fractions eluted with hexane–ether (7:3) consisted of the isomeric Δ^4 3-ketone **7f** (120 mg.), identical with a sample prepared as described below.

7ξ-Fluoro-17,20:20,21-bismethylenedioxy-B-homo-19-norpregn-4-en-3-one (**7f**).—A solution of the unconjugated ketone **3k** (1.0 g.) in 95% ethanol (25 ml.) containing oxalic acid (1.0 g.) was heated under reflux for 16 hr. The product (850 mg.) was isolated by dilution with water and filtration. Several recrystallizations from acetone afforded the analytical sample: m.p. 246–247°; $[\alpha]_D$ −137°; λ_{max} 240 mμ (log ε 4.17); ν_{max} 1670, 1625, 1095, 1080, and 940 cm.$^{-1}$; n.m.r. 50 (18-H, s), 240 (21-H, s), 304.5 (two protons), 303, 312.5 (methylenedioxy protons), 356 (4-H, s), 275, and 325 (7ξ-H, pair of m, J_{HF} = *ca.* 50 c.p.s.) c.p.s.

Anal. Calcd. for $C_{23}H_{31}FO_6$: C, 67.97; H, 7.69; F, 4.67. Found: C, 68.35; H, 7.62; F, 4.18.

17α,21-Dihydroxy-7ξ-fluoro-B-homo-19-norpregn-4-ene-3,20-dione (**7g**).—Ketone **7f** (215 mg.) was added to concentrated hydrochloric acid at 0° with good stirring. The steroid dissolved completely in 2.5 min. The mixture was stirred an additional minute and the product was then isolated by precipitation in aqueous sodium bicarbonate and extraction with ethyl acetate. Recrystallization from methanol afforded the analytical sample: m.p. 204–205°; $[\alpha]_D$ −60°; λ_{max} 238 mμ (log ε 4.19); ν_{max} 3350–3400, 1708, 1655, 1615, and 885 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{29}FO_4$: C, 69.18; H, 8.01; F, 5.21. Found: C, 69.13; H, 8.15; F, 5.57.

Product Development Control in the Reduction of 17-Keto-13α-androst-5-en-3β-ol

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Reduction of 17-keto-13α-androst-5-en-3β-ol with either sodium and isopropyl alcohol, lithium aluminum hydride, or sodium borohydride yields a mixture of epimeric 17-ols in which the 17α-ol predominates. The configurations of the products were deduced from rotational, infrared, and n.m.r. data. The results support the conclusion that the reductions with lithium aluminum hydride and sodium borohydride are product development controlled.

In a previous publication,[1] we indicated that the hydride reduction of a 17-keto-13α,14α steroid, as well as a 17-keto-13β,14α and a 17-keto-13β,14β steroid, was product development controlled. This paper presents additional evidence in support of this conclusion.

17-Keto-13α-androst-5-en-3β-ol (I)[2] was reduced with lithium aluminum hydride, sodium borohydride, and sodium in isopropyl alcohol. All three reductions were observed to give a mixture of products in which the predominant product is the more levorotatory epimer having the hydroxyl group at C-17 α oriented.[2] The crude mixture of products from each of the reductions was analyzed by paper chromatography.[3] The results reveal that the 17β epimer is also present in all three reduction mixtures; 17–20% when lithium aluminum hydride is used, 8–10% when the reduction is carried out with sodium and isopropyl alcohol, and 20–25% when the reducing agent is sodium borohydride.

Fractional crystallization of each of the reduction mixtures affords 13α-androst-5-ene-3β,17α-diol of comparable purity in 77, 87, and 48% yields when lithium aluminum hydride, sodium and isopropyl alcohol, and sodium borohydride are, respectively, employed.

The configurations at C-17 of the two reduction products were deduced from rotational, infrared, and n.m.r. data. Of a pair of 17-hydroxy steroids which are epimeric at C-17, the epimer having the greater levorotation has the 17α-hydroxy configuration.[2] For example, the specific rotation of 13α,17α-testosterone is about 40° more levorotatory than that of 13α-testosterone.[1,2]

The major product obtained from the reduction of 17-keto-13α-androst-5-en-3β-ol (I) exhibits a specific rotation of −122° while the minor product shows a rotation of −99°. Oppenauer oxidation of the former affords 13α,17α-testosterone in 38% yield, thereby establishing that the configuration at C-17 of the major reduction product is the same as that of 13α,17α-testosterone.

The molecular rotation difference ($\Delta MD^{13\beta-13\alpha}$) was found to be +53° for testosterone and 13α-testosterone and +65° for 17α-testosterone and 13α,17α-testosterone.[2]

Barton and Cox[4] reported the specific rotation of androst-5-ene-3β,17α-diol to be −61° in chloroform while Muller, *et al.*,[5] found that of androst-5-ene-3β,17β-diol to be −55° in the same solvent. Hence, the molecular rotation difference ($\Delta MD^{13\beta-14\alpha}$) is +128° for androst-5-ene-3β,17β-diol and 13α-androst-5-ene-3β,-17β-diol, and +177° for androst-5-ene-3β,17α-diol and 13α-androst-5-ene-3β,17α-diol. These results, together with the molecular rotation difference of 17α-estradiol 3-methyl ether and 13α,17α-estradiol 3-methyl ether, are tabulated in Table I.

The infrared spectrum of 13α-androst-5-ene-3β,17α-diol shows C–O stretching bands at 9.32 and 9.43 μ while the spectrum of the 3β,17β-diol displays the C–O band at 9.50 μ. Previous investigators[2,6] have reported that the C–O stretching band of an equatorial hydroxyl group appears at a lower wave length than that of an axial hydroxyl group. Our results suggest that the hydroxyl group at C-17 of the 3β,17β-diol has greater axial character than the corresponding group of the 3β,17α epimer. This is in accord with molecular models assembled on the premise that ring C has the chair conformation, ring D is puckered, and the C-17 substituents are not eclipsed by those of C-16.[1]

The n.m.r. spectrum of 13α,17α-testosterone reveals a triplet centered at 254 c.p.s. (τ 5.77) with observed splittings of 7.5 c.p.s. This triplet, which is due to the resonance of the 17β-proton, is reminiscent of the triplet centered at τ 6.33

(1) L. J. Chinn, *J. Org. Chem.*, **27**, 54 (1962).
(2) J. P. L. Bots, *Rec. trav. chim.* **77**, 1010 (1958).
(3) We are indebted to Dr. E. G. Daskalakis and members of our paper chromatography staff for performing the analyses.
(4) D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 783 (1948).
(5) G. Muller, J. Mathieu, A. Petit, and L. Velluz, *Bull. soc. chim. France*, 747 (1951).
(6) E. A. Braude and E. S. Waight, *Progr. Stereochem.*, **1**, 167 (1954).

TABLE I

MOLECULAR ROTATION DIFFERENCES OF 17-HYDROXY STEROIDS EPIMERIC AT THE 13-CARBON

Compd.	$[\alpha]_D$ (solvent), deg.	M_D, deg.	$\Delta M_D^{13\beta-13\alpha}$, deg.
Testosterone		+314[a]	
			+53[a]
13α-Testosterone	+91 (EtOH)[a]	+261[a]	
17α-Testosterone		+206[a]	
			+65[a]
13α,17α-Testosterone	+49 (EtOH)[a]	+141[a]	
Androst-5-ene-3β,17β-diol	−55 ($CHCl_3$)[b]	−160	
			+128
13α-Androst-5-ene-3β,17β-diol	−99 ($CHCl_3$)	−288	
Androst-5-ene-3β,17α-diol	−61 ($CHCl_3$)[c]	−177	
			+177
13α-Androst-5-ene-3β,17α-diol	−122 ($CHCl_3$)	−354	
17α-Estradiol 3-methyl ether	+60 ($CHCl_3$)[d]	+172	
			+128
13α,17α-Estradiol 3-methyl ether		+44[a]	

[a] Ref. 2. [b] Ref. 7. [c] Ref. 6. [d] In calculating $\Delta M_D^{13\beta-13\alpha}$ for 17α-estradiol 3-methyl ether and 13α,17α-estradiol 3-methyl ether, Bots[2] substituted the rotation of 17α-estradiol for that of its methyl ether in his calculation because the latter value was not available. He obtained a difference of +102° for 17α-estradiol and 13α,17α-estradiol 3-methyl ether. 17α-Estradiol 3-methyl ether, m.p. 112–113°, prepared in our laboratories by Dr. D. A. Tyner, to whom we are indebted, exhibits a specific rotation of +60° in chloroform.

with observed splittings of 8 c.p.s. associated with the 17α-proton of testosterone.[7] The 17α-proton of 13α-testosterone gives rise to a sextet centered at 230 c.p.s. (τ 6.16) with observed splittings of 1–2 c.p.s.

Although the 17β-proton of 13α,17α-testosterone resonates at a lower field than the 17α-proton of 13α-testosterone, the greater axial character of the 17β-proton is evident, nevertheless, from the sum of its coupling constants ($J_{AX} + J_{BX}$), which amounts to 15 c.p.s. and is about twice as large as $J_{AX} + J_{BX}$ (=7 c.p.s.) of the 17α-proton of 13α-testosterone.[8] Moreover, since the splitting pattern of the 17β-proton of 13α,17α-testosterone is practically identical with that of the axial 17α-proton of testosterone,[1,7] the argument that the 17β substituent of a 13α steroid has greater axial character than the 17α substituent is rendered more convincing.

In spite of the limitations of the Karplus equation, we found it instructive to compare the experimentally observed values for $J_{AX} + J_{BX}$ with the values (Table II) derived from it.

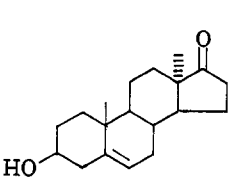
$$J = \begin{cases} 8.5\cos^2\phi - 0.28 & 0° \leqq \phi \leqq 90° \\ 9.5\cos^2\phi - 0.28 & 90° \leqq \phi \leqq 180° \end{cases}$$ [9,10]

The torsional angles (θ) of the maximally puckered envelope (C_s) and half-chair (C_2) conformations for cyclopentane[11] were used to determine the dihedral angles (ϕ) employed in the equation.

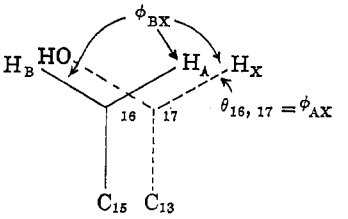
If ring C is assumed to be in the chair conformation with $\theta_{13,14} = 60°$, then the three possible conformations involving C-16 and -17 of 13α-testosterone are II, III, and IV.[1]

The corresponding conformations of 13α,17α-testosterone are V, VI, and VII.[1] In II and V, ring D has the envelope conformation in which the hydrogen and hydroxyl of C-17 are eclipsed by the two hydrogens of C-16. In III and VI, the other arrangements in which ring D also has the envelope conformation, the hydrogens of C-16 eclipse those of C-15. Arrangement IV and VII constitute a set of epimers in which ring D has the half-chair conformation.

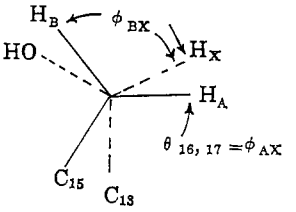
A priori, II and V are energetically the least favorable set of conformations because of the eclipse of the 17-hydroxyl group.[12,13] As both II and V give the same value for $J_{AX} + J_{BX}$, it follows that, if one of these two



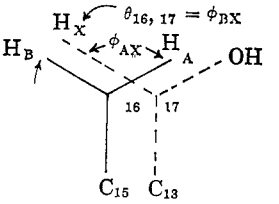
I



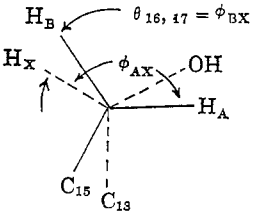
II (C_s), $\phi_{AX} = 0°$; $\phi_{BX} = 120°$



III (C_s), $\phi_{AX} = 36.5°$; $\phi_{BX} = 83.5°$
IV (C_2), $\phi_{AX} = 19°$; $\phi_{BX} = 101°$
VIII (C_s), $\phi_{AX} = 28.6°$; $\phi_{BX} = 91.4°$



V (C_s), $\phi_{AX} = 120°$, $\phi_{BX} = 0°$



VI (C_2), $\phi_{AX} = 156.5°$; $\phi_{BX} = 36.5°$
VII (C_2), $\phi_{AX} = 139°$; $\phi_{BX} = 19°$
IX (C_2), $\phi_{AX} = 148.6°$; $\phi_{BX} = 28.6°$

(7) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p. 79.

(8) K. W. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961).

(9) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Am. Chem. Soc.*, **85**, 2870 (1963).

(10) See also C. D. Jardetzky, *ibid.*, **82**, 229 (1960); **83**, 2919 (1961); **84**, 62 (1962).

(11) F. V. Brutcher, Jr., and W. Bauer, Jr., *ibid.*, **84**, 2233 (1962).

(12) While the eclipse of the hydroxyl group increases the torsional strain, 1,3-diaxial repulsion in other conformations may result, nevertheless, in either II or III being the preferred conformation.[13]

(13) *Cf.* F. V. Brutcher, Jr., and W. Bauer, Jr., *ibid.*, **84**, 2236 (1962).

TABLE II

SPIN–SPIN COUPLING CONSTANTS DERIVED FROM THE KARPLUS EQUATION

Compd.	$\theta_{13,14}$[a]	$\theta_{16,17}$[a]	ϕ_{AX}[a]	ϕ_{BX}[a]	J_{AX}[b]	J_{BX}	$J_{AX} + J_{BX}$[b]
13α-Testosterone (obsd.)							7
13α,17α-Testosterone (obsd.)							15
13α-Testosterone (II)	60	0	0	120	8.2	2.2	10.4
13α,17α-Testosterone (V)	60	0	120	0	2.2	8.2	10.4
13α-Testosterone (III)	60	36.5	36.5	83.5	5.2	−0.2	5.0
13α,17α-Testosterone (VI)	60	36.5	156.5	36.5	7.7	5.2	12.9
13α-Testosterone (IV)	60	19	19	101	7.4	0	7.4
13α,17α-Testosterone (VII)	60	19	139	19	5.1	7.4	12.5
13α-Testosterone (VIII)	46.1	28.6	28.6	91.4	6.3	−0.3	6.0
13α,17α-Testosterone (IX)	46.1	28.6	148.6	28.6	6.7	6.3	12.9
13α,17α-Testosterone			147.3	27.3	6.5	6.5	13.0

[a] In degrees. [b] In cycles per second.

conformations accurately depicts the arrangement of one of the two 17 isomeric 13α-testosterones, the other conformation cannot possibly be the correct arrangement of the other isomer.

The observed value for $J_{AX} + J_{BX}$ of 13α-testosterone is in qualitative agreement with those calculated for conformations III and IV. Likewise, the observed value for $J_{AX} + J_{BX}$ of 13α,17α-testosterone is in qualitative agreement with those calculated for conformations VI and VII.

If we assume (1) the observed equal splittings of the triplet centered at 254 c.p.s. of 13α,17α-testosterone are due to the equality of J_{AX} and J_{BX}, and (2) the constant and the coefficients in the Karplus equation are valid,[9,10] then the dihedral angles, ϕ_{AX} and ϕ_{BX}, should be 147.3 and 27.3°, respectively, for 13α,17α-testosterone.

These values for the dihedral angles are very close to those calculated from Pitzer–Donath's C_s model for cyclopentane.[14] If we apply their values, then the conformation about C-16 and C-17 of 13α,17α-testosterone would be represented by IX and that of 13α-testosterone by VIII. The torsional angle, $\theta_{13,14}$, involving C-13 and -14 would be 46.1°, which would imply that ring C has a conformation intermediate between a chair and twist-boat.[15]

While the distortion of the chair conformation of ring C increases the energy of the molecule, this increase is offset by the stability gained from the lessening of the 1,3-diaxial interactions, notably those involving the C-17 grouping and the hydrogens at C-8 and -11. Similarly, the greater torsional strain resulting from the reduction of the torsional angles of ring D is compensated by a decrease in the bond bending energy.[11] Thus, we cannot exclude the possibility that for the 13α,14α steroids, $\theta_{13,14}$ is less than 60° and ring D is not maximally puckered.

Because the 17β substituent of a 13α,14α steroid has greater axial character, the 17-hydroxyl group of 13α-androst-5-ene-3β,17β-diol is subjected to 1,3-diaxial repulsion, in contrast to the corresponding group of 13α-androst-5-ene-3β,17α-diol. If the difference in entropies of the two epimers is negligible, then equilibration should afford the 17α-ol as the predominant product. As the sodium and alcohol reduction mixture closely resembles the equilibrium mixture of the two 17-ols,[16] the results of our present study substantiate our previous conclusion[1] that the hydride reduction of a 17-keto-13α,14α steroid is product development controlled.

(14) K. S. Pitzer and W. E. Donath, *J. Am. Chem. Soc.*, **81**, 3213 (1959).

(15) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. J. Dreger, and W. N. Hubbard, *ibid.*, **83**, 606 (1961).

Experimental Section[17]

Sodium and Isopropyl Alcohol Reduction of 17-Keto-13α-androst-5-en-3β-ol (I).—To a stirred solution of 0.500 g. (0.00173 mole) of 17-keto-13α-androst-5-en-3β-ol, m.p. 185.5–187°,[2] in 10 ml. of isopropyl alcohol, heated under reflux, was added 1.5 g. (0.065 g.-atom) of sodium in several portions. The reaction mixture was stirred and heated under reflux for 1.75 hr. during which period two additional 10-ml. portions of isopropyl alcohol were added to dissolve the sodium. The reaction mixture was diluted with water and concentrated under reduced pressure to remove the alcohol. The residue was cooled to 0–5°, and the colorless crystalline product was collected, washed well with water, and dried: yield 0.47 g., m.p. 183–189°. A sample of the crude product was chromatographed on paper with toluene–propylene glycol as the solvent system, and the spots on the paper were developed with phosphomolybdic acid. The presence of **13α-androst-5-ene-3β,17β-diol** in 8–10% yield was estimated to be in the mixture by a comparison of the areas and the intensities of the spots. Fractional crystallization of the crude mixture from ether gave 0.439 g. (87%) of **13α-androst-5-ene-3β,17a-diol**, m.p. 188–194°, as colorless heavy plates. Admixed with the 3β,17α-diol, m.p. 192–193°, obtained from the lithium aluminum hydride reduction (*vide infra*), it melted at 189.5–192°. Their infrared spectra, determined in potassium bromide, were identical.

Lithium Aluminum Hydride Reduction of 17-Keto-13α-androst-5-en-3β-ol (I).—To a stirred mixture of 0.5 g. (0.132 mole) of lithium aluminum hydride and 50 ml. of anhydrous ether, heated under reflux, was added over a period of 0.25 hr. a solution of 0.500 g. (0.00173 mole) of 17-keto-13α-androst-5-en-3β-ol, m.p. 185.5–187°, in 2 ml. of redistilled tetrahydrofuran and 70 ml. of anhydrous ether. After the addition was complete, the reaction mixture was stirred and heated under reflux for 18 hr. Then it was cooled to 0–5°, decomposed with water, and acidified with 1.7 *N* hydrochloric acid. The ethereal phase was separated and washed with successive portions of 1.7 *N* hydrochloric acid, water, and a saturated solution of sodium chloride. After it was dried over anhydrous sodium sulfate, the ethereal solution was distilled to dryness under reduced pressure to yield *ca.* 0.5 g. of colorless plates, m.p. 183–189.5°. Papergram analysis of the crude mixture as before revealed the presence of **13α-androst-5-ene-3β,17β-diol** in 17–20% yield in the mixture. The crude product was fractionally crystallized from ether to afford 0.386 g. (77%) of **13α-androst-5-ene-3β,17α-diol** as colorless plates: m.p. 188–192.5° (two crystallizations from ether raised the melting point to 192–193°); $[\alpha]D$ −122° (1%, $CHCl_3$); λ^{KBr}

(16) G. Vavon, *Bull. soc. chim. France*, **49**, 937 (1931); W. Hückel, *Ann.*, **533**, 1 (1937); D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(17) Melting points were taken on a Fisher-Johns melting block and are corrected. Optical rotations were determined at 25°. N.m.r. signals are reported as downfield with reference to internal tetramethylsilane at 60 Mc./sec. as determined in $CDCl_3$ containing 1 drop of D_2O on a Varian A-60 instrument.

2.80 (sh), 2.88, 9.32, 9.43 μ. The infrared spectrum showed no carbonyl band.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.23; H, 10.48.

From the combined mother liquors 0.013 g. (2.6%) of 13α-androst-5-ene-3β,17β-diol, m.p. 154.5–156.5°, was obtained as colorless platelets. The residue from the remaining mother liquors was chromatographed on 10 g. of silica gel, and the column was eluted with varying proportions of benzene–ethyl acetate. Elution with 25% ethyl acetate in benzene gave an additional quantity of the 3β,17β-diol, which was crystallized from ether–pentane to yield 0.025 g. (5%) of colorless laths, m.p. 160.5–161°. The analytical sample of 13α-androst-5-en-3β,17β-diol was obtained as colorless rods from ether–pentane: m.p. 162.5–163.5°; $[\alpha]_D$ −99° (0.5%, $CHCl_3$); λ^{KBr} 3.02, 9.50 μ. The infrared spectrum showed no carbonyl band.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.95; H, 10.31.

Sodium Borohydride Reduction of 17-Keto-13α-androst-5-en-3β-ol (I).—A solution of 0.432 g. (0.0015 mole) of 17-keto-13α-androst-5-en-3β-ol, m.p. 185.5–187°, and 0.5 g. (0.132 mole) of sodium borohydride in 50 ml. of methanol was stirred and heated under reflux for 3 hr. After 0.5 g. (0.132 mole) more of sodium borohydride was added, stirring and heating were continued for an additional 1 hr. The reaction mixture was treated with 10 drops of glacial acetic acid and diluted with water. Then it was concentrated under reduced pressure to remove the alcohol. The residue was cooled to 0–5°. The solid was collected, washed with water, and dried, yield 0.42 g., m.p. 167–172°. A sample of the crude product was submitted for paper chromatography as before, and the results revealed the presence of **13α-androst-5-ene-3β,17β-diol** in 20–25% yield in the mixture. The crude product was fractionally crystallized from ether to yield 0.314 g. (72%) of **13α-androst-5-ene-3β,17α-diol**, m.p. 183–189°, as colorless heavy plates. Recrystallization from ether raised the melting point to 190–193°; yield was 0.21 g. (48%). The residue from the combined mother liquors was chromatographed on 10 g. of silica gel. Elution of the column with 25% ethyl acetate in benzene gave 13α-androst-5-ene-3β,17β-diol, which was crystallized from ether–pentane to afford 0.030 g. (7%) of colorless laths, m.p. 157.5–161.5°. The melting point was raised to 162.5–164.5° upon further crystallization from ether–pentane.

Oppenauer Oxidation of 13α-Androst-5-ene-3β,17α-diol.—A solution of 0.122 g. of 13α-androst-5-ene-3β,17α-diol, 4 ml. of cyclohexanone, and 0.8 g. of aluminum isoproxide in 24 ml. of anhydrous toluene was heated under reflux for 1 hr.[18] After 20 ml. of a saturated solution of Rochelle salt was added, the reaction mixture was steam distilled for 30 min. The cooled residue was extracted with ether. The ether extract was washed successively with water and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the ether extract was evaporated to dryness to afford a viscous orange oil.

The oil was chromatographed on 2 g. of silica gel. Elution of the column with 5% ethyl acetate in benzene gave, in succession, 13α-androstene-3,17-dione and 13α,17α-testosterone.

The combined fractions of 13α-androstene-3,17-dione were crystallized from ether–pentane to yield 7 mg. (6%) of the dione, m.p. 145.5–148.5° (lit.[2] m.p. 148–149°). Its infrared spectrum was identical with that of an authentic sample.

The combined fractions of 13α,17α-testosterone were crystallized from ether–pentane to afford 46 mg. (38%) of a crystalline product, m.p. 129–130° (lit.[1] m.p. 129.5–131°). Its infrared spectrum was identical with that of an authentic sample.

N.m.r. Signals of 13α-Testosterone and 13α,17α-Testosterone.—13α-Testosterone, m.p. 154–157°, showed signals at 346 (4-H); 276.5 (water); 235, 233.5, 231.5, 230.5, 229.5, 228 (17-H); 68 (19-CH_3); and 50.5 (18-CH_3) c.p.s. 13α,17α-Testosterone, m.p. 126–127°, showed signals at 346.5 (4-H); 261.5, 254, 246.5 (17-H); 67.5 (19-CH_3); and 53 (18-CH_3) c.p.s.

(18) *Cf.* A. F. St. Andre's unpublished work cited by C. Djerassi in *Org. Reactions*, **6**, 207 (1951).

Studies Directed toward the Synthesis of Plasmalogens. II. (±)-*cis*- and -*trans*-3-(*n*-Hexadec-1′-enyloxy)-1,2-propanediol[1]

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Condensation of 2-bromo-1,1-dimethoxy-*n*-hexadecane with 2-benzyloxypropan-1,3-diol gave the epimeric *trans*- and *cis*-2-(1′-bromopentadecyl)-5-benzyloxy-1,3-dioxane (IIa and IIIa), separated by chromatography. Catalytic debenzylation led to the epimeric alcohols IIb and IIIb. Debromination of either IIb or IIIb with lithium in 1,2-dimethoxyethane afforded the same mixture of (±)-*cis*- and -*trans*-3-(*n*-hexadec-1′-enyloxy)-1,2-propanediols (VIIa and b), separated by preparative gas–liquid partition chromatography of their diacetates (VIIc and d). Alkaline hydrolysis of VIIc and d gave the individual *cis*- and *trans*-1-alk-1′-enylglycerols VIIa and b, which after hydrogenation were identical with (±)-chimyl alcohol. The *cis* isomer VIIa and the *cis* diacetate VIIc were structurally identical with the alkenylglycerol obtained from natural plasmalogen and its diacetate. Although the allyl ether Xa rearranged to the desired *cis*-1-propenyl ether XIa, the crotyl ether Xb did not undergo this reaction, and a possible reason is discussed.

The plasmalogens[2] are a group of aldehydogenic lipids widely distribution in both the animal and plant kingdoms and are phosphorylated derivatives of *cis*-1-alk-1′-enylglycerol (VIIa) where R = mainly *n*-$C_{14}H_{29}$ and *n*-$C_{16}H_{33}$. The plasmalogens are of considerable chemical and biological interest in view of their probable biogenetic relationship to the 1,2-diacylglycerols either by hydration of the double bond to the hemiacetal and thence by oxidation,[3a] or by reduction of the 1-acyl moiety to the hemiacetal followed by a *cis* dehydration.[3b]

The availability of synthetic plasmalogens for chemical and biological studies requires the initial preparation of the appropriate *cis*-1-alk-1′-enylglycerols.

It has been demonstrated[4] that published methods[5]

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(2) (a) For review, see E. Klenk and H. Debuch, *Progr. Chem. Fats Lipids*, **6**, 3 (1963).

(3) (a) J. C. Craig and E. C. Horning, *J. Org. Chem.*, **26**, 2098 (1960); (b) H. Goldfine and N. Baumann, Proceedings of the 6th International Congress of Biochemistry, New York, N. Y., 1964, p. 574; N. A. Baumann, P. O. Hagen, and H. Goldfine, *J. Biol. Chem.*, **240**, 1559 (1965).

(4) J. C. Craig, D. P. G. Hamon, H. W. Brewer, and H. Härle, *J. Org. Chem.*, **30**, 907 (1965).

(5) (a) C. Piantadosi and A. F. Hirsch, *J. Pharm. Sci.*, **50**, 978 (1961); (b) C. Piantadosi, A. F. Hirsch, C. L. Yarbro, and C. E. Anderson, *J. Org. Chem.*, **28**, 2425 (1963).