Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03; O, 14.70. Found: C, 77.04; H, 8.22; O, 14.51.

6-Chloro-6-dehydro-17α-ethynyltestosterone (XX).—A suspension of 2.29 g. of epoxide XIXa in 150 ml. of glacial acetic acid was saturated at room temperature with anhydrous hydrogen chloride and allowed to stand for 4 hours before pouring into water. The product was isolated by methylene dichloride extraction and then purified by chromatography on 60 g. of neutral alumina. The hexane–benzene (1:4) fractions were crystallized from acetone–ether to yield 380 mg. of XX, m.p. 190–195°. The analytical specimen, from the same solvents, melted at 193–195°, λ_{max} 286 mμ, log ε 4.33, $[\alpha]_D$ −58°.

Anal. Calcd. for $C_{21}H_{25}ClO_2$: C, 73.13; H, 7.31; Cl, 10.30. Found: C, 73.40; H, 7.20; Cl, 10.25.

17α-Ethynyl-19-nor-3-ethoxy-$\Delta^{3,5}$-androstadien-17β-ol (XVII).—17α-Ethynyl-19-nortestosterone (2 g.) was treated with ethyl orthoformate as described for the preparation of XIVa. Crystallization of the water-precipitated product from hexane yielded 1.55 g. of still somewhat impure enol ether, m.p. 165–170°. The analytical specimen of XVIII (from hexane) melted at 187–189°, λ_{max} 242 mμ, log ε 4.35, $[\alpha]_D$ −228°.

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26; O, 9.81. Found: C, 80.60; H, 9.02; O, 10.02.

6-Dehydro-17α-ethynyl-19-nortestosterone (XVIIIb).—17α-Ethynyl-19-nortestosterone enol ether (XVII) (4.3 g.) was treated, according to the preparation of XVIIIa, with N-bromosuccinimide and the crude total 6β-bromo-17α-ethynyl-19-nortestosterone dehydrobrominated with calcium carbonate in dimethylformamide. Crystallization of the crude product from ethyl acetate gave 2.53 g. of XVIIIb, m.p. 243–247°. The analytical sample (from methanol) exhibited m.p. 251–252°, λ_{max} mμ, log ε 4.38, $[\alpha]_D$ −151°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16; O, 10.80. Found: C, 80.79; H, 8.29; O, 11.20.

6α,7α-Oxido-17α-ethynyl-19-nortestosterone (XIXb).—A solution of 2.2 g. of 6-dehydro-17α-ethynyl-19-nortestosterone (XVIIIb) in 240 ml. of methylene dichloride was allowed to stand for 40 hours at room temperature with 65 ml. of 1.04 *N* monoperphthalic acid in ether. The solution was washed with aqueous saturated sodium carbonate and water to neutrality then dried and evaporated. Crystallization of the residue from acetone provided 380 mg. of XIXb, m.p. 260–264°, raised by further crystallization from acetone to 264–267°, λ_{max} 241 mμ, log ε 4.18, $[\alpha]_D$ −50°.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74; O, 15.37. Found: C, 76.71; H, 7.83; O, 15.60.

6-Chloro-6-dehydro-17α-ethynyl-19-nortestosterone (XXb).—A solution of 250 mg. of epoxide XIXb in 10 ml. of glacial acetic acid saturated with hydrogen chloride was kept at 20–25° for 3 hours and then diluted with ice-water. The resultant crystals, 150 mg., m.p. 108–112°, λ_{max} 284 mμ, log ε 4.16, were chromatographed on 3 g. of neutral alumina. Benzene elution gave 100 mg. of XXb, m.p. 145–150°, recrystallized several times from ether–pentane to give a pure sample of 6-chloro-6-dehydro-17α-ethynyl-19-nortestosterone, m.p. 156–158°, λ_{max} 283 mμ, log ε 4.35, $[\alpha]_D$ −83°.

Anal. Calcd. for $C_{20}H_{23}ClO_2$: C, 72.60; H, 7.00; O, 9.60. Found: C, 72.44; H, 7.02; O, 9.84.

APDO. POSTAL 2679, MÉXICO, D. F.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

16-Hydroxylated Steroids. XIV.[1] 16α-Hydroxy-6α-methyl-corticoids. Part I

BY SEYMOUR BERNSTEIN AND RUDDY LITTELL

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The synthesis of a number of related 16α-hydroxy-6α-methyl-corticoids is described. 16α-Hydroxy-6α-methylprednisolone (XVI) has been prepared in an over-all yield of 2.3% *via* a seventeen-stage synthesis from cortisone (I). Compound XVI was also prepared in an over-all yield of 7.6% *via* a nine-stage synthesis from 6α-methylcortisone (XXII).

Recently this Laboratory has published on the preparation and biological properties of 16α-hydroxy-2-methyl-corticoids.[2] We now wish to report in part[3] on the preparation of 16α-hydroxy-6-methyl-corticoids, in particular the preparation of the 16α-hydroxy-derivatives of 6α-methylhydrocortisone and 6α-methylprednisolone.[4]

The chemical syntheses[5] elaborated utilized the 5α,6α-epoxide II of hydrocortisone 3,20-bis-ethylene ketal[6] as the starting material. Treatment of II with methylmagnesium bromide afforded in 75% yield 3,20 - bis - ethylenedioxy - 6β - methylpregnane-5α,11β,17α,21-tetrol (III).[7] Oxidation of the latter with chromium trioxide–pyridine complex[8] gave the desired 3,20-bis-ketal 11-one Va for which suitable elemental analyses could not be obtained. The compound on recrystallization gave variable melting points, probably ascribable to solvation. Acetylation provided the 3,20-bis-ketal 11-one 21-acetate Vb. This intermediate was also obtained by acetylation (90% yield) of III followed by oxidation (93% yield). This latter procedure was the preferred preparative route to Vb. Heat-

(1) Paper XIII, S. Bernstein, R. H. Lenhard, N. E. Rigler and M. A. Darken, *J. Org. Chem.*, in press.

(2) S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard, W. S. Allen and I. Ringler, THIS JOURNAL, **81**, 1696 (1959).

(3) The preparation of the 16α-hydroxy-derivatives of 9α-halogeno-6-methylcorticoids will be described in the forthcoming Part II of this research.

(4) (a) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, THIS JOURNAL, **78**, 6213 (1956); (b) G. B. Spero, J. L. Thompson, F. H. Lincoln, W. J. Schneider and J. A. Hogg, *ibid.*, **79**, 1515 (1957); (c) G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4112 (1957); (d) J. H. Fried, G. E. Arth and L. H. Sarett, THIS JOURNAL, **81**, 1235 (1959).

(5) Preliminary attempts to effect 16α-hydroxylation of 6α-methylhydrocortisone and 6α-methylprednisolone with *Streptomyces roseochromogenus* (Lederle AE 409) were not promising. This observation also pertains to 2-methyl-corticoids.

(6) The three stage-synthesis (24% over-all yield) of the bis-ketal epoxide II from cortisone (I) has been described by R. Littell and S. Bernstein, THIS JOURNAL, **78**, 984 (1956); see also, S. Bernstein and R. H. Lenhard, *ibid.*, **77**, 2233 (1955).

(7) This intermediate has been described by G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, ref. 4c. Its preparation was accomplished independently in this Laboratory prior to the British publication. In this connection see also ref. 4a.

(8) The stability of the C21-hydroxy group adjacent to a C20-ketal group under these oxidation conditions has been noted by W. S. Allen, S. Bernstein and R. Littell, THIS JOURNAL, **76**, 6116 (1954), and subsequently utilized by S. Bernstein and R. H. Lenhard, ref. 6 and R. Littell and S. Bernstein, ref. 6.

ing Vb with aqueous acetic acid selectively hydrolyzed the ketal group at C3,[9] and 21-acetoxy-20-ethylenedioxy-5α,17α-dihydroxy-6β-methylpregnane-3,11-dione (VI) was obtained in 90% yield. Treatment of VI with dilute sodium hydroxide resulted simultaneously in the elimination of the 5α-hydroxyl group, saponification of the C21-acetate group and epimerization of the C6-methyl group into the equatorial α-configuration.[4a] The product VII so obtained in quantitative yield was acetylated (80% yield) to give 21-acetoxy-20-ethylenedioxy-17α-hydroxy-6α-methyl-4-pregnene-3,11-dione (VIII). Ketalization of the latter with ethylene glycol in benzene and *p*-toluenesulfonic acid provided in 91% yield 21-acetoxy-3,20-bis-ethylenedioxy-17α-hydroxy-6-methyl-5-pregnen-11-one (IX). Assignment of the double bond to the C5,6-position was based on the assumption that the 6-methyl group did not prevent the now well-established double bond shift during ketalization.[10] Some support, albeit inconclusive, was obtained from ultraviolet spectroscopy. Its absorption spectrum in the 190–210 mμ region was characteristic of a tetrasubstituted ethylene bond.[11]

The 3,20-bis-ketal 21-acetate IX was also prepared from (XXII) the known 6α-methylcortisone.[4a] Ketalization of XXII gave XXIII in a solvated state.[12] Acetylation gave the desired IX (38% over-all yield from XXII).

Treatment of IX with thionyl chloride in pyridine[13] resulted in dehydration of the unprotected 17α-hydroxyl group to afford 21-acetoxy-3,20-bis-ethylenedioxy-6-methyl-5,16-pregnadien-11-one (X) which was not characterized.[14] Reduction of X to 3,20-bis-ethylenedioxy-6-methyl-5,16-pregnadiene-11β,21-diol (XI) was initially done with sodium borohydride, but later experiments showed that the reaction proceeded more rapidly and in better yield (70% over-all yield from IX) when performed with lithium aluminum hydride. Treatment of XI with osmic acid in benzene[15] gave the 3,20 - bis - ketal 11β,16α,17α,21 - tetrol XII in 87% yield. Sulfuric acid hydrolysis provided in 74% yield 11β,16α,17α,21-tetrahydroxy-6α-methyl-4-pregnene-3,20-dione (XIII). Acetylation gave the diacetate XIV (75% yield), and reaction with acetone and perchloric acid gave the acetonide XVIIIa.[16] The acetate XVIIIb was also prepared.

The pathway, XI → XVII → XIII in which hydroxylation followed ketal removal, was also explored. While this was shown to give the desired product XIII the yields obtained were low.[17]

Introduction of Δ^1-unsaturation was readily accomplished by treatment of the diacetate XIV with selenium dioxide in *t*-butyl alcohol[18] to give 16α,21 - diacetoxy - 11β,17α - dihydroxy - 6α-methyl - 1,4 - pregnadiene - 3,20 - dione (XV) in 65% yield. Mild saponification with potassium bicarbonate (91% yield) gave the desired 11β,16α,17α,21-tetrahydroxy-6α-methyl-1,4-pregnadiene - 3,20 - dione (16α - hydroxy - 6α - methylprednisolone) (XVI). The formation of the acetonide XIX has already been described.[16]

The biological properties of compounds XIII, XVI and their acetonides (XVIIIa and XIX, resp.) are reported elsewhere.[16]

Acknowledgment.—We wish to thank Louis M. Brancone and associates for the analytical data, William Fulmor and associates for the spectral and optical rotational data, and Charles Pidacks for carrying out the partition chromatography.

Experimental

Melting Points.—All melting points are uncorrected.

Optical Rotations.—All rotations are for a chloroform solution unless otherwise noted.

Absorption Spectra.—The ultraviolet absorption spectra were determined in methanol with a Cary recording spectrophotometer (model 11 MS) unless otherwise noted. The infrared absorption spectra were determined in a pressed potassium bromide disk.

Petroleum Ether.—The fraction used had a b.p. 60–70° (Skellysolve B).

3,20-Bis-ethylenedioxy-6β-methylpregnane-5α,11β,17α,21-tetrol (III).—A solution of methylmagnesium bromide in ether (50 ml., 3 *N*) was added slowly to a vigorously stirred solution of 5.8 g. of 3,20-bis-ethylenedioxy-5α,6α-epoxidopregnane-11β,17α,21-triol (II) in 400 ml. of tetrahydrofuran. The solution was refluxed for 24 hours, cooled and treated with 32 ml. of saturated ammonium chloride solution. The supernatant liquid was decanted and the residue was washed with several portions of tetrahydrofuran. The combined decantates were evaporated and extracted with ethyl acetate, washed with saturated saline, dried and evaporated to give, after crystallization from acetone–petroleum ether, 4.55 g. (75%) of III, m.p. 170–172°. The analytical specimen from acetone–petroleum ether had a m.p. 175–177°, $[\alpha]^{25}D$ −11°.

(9) It has been established previously in these laboratories that reaction of a 3,20-bis-ethylene ketal 21-acetate with dilute acetic acid resulted in a selective hydrolysis of the C3-ethylene ketal group.[2]

(10) E. Fernholz and H. Stavely, Abstracts of the 102nd Meeting of the American Chemical Society, Atlantic City, N. J., September 8–12, 1941, p. M39; see also E. Fernholz, U. S. Patents 2,356,154 (August 22, 1944) and 2,378,918 (June 26, 1945); R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(11) P. Bladon, H. B. Henbest and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

(12) The first attempt to form the 3,20-bis-ketal 21-ol XXIII from 6α-methylcortisone (XXII) resulted for some inexplicable reason in the formation in a solvated state of the 3-mono-ketal XXIV, m.p. 203–205°, positive Blue Tetrazolium test for the α-ketol group. *Anal.* Calcd. for $C_{32}H_{54}O_8$ (418.51): C, 68.81; H, 8.19. Found: C, 67.81, 68.00; H, 8.09, 8.32. Acetylation gave 21-acetoxy-3-ethylenedioxy-17α-hydroxy-6-methyl-5-pregnene-11,20-dione (XXIVb), m.p. 248–249°, $[\alpha]^{25}D$ +28° (chloroform); ν_{max}^{KBr} 3448, 1760, 1736, 1709, 1234 and 1111 cm.$^{-1}$. *Anal.* Calcd. for $C_{26}H_{36}O_7$ (460.55): C, 67.80; H, 7.88. Found: C, 67.48; H, 8.21.

(13) W. S. Allen and S. Bernstein, THIS JOURNAL, **77**, 1028 (1955).

(14) Several attempts were made to dehydrate simultaneously the 5α- and 17α-hydroxyl groups in 21-acetoxy-3,20-bis-ethylenedioxy-5α,17α-dihydroxy-6β-methylpregnan-11-one (Vb) to give X directly. In each case, it appeared that, inexplicably, partial removal of the 3-ketal group had taken place. This approach was abandoned because of the difficulty in effecting a separation of the resulting mixture.

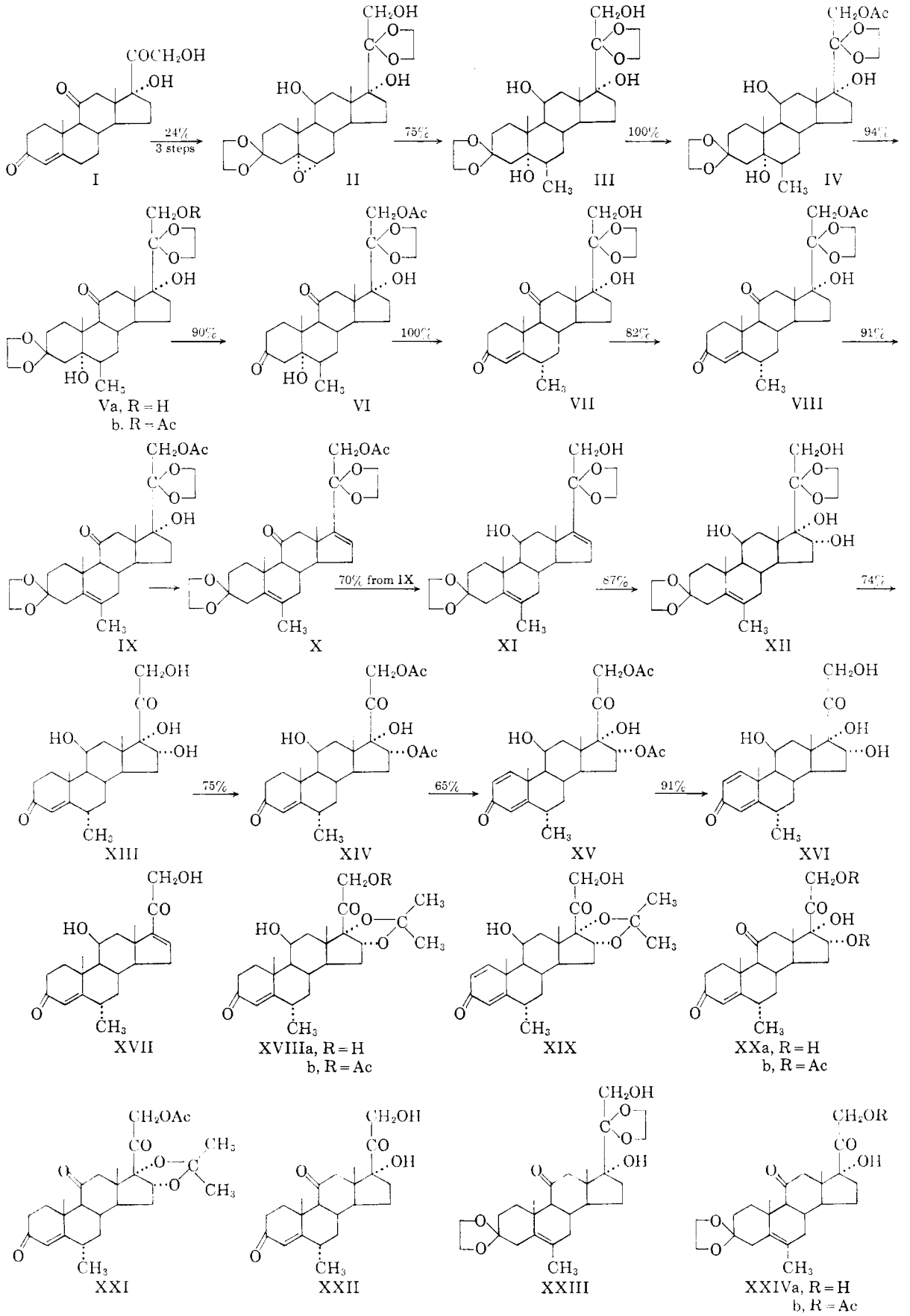
(15) W. S. Allen and S. Bernstein, THIS JOURNAL, **78**, 1909 (1956).

(16) The preparation of the acetonide XVIIIa is described elsewhere; S. Bernstein, R. Littell, J. J. Brown and I. Ringler, *ibid.*, **81**, 4573 (1959).

(17) During partition chromatographic purification of XVII a more polar compound was isolated and purified. It was indicated by its physical constants to be 6α methylhydrocortisone,[4a,c] and the structure was unequivocally established by comparison of its 21-acetate with an authentic sample kindly supplied by the Upjohn Co. The presence of this 17α-hydroxy-compound may be explained by incomplete dehydration of IX. Examination of the infrared spectrum of crude X indicated the presence of a trace amount of a hydroxyl group.

The obtaining of 6α-methylhydrocortisone in this manner provides evidence for the formation of the equatorial 6α-methyl-group on the hydrolysis of a 3-ketal-Δ^5-6-methyl moiety. In this connection, the same conclusion has been stated independently by J. H. Fried, G. E. Arth and L. H. Sarett, ref. 4d, and by O. Burn, B. Ellis, V. Petrow, I. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.*, 4092 (1957).

(18) C. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta.*, **39**, 734 (1956); S. Szpilfogel, T. Posthumus, M. De Winter and D. Van Dorp, *Rec. Trav. Chim.*, **75**, 475 (1956).



I II III IV

Va, R = H
b, R = Ac

VI VII VIII

IX X XI XII

XIII XIV XV XVI

XVII

XVIIIa, R = H
b, R = Ac

XIX

XXa, R = H
b, R = Ac

XXI XXII XXIII

XXIVa, R = H
b, R = Ac

Anal. Calcd. for $C_{28}H_{42}O_8$ (482.60): C, 64.70; H, 8.77. Found: C, 64.59; H, 8.59.

In a later experiment the product III, after crystallization from acetone–petroleum ether, had m.p. 229–231°, $[\alpha]^{25}D$ −22° (pyridine), ν_{max} 3520 and 1058 cm.$^{-1}$; literature[4c] m.p. 229–230°, $[\alpha]^{23}D$ −29° (pyridine). Found: C, 64.43; H, 9.03.

21-Acetoxy-3,20-bis-ethylenedioxy-6β-methylpregnane-5α,11β,17α-triol (IV).—A mixture of 1.2 g. of 3,20-bis-ethylenedioxy-6β-methylpregnane-5α,11β,17α,21-tetrol(III), 20 ml. of pyridine and 2 ml. of acetic anhydride was allowed to stand at room temperature overnight after which it was poured into water. Filtration gave 1.3 g. (100%) of the 21-acetate IV, m.p. 231–233°. Two crystallizations from acetone–petroleum ether gave the analytical sample, m.p. 237–238°, $[\alpha]^{25}D$ −13°; ν_{max} 3550, 1750 and 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{44}O_9$ (524.63): C, 64.10; H, 8.45. Found: C, 64.38; H, 8.74.

3,20-Bis-ethylenedioxy-5α,17α,21-trihydroxy-6β-methylpregnan-11-one (Va).—To a previously prepared mixture of chromic anhydride (630 mg.) in 3 ml. of pyridine was added a solution of 964 mg. of III in 20 ml. of pyridine, and the mixture was allowed to stand overnight at room temperature. The mixture was stirred for 1 hour with 23 ml. of a saturated sodium sulfite solution, and then was extracted with ethyl acetate. The extract was washed with water, dried and evaporated. The resulting oil gave, upon addition of ether, a brown low-melting solid. Evaporation of the mother liquor, and crystallization from methanol–water gave 500 mg. (52%) of a white solid Va, m.p. 170–172°. Repeated crystallization from several solvents failed to give an analytically pure sample.

21-Acetoxy-3,20-bis-ethylenedioxy-5α,17α-dihydroxy-6β-methylpregnan-11-one (Vb).—A.—A mixture of 300 mg. of 3,20-bis-ethylenedioxy-5α,17α-21-trihydroxy-6β-methylpregnan-11-one (Va), 3 ml. of pyridine and 0.5 ml. of acetic anhydride was allowed to stand at room temperature overnight, after which it was poured into water. Filtration gave 300 mg. (93%) of the 21-acetate Vb, m.p. 211–214°. Several crystallizations from acetone–petroleum ether gave the analytical sample, m.p. 220°, $[\alpha]^{25}D$ +2°; ν_{max} 3520, 1750, 1720 and 1229 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{42}O_9$ (522.62): C, 64.35; H, 8.10. Found: C, 64.47; H, 8.37.

B.—To a previously prepared mixture of 19 g. of chromic anhydride in 250 ml. of pyridine was added at 0°, 31.8 g. of IV in 350 ml. of pyridine. The mixture was stirred at room temperature for 16 hours, then diluted with ethyl acetate, washed with sodium bicarbonate solution and finally with saturated saline to neutrality. The extract was dried and evaporated to afford 29.7 g. (94%) of Vb, m.p. 219–221.° The infrared absorption spectrum was identical with the sample prepared above (A).

21-Acetoxy-20-ethylenedioxy-5α,17α-dihydroxy-6β-methyl pregnane-3,11-dione(VI).—A solution of 29.6 g. of the bis-ketal acetate Vb in 300 ml. of 75% aqueous acetic acid was heated on a steam-bath for 45 minutes after which 1.5 l. of water was added. The resulting precipitate was collected to afford 24.3 g. (90%) of VI, m.p. 245–247°.

An analytical specimen, prepared as above and crystallized twice from acetone–petroleum ether, had m.p. 249–251°, λ_{max} none, $[\alpha]^{24}D$ +25° (pyridine); ν_{max} 3490, 3395, 1742, 1710, 1688 and 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{38}O_8$ (478.56): C, 65.25; H, 8.00. Found: C, 65.56; H, 8.12.

20-Ethylenedioxy-17α,21-dihydroxy-6α-methyl-4-pregnene-3,11-dione (VII).—A solution of 4.45 g. of the 5α-hydroxy-21-acetate VI in 760 ml. of 0.05 *N* sodium hydroxide in 50% aqueous methanol was allowed to stand at room temperature for 17 hours in an atmosphere of nitrogen. After the addition of 4 ml. of acetic acid, the reaction mixture was concentrated to one-half volume, extracted with ethyl acetate washed with saturated saline, dried and evaporated. Crystallization of the crude residue from acetone–petroleum ether gave 3.9 g. (100%) of 20-ethylenedioxy-17α-21-dihydroxy-6α-methyl-4-pregnene-3,11-dione (VII), m.p. 175–179°. In another run, the analytical sample, obtained by crystallization from acetone–petroleum ether had a m.p. 175–179°, λ_{max} 238 mμ (ε 14,800), $[\alpha]^{25}D$ +138°; ν_{max} 3450, 1706, 1668, 1613 and 1058 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_6$ (418.51): C, 68.87; H, 8.19. Found: C, 68.57; H, 8.37.

21-Acetoxy-20-ethylenedioxy-17α-hydroxy-6α-methyl-4-pregnene-3,11-dione (VIII).—A solution of 250 mg. of 20-ethylenedioxy-17α-21-dihydroxy-6α-methyl-4-pregnene-3,11-dione (VII) in 4 ml. of pyridine and 0.5 ml. of acetic anhydride was allowed to stand at room temperature overnight after which it was poured into water. Filtration gave 215 mg. (82%) of the 21-acetate VIII, m.p. 176–180°. Crystallization from acetone–petroleum ether, and methanol–water gave pure VIII, m.p. 182–183°, $[\alpha]^{25}D$ +150°; ν_{max} 3520, 1752, 1710, 1670, 1610 and 1228 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{36}O_7$ (460.55): C, 67.80; H, 7.88. Found: C, 67.46; H, 8.03.

21-Acetoxy-3,20-bis-ethylenedioxy-17α-hydroxy-6-methyl-5-pregnen-11-one (IX). A.—A mixture of 2.0 g. of 21-acetoxy-20-ethylenedioxy-17α-hydroxy-6α-methyl-4-pregnene-3,11-dione (VIII), 100 ml. of benzene, 2.0 ml. of ethylene glycol and 50 mg. of *p*-toluenesulfonic acid monohydrate was refluxed with constant water removal for 6 hours, cooled and neutralized with saturated sodium bicarbonate solution. After dilution with ethyl acetate, the organic layer was washed twice with saturated saline, dried and evaporated. Crystallization of the crude product from acetone–petroleum ether gave 2.0 g. (91%) of the bis-ketal IX, m.p. 182–185°.

An analytical specimen prepared as above and crystallized from acetone–petroleum ether, then from methanol had m.p. 195–197°, $[\alpha]^{24}D$ −18°; ultraviolet spectrum: ϵ_{199} mμ 10,250, ϵ_{195} mμ 9,650, ϵ_{200} mμ 8,100, ϵ_{205} mμ 6,320, ϵ_{210} mμ 3,790, ϵ_{215} mμ 2,280 ϵ_{220} mμ 1,270, ϵ_{225} mμ 630 and ϵ_{230} mμ 380[19]; $_{max}$ 3496, 1755, 1705 and 1228 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{40}O_8$ (504.60): C, 66.64; H, 7.99. Found: C, 66.76; H, 8.15.

B.—Acetylation of 155 mg. of XXIII with 3 ml. of pyridine and 0.5 ml. of acetic anhydride gave 160 mg. (95%) of IX, m.p. 210–212°. Two crystallizations from acetone–petroleum ether gave a product with a constant melting point of 217–218°, $[\alpha]^{25}D$ −18°. Infrared spectral analysis showed identity with the sample in A above.

3,20-Bis-ethylenedioxy-17α,21-dihydroxy-6-methyl-5-pregnen-11-one (XXIII). A.—A mixture of 1.0 g. of 17α,21-dihydroxy-6α-methyl-4-pregnen-3,11,20-trione (XXII), 60 ml. of benzene, 6 ml. of ethylene glycol and 30 mg. of *p*-toluenesulfonic acid monohydrate was refluxed with constant water removal for 6 hours. After neutralization with sodium bicarbonate and extraction with ethyl acetate, 485 mg. (40%) of the bis-ketal XXIII was obtained from acetone–petroleum ether. Two further crystallizations from the same solvent pair gave a constant melting solvate, m.p. 260–261°, $[\alpha]^{26}D$ −22°, ν_{max} 3420 and 1698 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{38}O_7$ (462.56): C, 67.51; H, 8.28. Found: C, 66.80; H, 8.47.

B.—A solution of 600 mg. of pure 21-acetoxy-3,20-bis-ethylenedioxy-17α-hydroxy-6-methyl-5-pregnen-11-one (IX) in 30 ml. of 2.5% methanolic potassium hydroxide was refluxed for 0.5 hour. Addition of water gave, after filtration, 510 mg. of XXIII, m.p. 261–262°. Two crystallizations from acetone–petroleum ether did not alter the melting point. Found: C, 66.84; H, 8.55.

21-Acetoxy-3,20-bis-ethylenedioxy-6-methyl-5,16-pregnadien-11-one (X).—To a cooled solution of 270 mg. of 21-acetoxy-3,20-bis-ethylenedioxy-17α-hydroxy-6-methyl-5-pregnen-11-one (IX) in 5 ml. of pyridine was added 0.4 ml. of thionyl chloride. The mixture was allowed to stand at +5° for 4 hr. when it was poured into ice-water. Filtration of the resulting precipitate gave 240 mg. of low melting solid which was dissolved in ethyl acetate, washed with saturated saline, dried and evaporated to give 190 mg. of the diene X, m.p. 92–94°; ν_{max} 1754, 1706, 1660, 1630 and 1240 cm.$^{-1}$. The product did not lend itself to further purification.

(19) Similarly, 21-acetoxy-3,20-bis-ethylenedioxy-17α-hydroxy-5-pregnen-11-one [R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953)] exhibited the following ultraviolet absorption spectrum: ϵ_{190} mμ 9300, ϵ_{195} mμ 6500, ϵ_{200} mμ 4260, ϵ_{205} mμ 2400, ϵ_{210} mμ 2040, ϵ_{215} mμ 550, ϵ_{220} mμ 340, ϵ_{225} mμ 180 and ϵ_{230} mμ 0. All the "end" ultraviolet absorption spectra reported herein were determined with a Cary recording spectrophotometer (model 14M).

3,20-Bis-ethylenedioxy-6-methyl-5,16-pregnadiene-11β,21-diol (XI). A.—A mixture of 190 mg. of 21-acetoxy-3,20-bis-ethylenedioxy-6-methyl-5,16-pregnadien-11-one (X) and 300 mg. of sodium borohydride in 10 ml. of tetrahydrofuran and 1.5 ml. of 2.5% aqueous sodium hydroxide was refluxed for 18 hours. The reaction mixture was extracted with ethyl acetate, washed with saturated saline, dried and evaporated. The crude product, 170 mg. of a white glass, on crystallization from acetone, gave 40 mg. of white crystals, m.p. 161–162°. Five crystallizations from acetone–petroleum ether gave pure XI, m.p. 203–205°, $[\alpha]^{25}D$ −21°; ultraviolet absorption spectrum: ϵ_{190} mμ 14,100, ϵ_{195} mμ 14,100, ϵ_{200} mμ 12,100, ϵ_{205} mμ 9,830, ϵ_{210} mμ 5,700, ϵ_{215} mμ 3,220, ϵ_{220} mμ 1,390, ϵ_{225} mμ 782 and ϵ_{230} mμ 440[20]; ν_{max} 3448, 1620 and 1042 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{36}O_6$ (446.56): C, 69.93; H, 8.58. Found: C, 69.78; H, 8.62.

B.—To a solution of 2.4 g. of X (obtained from the dehydration of 2.7 g. of IX) in 250 ml. of tetrahydrofuran at 0° was added 2.0 g. of lithium aluminum hydride and the mixture was refluxed for 2 hours. Upon cooling, water was added cautiously to decompose excess hydride. Filtration of the inorganic precipitate followed by evaporation of the filtrate gave, after a single crystallization from acetone–petroleum ether, 1.70 g. (70% from IX) of XI, m.p. 183–186°. Infrared spectral analysis showed identity with the sample prepared in A above.

11β,21-Dihydroxy-6α-methyl-4,16-pregnadiene-3,20-dione (XVII).—A solution of 2.4 g. of 3,20-bis-ethylenedioxy-6-methyl-5,16-pregnadiene-11β,21-diol (XI) in 100 ml. of methyl alcohol and 6 ml. of 8% sulfuric acid was refluxed for 0.5 hour. The solution was concentrated under reduced pressure until an oil separated. Crystallization was effected by the addition of a few drops of benzene to give 1.72 g. (89%) of the diene-dione XVII as a solvate, m.p. 113–115°. The analytical specimen was not obtained due to variable melting points and solvation.

3,20-Bis-ethylenedioxy-6-methyl-5-pregnene-11β,16α,17α,21-tetrol (XII).—A solution of 11.0 g. of osmic acid in 165 ml. of benzene was added to 10.0 g. of 3,20-bis-ethylenedioxy-6-methyl-5,16-pregnadiene-11β,21-diol (XI) in 750 ml. of benzene and 6.8 ml. of pyridine and the mixture was stirred at room temperature for 30 minutes. The osmate ester was decomposed by the addition of 72 g. each of sodium sulfite and potassium bicarbonate in 900 ml. of water followed by 450 ml. of methanol. The mixture was then vigorously stirred for 3 hours. The inorganic precipitate was filtered and washed first with chloroform, then several times with hot tetrahydrofuran. The combined filtrates were concentrated and extracted extensively with chloroform. The crude product obtained by evaporation of the solvent, was triturated with water and filtered to give a total of 9.4 g. (87%) of XII, m.p. 265–267°.[21]

The analytical sample (obtained from another run) was prepared by crystallization of the crude material twice from acetone and twice from methanol to give m.p. 280–282°, $[\alpha]^{25}D$ −54° (pyridine), ν_{max} 3510 and 1044 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_8$ (480.58): C, 64.98; H, 8.39. Found: C, 64.86; H, 8.66.

11β,16α,21-Tetrahydroxy-6α-methyl-4-pregnene-3,20-dione (XIII). A.—To a suspension of 7.11 g. of the bis-ketal XII in 370 ml. of methanol was added 75 ml. of 8% sulfuric acid and the solution was refluxed for 1 hour. After concentration to one-third volume the residue was extracted with ethyl acetate, washed once with saturated sodium bicarbonate solution and twice with saturated saline, dried and evaporated. The residue, crystallized from acetone–petroleum ether, gave 4.28 g. (74%) of XIII, m.p. 218–220°.[21]

An analytical specimen, prepared by crystallization of XIII, m.p. 218–222°, from acetone and acetone–petroleum ether, had m.p. 225–227°, $[\alpha]^{25}D$ +92° (pyridine); λ_{max} 241 mμ (ε 15,600); ν_{max} 3380, 1710, 1660 and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_6$ (392.48): C, 67.32; H, 8.22. Found: C, 67.31; H, 8.35.

B.—To a stirred solution of 120 mg. of 11β,21-dihydroxy-6α-methyl-4,16-pregnadiene-3,20-dione (XVII) in 10 ml. of methylene chloride, 10 ml. of benzene and 0.1 ml. of pyridine was added 90 mg. of osmic acid. The solution was stirred at room temperature for 1 hour after which 5 ml. of methanol was added followed by 650 mg. each of sodium sulfite and potassium bicarbonate in 7 ml. of water. The mixture was stirred for 3 hours, filtered and the inorganic precipitate was washed with 200 ml. of chloroform. The combined filtrates were washed with saturated saline, dried and evaporated to a white solid. Crystallization from acetone–ether gave 20 mg. of XIII, m.p. 216–217°, which was shown by infrared spectral analysis to be identical with the sample prepared in A above.

16α,21-Diacetoxy-11β,17α-dihydroxy-6α-methyl-4-pregnene-3,20-dione (XIV).—A solution of 110 mg. of the tetrol XIII in 3 ml. of pyridine and 0.4 ml. of acetic anhydride was allowed to stand at room temperature for 18 hours. The solvents were then evaporated and the residue was extracted with ethyl acetate, washed with saturated saline, dried and evaporated. The crude product, upon crystallization, gave 101 mg. (75%) of XIV, m.p. 169–172°.

An analytical sample, crystallized from acetone–petroleum ether, gave a m.p. 178–179°, λ_{max} 241 mμ (ε 15,200), $[\alpha]^{25}D$ +53°; ν_{max} 3480, 1750, 1720(shoulder), 1678, 1616 and 1242 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{36}O_8$ (476.55): C, 65.53; H, 7.61. Found: C, 65.18; H, 8.21.

16α,21-Diacetoxy-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (XV). A.—To a solution of 165 mg. of XIV in 16 ml. of *t*-butyl alcohol and 0.7 ml. of glacial acetic acid was added 150 mg. of selenium dioxide. After being refluxed in an atmosphere of nitrogen for 20 hours, the mixture was cooled, diluted with ethyl acetate and filtered. The filtrate was washed successively with saturated saline, cold 1 *N* sodium hydroxide, cold dilute sulfuric acid and finally with saturated saline. Drying and evaporation gave 135 mg. of a tan glass. The crude glass was subjected to partition chromatography on 230 g. of diatomaceous earth with the system consisting of 2 parts ethyl acetate, 4 parts petroleum ether (b.p. 90–100°), 3 parts methyl alcohol and 2 parts water. The fourth hold back volume upon evaporation and crystallization from acetone–petroleum ether gave 61 mg. of 16α,21-diacetoxy-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (XV), m.p. 183–184°, λ_{max} 242 mμ (ε 10,800), $[\alpha]^{25}D$ +4°; ν_{max} 3448, 1750, 1722(shoulder), 1665, 1630, 1612(shoulder) and 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{34}O_8$ (474.53): C, 65.80; H, 7.22. Found: C, 65.49; H, 7.55.

B.—In another run, a solution of 2.0 g. of XIV and 2.2 g. of selenium dioxide in 200 ml. of *t*-butyl alcohol was refluxed in an atmosphere of nitrogen for 24 hours. After filtration the mixture was evaporated, then agitated for 2 hours with 50 ml. of methyl alcohol and about 3 g. of deactivated Raney nickel catalyst.[22] After filtration the methanol was evaporated. The residue was then dissolved in chloroform, washed with 10% acetic acid and with saturated saline, dried and evaporated. Crystallization of the crude residue from acetone–petroleum ether gave 1.30 g. (65.5%) of yellow crystals, m.p. 176–178° (suitable for further transformations). Further crystallization from acetone–petroleum ether gave XV, m.p. 183–184°.[21]

11β,16α,17α,21-Tetrahydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (XVI).—To a solution of 302 mg. of the diacetate XV in 35 ml. of methanol was added 0.92 ml. of 10% aqueous potassium carbonate solution. The mixture was stirred with a stream of nitrogen at room temperature for 20 minutes after which 0.35 ml. of acetic acid was added. The mixture was concentrated to one-third volume, extracted with chloroform, dried and evaporated. Crystallization from acetone–petroleum ether gave 225 mg. (91%) of the tetrol XVI, m.p. 224–226°.

The analytical specimen, obtained from another run, had m.p. 227–228°, $[\alpha]^{25}D$ +57° (methanol), λ_{max} 242 mμ (ε 14,100); ν_{max} 3450, 1724, 1668, 1622 and 1612 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{30}O_6$ (390.46): C, 67.67; H, 7.44. Found: C, 67.80; H, 7.76.

21-Acetoxy-11β-hydroxy-16α,17α,-isopropylidenedioxy-6α-methyl-4-pregnene-3,20-dione (XVIIIb).—Acetylation in

(20) Similarly, the 3,20-bis-ethylenedioxy-5,16-pregnadiene-11β,21-diol[13] exhibited the ultraviolet absorption spectrum: ϵ_{190} mμ 13,000, ϵ_{195} mμ 12,500, ϵ_{200} mμ 10,800, ϵ_{205} mμ 7800, ϵ_{210} mμ 4340, ϵ_{215} mμ 1080, ϵ_{220} mμ 108 and ϵ_{225} mμ 0.

(21) This preparation was carried out by Francis J. McEvoy.

(22) We are indebted for this procedure to Dr. Sidney Fox of the Chemical Production Section, Lederle Laboratories. The catalyst was prepared essentially according to P. L. Julian, C. C. Cochrane, A. Magnani and W. J. Karpel, THIS JOURNAL, **78**, 3153 (1956).

the usual manner of 11β,21-dihydroxy-16α,17α-isopropylidenedioxy-6α-methyl-4-pregnene-3,20-dione (XVIIIa)[16] gave the 21-acetate (crystallized from acetone–petroleum ether), m.p. 218–219°, $[\alpha]^{25}D$ + 131°, λ_{max} 242 mμ (ε 14,100); ν_{max} 3390, 1760, 1730, 1668, 1612, 1374, 1093, 1055 and 862 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{38}O_7$ (474.57): C, 68.33; H, 8.07. Found: C, 67.93; H, 8.19.

16α,21-Diacetoxy-17α-hydroxy-6α-methyl-4-pregnene-3,11,20-trione (XXb).—To a previously prepared mixture of 800 mg. of chromic anhydride in 10 ml. of pyridine was added a solution of 1.25 g. of 16α,21-diacetoxy-11β,17α-dihydroxy-6α-methyl-4-pregnene-3,20-dione (XIV) in 20 ml. of pyridine. The mixture was allowed to stand at room temperature for 20 hours with occasional stirring after which methanol was added and the solvents were evaporated. The residue was extracted with ethyl acetate, washed with dilute sulfuric acid, dilute sodium bicarbonate and finally with water to neutrality. After drying and evaporation the residue was crystallized from acetone–petroleum ether to yield 630 mg. of white solid, m.p. 201–202°. A small portion was crystallized several times from acetone–petroleum ether to give pure XXb, m.p. 207–208°, $[\alpha]^{25}D$ +123°, λ_{max} 238 mμ (ε14,900); ν_{max} 3450, 1754, 1712, 1674, 1612 and 1232 cm.$^{-1}$

Anal. Calcd. for $C_{26}H_{34}O_8$ (474.55): C, 65.80; H, 7.22. Found: C, 65.54; H, 7.21.

16α,17α,21-Trihydroxy-6α-methyl-4-pregnene-3,11,20-trione (XXa).—To a solution of 604 mg. of the 16,21-diacetate XXb in 80 ml. of methanol was added 2.0 ml. of 10% aqueous potassium carbonate and the mixture was agitated at room temperature with a stream of nitrogen for 20 minutes. After the addition of 1.0 ml. of glacial acetic acid and evaporation to one-third volume, water was added and 350 mg. of white needles, m.p. 236–237°, were filtered. Crystallization of a portion twice from acetone–petroleum ether gave the pure triol XXa, m.p. 236–238°, λ_{max} 238 mμ (ε 15,00), $[\alpha]^{25}D$ +148° (pyridine); ν_{max} 3420, 3300, 1710, 1658 and 1612 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{30}O_6$ (390.46): C, 67.67; H, 7.74. Found: C, 67.81; H, 7.91.

21-Acetoxy-16α,17α-isopropylidinedioxy-6α-methyl-4-pregnene-3,11,20-trione (XXI).—A solution of 245 mg. of the triol-trione XXa in 12 ml. of acetone and 0.025 ml. of 70% perchloric acid was stirred at room temperature for 2.5 hours after which 0.4 ml. of saturated sodium bicarbonate and 5 ml. of water were added. Extraction with ethyl acetate and evaporation gave 270 mg. of oil which resisted all attempts to induce crystallization. Chromatography resulted again in an intractable oil. This oil (190 mg.) was acetylated to give 160 mg. of white solid, m.p. 212–214°, from acetone–petroleum ether. Two additional crystallizations from the same solvent pair gave the pure acetonide XXI, m.p. 214–216°, λ_{max} 236 mμ (ε 16,000), $[\alpha]^{25}D$ +183°; ν_{max} 1754, 1730, 1708, 1672, 1610 and 862 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{36}O_7$ (472.56): C, 68.62; H, 7.68. Found: C, 68.51; H, 7.82.

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[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Some 2- and 7-Derivatives of Benznorbornene

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exo- and *endo* 2-benznorbornenol, *anti*-7-benznorbornenol and *anti*-7-benznorbornadienol (II, IV, VII and IX, respectively) have been prepared and the rates of acetolysis of their *p*-bromobenzenesulfonates have been measured for comparison with the esters of the corresponding norborneols and norbornenols. All four esters undergo acetolysis without rearrangement. The results are shown in Tables I and II. Compared with the C–C double bond, the fused benzene ring has a similar effect on the 2-bromobenzenesulfonates, but it provides only about half (on an energy scale) of the large assistance to ionization at C_7 which the double bond offers. The additional double bond in the *p*-bromobenzenesulfonate of IX favors ionization by a factor of 100.

Introduction

Wittig's elegant procedure[1] for the addition of dehydrobenzene (benzyne) to dienes has made readily available benznorbornadiene (I) from which the benzo analogs of *endo*-, *exo*- and 7-norbornenol can be prepared. These compounds are of special interest in view of the extraordinary spread of reactivities observed in the solvolysis of the sulfonate esters of 2- and 7-norborneol and norbornenol. Figure 1 summarizes the reported rate constants relative to the corresponding cyclohexyl ester at 25°. The high driving force for ionization of *exo*-2-norbornenyl *p*-bromobenzenesulfonate is associated with homoallylic delocalization of the π-electron pair in the double bond and leads to a rearranged product. The much greater driving force observed in *anti*-7-norbornenyl *p*-bromobenzenesulfonate has been attributed to delocalization of the same electron pair among the three centers represented by carbon atoms 5, 6 and 7, but this ionization leads to a product in which both structure and configuration have been fully retained.

In the S_N1 reactions of allylic and benzylic compounds, the benzene ring affords a driving force between those of the vinyl and 1-propenyl groups. For example, from rate constants in the literature, α-phenylethyl chloride undergoes ethanolysis at 25° in absolute alcohol at a first-order rate about 3.5 times that of α-methylallyl chloride,[2–4] but a thousand times more slowly than α, γ-dimethylallyl chloride.[5]

Since allylic delocalization is entirely by π-interactions, while homoallylic delocalization depends strongly upon oriented σ-overlap of orbitals,[6,7] it was of special interest to compare the effects of the benzene ring fused at 5,6 with those of the double bond in the same position.

Preparation of Compounds.—The flow sheet summarizes the preparations starting with benznorbornadiene prepared by the method of Wittig and Knauss. As expected, direct hydration of the double bond led to *exo*-2-benznorbornenol, m.p. 74.1–75.4°, which could be oxidized to the corre-

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