls), a triplet centered at 0.98 p.p.m. (CH_3, J = 7 c.p.s.), and a broad signal centered at 1.72 p.p.m. (remaining cyclic and acylic protons).

The copper salt was also obtained, in 53% yield, by oxidation[2] of the diol **13**. Recrystallized to constant melting point from hexane, the compound was obtained as gray-green plates possessing a silvery luster, m.p. 153–154.5°,[33] λ_{max}^{Nujol} 6.35 μ (s, C=O st.).

(33) This compound has previously been prepared by the condensation of a butyric ester or anhydride with cyclohexanone. J. T. Adams and C. R. Hauser [*J. Am. Chem. Soc.*, **67**, 284 (1945)] reported b.p. 133–134° (20 mm.) for the diketone and m.p. 156–157° for its gray copper salt.

Acknowledgment.—We would like to thank the Argonne National Laboratory for financial support with a research and development subcontract (no. 31-109-38-889), the National Science Foundation for aid through its Undergraduate Science Education program, and the National Cancer Institute for a Fellowship (to I. A. K.) during which part of this investigation was completed. We are also indebted to Professor David Lavie of The Weizmann Institute of Science for the use of the institute's facilities in part of the experimental work and to Dr. Youval Shvo, of the same institute, for determining and interpreting the n.m.r. spectra.

Steroids. CCLI. Lead Tetraacetate Oxidation of 17β-Hydroxy-5α-androst-1-en-3-one Acetate[1]

STEPHEN KAUFMANN

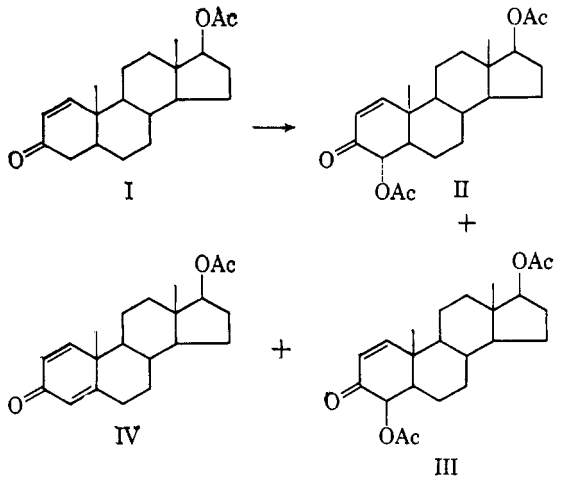
The Research Laboratories of Syntex, S. A., Apartado 2679, Mexico, D. F., Mexico

Received November 13, 1963

Oxidation of 17β-hydroxy-5α-androst-1-en-3-one acetate (I) with lead tetraacetate gave a mixture of 4α,17β-dihydroxy-5α-androst-1-en-3-one diacetate (II), 4β,17β-dihydroxy-5α-androst-1-en-3-one diacetate (III), and 17β-hydroxyandrosta-1,4-dien-3-one acetate (IV). Alkaline hydrolysis of II and III resulted in the formation of 4-hydroxytestosterone. Proof for the assignment of the steric configuration of the epimeric 4-acetoxy groups in II and III has been presented.

The reaction of ring A α,β-unsaturated keto steroids with lead tetraacetate has been studied in the past. The most important representatives of this group, the Δ^4-3-keto steroids have been subjected to the oxidation with this reagent by several investigators.[2,3] It has been established that oxidation results mainly in the introduction of an acetoxy group into the 2α- and 2β-positions and the formation of the corresponding $\Delta^{1,4}$-3-ketone to a lesser degree. More recently,[4] the lead tetraacetate oxidation of 17β-acetoxy-5α-estr-1(10)-en-2-one has been described, which yields a mixture of epimeric 3-acetoxy compounds.

In analogy, we have investigated the behavior of a Δ^1-3-keto steroid with lead tetraacetate, whereby attack on C-4 could be expected. As a suitable compound, we selected the acetate of 17β-hydroxy-5α-androst-1-en-3-one (I), the Δ^1 isomer of testosterone acetate. In accordance with expectations, the 4α,-17β-dihydroxy-5α-androst-1-en-3-one diacetate (II) and 4β,17β-dihydroxy-5α-androst-1-en-3-one diacetate (III) could be isolated from the reaction mixture together with the $\Delta^{1,4}$-3-ketone (IV). The less soluble β isomer (III) was separated by direct crystallization, whereas the α isomer (II) and the doubly unsaturated ketone (IV) could be obtained only by chromatography of the mother liquors. It is significant that the yield of IV is considerably higher (about 20%) than that obtained by lead tetraacetate oxidation of testosterone acetate,[3] probably because of the easier removal of the



(1) Steroids CCL: J. A. Edwards, M. C. Calzada, and A. Bowers, *J. Med. Chem.*, in press.

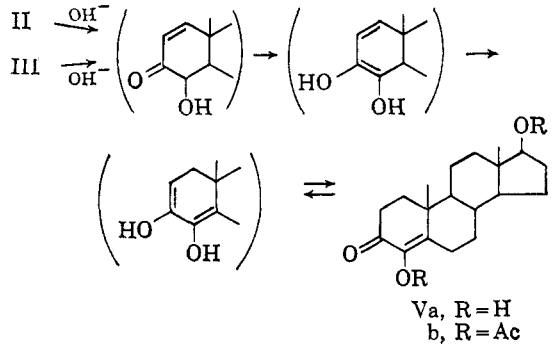
(2) (a) G. Erhart, M. Ruschig, and W. Aumüller, *Angew. Chem.*, **52**, 363 (1939); (b) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **27**, 948 (1944); (c) F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953).

(3) R. L. Clarke, K. Dobriner, A. Mooradian, and C. M. Martini, *ibid.*, **77**, 661 (1955).

(4) J. Fishman, *J. Org. Chem.*, **28**, 1528 (1963).

5α-hydrogen in comparison to the secondary hydrogens at C-1.

The structures of II and III have been established through alkaline hydrolysis, whereby both compounds are converted to the known 4-hydroxytestosterone (Va). Under these conditions, the Δ^1 double bond shifts through different enol intermediates, which can be formulated as follows.



Va, R=H
b, R=Ac

The configuration of the 4-acetoxy group has been determined in compound II as α and in compound III as β, on the basis of molecular rotation changes relative to the parent compound I (see Table I). It was

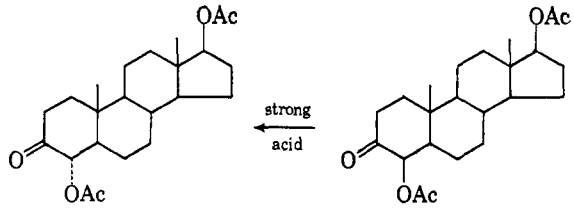
TABLE I

Compound	MD	ΔMD	A	B
I	+148.8			
II	+126.8	−22		
III	+396.9	+248	+113	+135
17β-Hydroxy-5α-androstan-3-one acetate	+86.3			
VI	−102.2	−188.5		
VII	+261.3	+175.0	−6.7	+181.7

first pointed out by Barton and Klyne[5] and later by Stokes and Bergmann[6] that displacement of a hydrogen on C-4 by a hydroxy or acetoxy group in the α-position has a negative contribution to the optical rotation, whereas substitution in the isomeric β-position is followed by an increase in rotation. Following the reasoning of Stokes and Bergman,[6] if the vicinal effect is represented by "A" and the contribution of the new asymmetric center by "B", the α-substitution changes the molecular rotation by "A − B" and the β-substitution by "A + B". The calculated "A" and "B" values for compounds II and III and for VI and VII are shown in Table I.

Further proof for the α-position of the 4-acetoxy group in II has been obtained by hydrogenating the latter to the known[7] 4α,17β-dihydroxy-5α-androstan-3-one diacetate (VI) with palladium–charcoal catalyst. Under the same conditions, compound III is transformed into the β isomer, 4β,17β-dihydroxy-5α-androstan-3-one diacetate (VII). Compound VII is unstable in strong acidic medium (acetic acid and hydrobromic acid) and is isomerized to the more stable 4α-acetoxy compound VI. The chair conformation of ring A favors the equatorial configuration of the substituents on C-4. It is remarkable that the Δ^1-unsaturated analog III remains unchanged by treatment with *p*-toluenesulfonic acid or potassium acetate in acetic acid, which means that the β isomer is thermodynamically as stable as the α isomer.[8]

The ΔMD values (Table I) of VI and VII compared with the parent compound 17β-hydroxy-5α-androstan-3-one acetate are in good agreement with the theory. The "B" values for II and III (+135) and for VI and VII (+181.7) are of the same magnitude, as should be expected on the basis of the rules given by Stokes and Bergmann.[6] On the other hand, it is interesting to note that the vicinal effect on "A" of the $-\overset{O}{\overset{\|}{C}}CH_2-$ moiety is negative and the one of $-\overset{O}{\overset{\|}{C}}CH{=}CH-$ positive.



VI VII

The ultraviolet absorption of compound III shows a λ_{max} at 235 mμ, whereas the α isomer II has the same λ_{max} (at 230 mμ) as the parent compound I. The bathochromic shift caused by the β-substitution confirms the fact that the latter is accompanied by strain in ring A.

Experimental[9]

4α,17β-Dihydroxy-5α-androst-1-en-3-one Diacetate (II), 4β,-17β-Dihydroxy-5α-androst-1-en-3-one Diacetate (III), and 17β-Hydroxyandrosta-1,4-dien-3-one Acetate (IV).—A solution of 20 g. of 17β-hydroxy-5α-androst-1-en-3-one acetate (I) in 800 ml. of glacial acetic acid was heated on the steam bath and 24 g. of lead tetraacetate was added in a 6-g. portion every hour. The heating was continued for an additional hour and the reaction mixture was concentrated under vacuum to dryness. Water (4 l.) was added and the oily precipitate was extracted with several portions of methylene chloride. The organic layer was washed with water and with dilute sodium hydroxide solution, and dried with anhydrous sodium sulfate; the solvent was evaporated to dryness. The residual gummy material (21 g.) was dissolved in 200 ml. of methanol. Water was added until crystallization started, which was completed after standing and yielded 2.5 g. of 4β,17β-dihydroxy-5α-androst-1-en-3-one diacetate (III). Recrystallization from methanol yielded 2.1 g. of pure product, m.p. 242–244°, $[\alpha]D$ +102.3°; $\lambda_{max}^{C_2H_5OH}$ 235 mμ (log ε 4.05); $\lambda_{max}^{CCl_4}$ 3.42, 5.70, 5.90, 7.30, and 8.16 μ.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.15; H, 8.31.

The mother liquors of III were concentrated to dryness and the oily residue (18 g.) was chromatographed on 500 g. of silica gel. Elution with benzene–ethyl acetate (9:1) gave in the first fractions an oily material which crystallized after addition of ether. Two recrystallizations from methanol yielded 0.85 g. of pure 4α,17β-dihydroxy-5α-androst-1-en-3-one diacetate (II), m.p. 191–192°, $[\alpha]D$ +32.7°; $\lambda_{max}^{C_2H_5OH}$ 230 mμ (log ε 3.95); $\lambda_{max}^{CCl_4}$ 3.42, 5.69, 5.84, 7.27, and 8.10 μ.

(5) D. H. R. Barton and W. Klyne, *Chem. Ind.* (London), 755 (1948).

(6) W. M. Stokes and W. Bergmann, *J. Org. Chem.*, **17**, 1194 (1952).

(7) R. Gardi, P. P. Castelli, and A. Ercoli, *Tetrahedron Letters*, 499 (1962).[11]

(8) On the contrary, 2β-hydroxytestosterone diacetate is epimerized to 2α-hydroxytestosterone diacetate by refluxing with potassium acetate in acetic acid solution.[4]

(9) All melting points are corrected. Optical rotations were measured in chloroform, ultraviolet absorption spectra in 95% ethanol, and infrared absorption spectra in carbon tetrachloride. We are indebted to Dr. C. Zapata and his staff for these determinations. Microanalyses were performed by Dr. G. M. Maciak (Midwest Microlab, Inc., Indianapolis, Ind.).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.02; H, 8.30.

Continued elution with benzene–ethyl acetate (9:1) yielded a crystalline material (3.9 g.) which after recrystallization from methanol proved to be identical with 17β-hydroxyandrosta-1,4-dien-3-one acetate (IV) by mixture melting point comparison with an authentic sample. The melting point was 152–153°, $[\alpha]_D$ +32°; $\lambda_{max}^{C_2H_5OH}$ 244 mμ (log ε 4.18); lit.[10] m.p. 151–152°, $[\alpha]_D$ +28°.

4-Hydroxytestosterone (Va).—A solution of 1 g. of 4α,17β-dihydroxy-5α-androst-1-en-3-one diacetate (II) in 50 ml. of methanol was treated with 5 ml. of a 20% sodium hydroxide solution. The mixture was heated under reflux for 1 hr. The slightly yellow solution was poured into water, acidified with hydrochloric acid, and extracted with ether. The ether solution, after drying, was concentrated to a small volume, whereby the 4-hydroxytestosterone (Va) crystallized. After recrystallization from methanol–water, 0.45 g. of pure product was obtained, m.p. 216.5–218°, $\lambda_{max}^{C_2H_5OH}$ 278 mμ (log ε 4.076), lit.[11] m.p. 222–223°.

In the same way, 4-hydroxytestosterone was obtained by saponification of 4β,17β-dihydroxy-5α-androst-1-en-3-one diacetate (III).

Diacetate (Vb).—The diacetate was obtained in the usual way by acetylation with acetic anhydride–pyridine at room temperature. It melted at 168.5–169.5°, $[\alpha]_D$ +96.5°, $\lambda_{max}^{C_2H_5OH}$ 246 mμ (log ε 4.135); lit.[11] m.p. 170–172°, $[\alpha]_D$ +105°, $\lambda_{max}^{C_2H_5OH}$ 246 mμ (log ε 4.19). There was no depression of melting point by admixture with an authentic sample of 4-hydroxytestosterone diacetate.

4β,17β-Dihydroxy-5α-androstan-3-one Diacetate (VII).—A solution of 1 g. of 4β,17β-dihydroxy-5α-androst-1-en-3-one diacetate (III) in 150 ml. of ethyl acetate was hydrogenated under 30-p.s.i. pressure with 0.1 g. of 5% palladized charcoal catalyst. After 1 hr. the catalyst was separated by filtration and the filtrate was concentrated to dryness. The crystalline residue was recrystallized from ether–hexane to give 0.85 g. of pure 4β,17β-dihydroxy-5α-androstan-3-one diacetate (VII), m.p. 166–169.5°, $[\alpha]_D$ +67°; $\lambda_{max}^{CCl_4}$ 3.63, 5.76, 7.29, and 8.20 μ.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.77. Found: C, 70.63; H, 8.70.

4α,17β-Dihydroxy-5α-androstan-3-one Diacetate (VI). A. From 4α,17β-Dihydroxy-5α-androst-1-en-3-one Diacetate (II).—Hydrogenation of 0.5 g. of compound II in the above-described manner and crystallization from ether–hexane gave 0.3 g. of pure 4α,17β-dihydroxy-5α-androstan-3-one diacetate (VI), m.p. 197.5–198°, $[\alpha]_D$ −26.2°; $\lambda_{max}^{CCl_4}$ 3.43, 5.74, 7.27, and 8.10 μ; lit.[7] m.p. 196.5–197.50, $[\alpha]_D$ −24°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.77. Found: C, 70.76; H, 8.68.

B. From 4β,17β-Dihydroxy-5α-androstan-3-one Diacetate (VII).—A solution of 1 g. of VII in 50 ml. of glacial acetic acid was treated with a saturated solution of 1 ml. of hydrobromic acid in glacial acetic acid. The mixture was left to stand overnight, after which it was poured into water and extracted with ether. The ether solution was washed to neutrality, dried, and concentrated to dryness. Recrystallization of the residue from ether–hexane afforded 0.82 g. of 4α,17β-dihydroxy-5α-androstan-3-one diacetate (VI), m.p. 197.5–198°, $[\alpha]_D$ −24.7°.

The products obtained by methods A and B were identical by infrared spectral comparison and no depression was observed in the mixture melting point.

(10) H. H. Inhoffen, G. Zühlsdorff, and Huang-Minlon, *Ber.*, **73**, 451 (1950).

(11) B. Camerino, B. Patelli, and A. Vercellone, *J. Am. Chem. Soc.*, **78**, 3541 (1956).

Reaction of Nitrosyl Chloride with Steroid 5-Enes.[1] Nuclear Magnetic Resonance as a Stereochemical Tool in Steroids

ALFRED HASSNER AND CLAYTON HEATHCOCK[1d]

Department of Chemistry, University of Colorado, Boulder, Colorado

Received September 10, 1963

Steroid 5-enes, on treatment with an excess of nitrosyl chloride, give 5α-chloro-6β-nitro steroids in good yield. These nitrochloro adducts are transformed by pyridine into the corresponding 6-nitro-5-enes. The latter are reduced stereospecifically by sodium borohydride to 6α-nitro 5α-steroids. 6β-Nitro-5α-chlorocholestan-3β-ol acetate reacts with chromous chloride in methanolic hydrochloric acid to give 6-oximino-5α-methoxycholestan-3β-ol acetate. It is shown that the half-width of a band in the n.m.r. may be correlated with the conformation of the proton giving rise to the band. Thus, equatorial protons give rise to a narrow band (5–12 c.p.s.), while axial protons give a broad band (15–30 c.p.s.).

It has been shown by Closs and Brois that olefins may be transformed *via* their nitrosyl chloride adducts into aziridines.[2] In connection with our interest in the preparation of steroidal aziridines,[3] we investigated the reaction of nitrosyl chloride with some steroid 5-enes. Although nitrosyl chloride has been widely used in the terpene field,[4] it had apparently found no application in steroids.[5]

Cholesteryl acetate (**1a**) reacts with excess nitrosyl chloride at 0° in methylene chloride or carbon tetrachloride to give in 85% yield a crystalline product, m.p. 142–143°, for which structure **2a** is suggested on the basis of elemental analysis and characteristic nitro absorption bands in the infrared (1559, 1370, 864, and 640 cm.$^{-1}$).[5,6] Furthermore, the ultraviolet spectrum of **2a** in neutral and basic medium is very similar to that of nitrocyclohexane. On treatment with pyridine at room temperature, **2a** is transformed into the known 6-nitrocholesteryl acetate (**4a**).[5,6] Methanolic hydrochloric acid converts the acetate **2a** into the corresponding alcohol **3a**. Similar transformations are observed with 5-androsten-3β-ol-17-one acetate (**1b**), methyl 3β-acetoxy-5-cholenate (**1c**), and 5-pregnen-3β-ol-20-one formate (**1d**). The 5α,6β-configuration in **2a** has been assigned largely because ready elimination of

(1)(a) Nitro Steroids. II. Paper I: A. Hassner and J. M. Larkin, *J. Am. Chem. Soc.*, **85**, 2181 (1963). (b) This investigation was supported in part by Public Health Service Grant CY-4474, from the National Cancer Institute. (c) Presented in part before the Division of Organic Chemistry at the 146th National Meeting of the American Chemical Society, Denver, Colo., Jan., 1964. (d) National Science Foundation Fellow, 1961–1963.

(2) G. Closs and S. J. Brois, *J. Am. Chem. Soc.*, **82**, 6068 (1960).

(3) A. Hassner and C. Heathcock, *Tetrahedron Letters*, 393 (1963).

(4) For a review of nitrosyl chloride chemistry, see L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 319 (1951).

(5) After the present work was essentially complete, however, the work of Tanabe and Hayashi appeared in print.[6] These workers describe the preparation of compounds **2a**, **2b**, **3a**, **4a**, and **4b** in the same manner as that described here.

(6) K. Tanabe and R. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **10**, 1177 (1962).