with ethyl acetate. The extract was washed with saline and water, dried, treated with Norite and evaporated. This afforded an oil which on paper chromatographic analysis (4 hours) showed the presence of 6 distinct compounds. The mixture was then acetylated with acetic anhydride (0.5 ml.) and pyridine (2 ml.) (overnight at room temperature) to afford 88 mg. of an oil which on paper chromatographic analysis (3 hours) consisted of about equal amounts of 9α-hydroxyhydrocortisone acetate (VIIIb) (at 11 cm.) and material of the same polarity as starting material (at 18 cm.). There were also very minor traces of two other compounds at 1 and 14 cm.

The oil (85 mg.) was submitted to partition chromatography on Celite (60 g.) in the same manner described above, and 25-ml. fractions were taken. Fraction 2 consisted of 15 mg., m.p. 237–244° dec. (not further investigated), whereas the desired 9α-hydroxy-compound VIIIb was in fractions 9 and 10, which were evaporated. This furnished 25 mg. (29% yield), m.p. 215.5–217°. Two crystallizations from acetone–petroleum ether gave pure VIIIb, m.p. 218–219°, $[\alpha]_D$ +171° (*c* 0.662, pyridine). Its infrared absorption spectrum was identical to that of A.

PEARL RIVER, NEW YORK

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

Steroidal Cyclic Ketals. XIX.[1] The Synthesis of 7-Keto-desoxycorticosterone

BY ROBERT H. LENHARD AND SEYMOUR BERNSTEIN

RECEIVED SEPTEMBER 2, 1955

Reaction of the bis-ethylene ketal I of desoxycorticosterone acetate with N-bromosuccinimide followed by alumina furnished the 7α,21-diol 21-acetate bis-ketal IIb. Saponification with potassium carbonate gave the 7α,21-diol bis-ketal IIa (97% yield). Oxidation of IIb with chromic anhydride–pyridine complex gave the 3,7,20-trione 21-acetate 3,20-bis-ketal IIIb (89% yield). Reduction of the latter with lithium aluminum hydride produced both the 7α,21-diol bis-ketal IIa (13% yield) and the 7β,21-diol bis-ketal IV (29% yield). Hydrolysis of either epimer resulted in $\Delta^{4,6}$-pregnadiene-21-ol-3,20-dione (Va). The latter was further characterized by conversion into its 21-acetate Vb. Saponification of the 3,7,20-trione 21-acetate 3,20-bis-ketal IIIb with potassium bicarbonate afforded Δ^5-pregnene-21-ol-3,7,20-trione 3,20-bis-ethylene ketal (IIIa) (14% yield), and also, as the major product (73% yield), $\Delta^{3,5}$-pregnadiene-3-(β-hydroxy)-ethoxy-21-ol-7,20-dione 20-ethylene ketal (VIa). The diacetate VIb was obtained on acetylation. Hydrolysis of VIa gave in 80% yield the desired 7-keto-desoxycorticosterone which exists in its enol form, $\Delta^{3,5}$-pregnadiene-3,21-diol-7,20-dione (VII).

In a recent publication[2] from this Laboratory there was described the synthesis of the bis-ethylene ketal I of desoxycorticosterone acetate which was successfully transformed into a new derivative of desoxycorticosterone, namely, pregnane-5α,21-diol-3,20-dione. Subsequently, the possible utilization of I for the synthesis of 7-oxygenated derivatives of desoxycorticosterone[3] was explored, and the results obtained form the basis of this paper.

The bis-ethylene ketal I of desoxycorticosterone acetate in carbon tetrachloride and petroleum ether in the presence of anhydrous potassium carbonate was brominated in the allylic position (C-7) with N-bromosuccinimide.[4] The bromination product was not isolated but was treated immediately (after the removal of succinimide) with ethyl acetate washed alumina, and was stirred for 2.5 hours at room temperature.[5] In this manner, Δ^5-pregnene-7α,21-diol-3,20-dione 21-acetate 3,20-bis-ethylene ketal (IIb) was obtained. Saponification in alcohol with an aqueous solution of potassium carbonate afforded Δ^5-pregnene-7α,21-diol-3,20-dione 3,-20-bis-ethylene ketal (IIa) (97% yield) ($[\alpha]^{24}_D$ −49°).

Oxidation of the 7α,21-diol 21-acetate bis-ketal IIb with chromic anhydride–pyridine complex[6] gave in 89% yield Δ^5-pregnene-21-ol-3,7,20-trione 21-acetate 3,20-bis-ethylene ketal (IIIb) which exhibited an ultraviolet absorption maximum at 240–241 mμ, with a molecular extinction coefficient of 12,700 characteristic of a Δ^5-7-ketone.[7]

Reduction of the 3,7,20-trione 21-acetate 3,20-bis-ketal IIIb in ether with lithium aluminum hydride afforded, after chromatography on silica gel, Δ^5-pregnene-7α,21-diol-3,20-dione 3,20-bis-ethylene ketal (IIa) (13% yield) and Δ^5-pregnene-7β,21-diol-3,20-dione 3,20-bis-ethylene ketal (IV) ($[\alpha]^{24}_D$ +29°) (29% yield). It is to be noted that the epimeric alcohols conform to the generalization established with other types of steroids that 7β-derivatives are dextrorotatory whereas the corresponding 7α-epimers are levorotatory.[5b,8]

The 7β,21-diol bis-ketal IV in methanol on hydrolysis with 8% (v./v.) sulfuric acid did not afford the desired 7β-hydroxydesoxycorticosterone. Under the conditions of the hydrolysis the C_7-hydroxyl group was eliminated and $\Delta^{4,6}$-pregnadiene-21-ol-3,20-dione (Va) in a solvated state (λ_{max} 283 mμ, ϵ 25,500) was formed in 67% yield.[9,10] The same compound (70% yield) was obtained by hydrolysis of the 7α,21-diol bis-ketal

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[1] Paper XVIII, R. Littell and S. Bernstein, THIS JOURNAL, **78**, 984 (1956).

[2] S. Bernstein and R. H. Lenhard, *ibid.*, **77**, 2233 (1955).

[3] The only such derivative known is 7α-hydroxy-desoxycorticosterone which has been synthesized *microbiologically* by Ch. Meystre, E. Vischer and A. Wettstein, *Helv. Chim. Acta*, **38**, 381 (1955).

[4] R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

[5] (a) J. A. K. Buisman, W. Stevens and J. v. d. Vliet, *Rec. trav. chim.*, **66**, 83 (1947); (b) H. J. Ringold, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 3318 (1952).

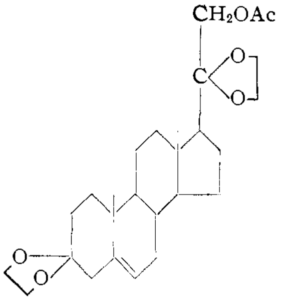
[6] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

[7] L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

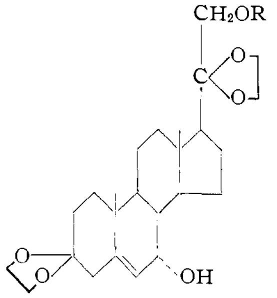
[8] (a) A. E. Bide, H. B. Henbest, E. R. H. Jones and P. A. Wilkinson, *J. Chem. Soc.*, 1788 (1948); and (b) C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *ibid.*, 2375 (1952).

[9] After the completion of this work, the compound Va was described by Meystre, Vischer and Wettstein.[3]

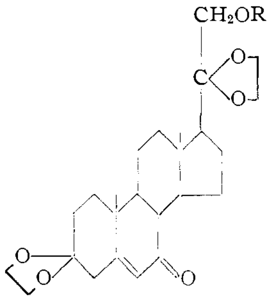
[10] Only one example of a 7-ol-Δ^4-3-one synthesized by *chemical* means has been described, namely, Δ^4-cholestene-7β-ol-3-one.[8b] This compound was synthesized in 10% yield by an Oppenauer oxidation of Δ^5-cholestene-3β,7β-diol. The principal oxidation product (40%) was $\Delta^{4,6}$-cholestadiene-3-one. A similar pathway to Δ^4-cholestene-7α-ol-3-one was unsuccessful. The $\Delta^{4,6}$-diene was again the principal product (*ca.* 75% yield).



I



IIa, R = H
b, R = Ac



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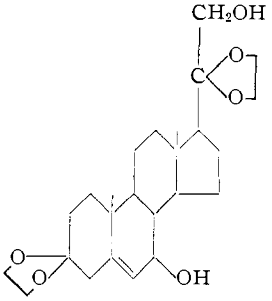
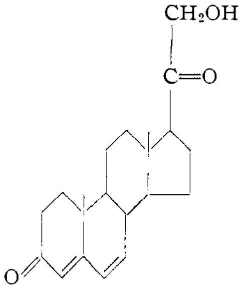
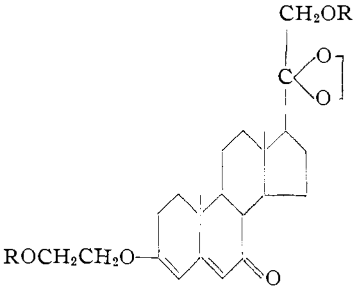


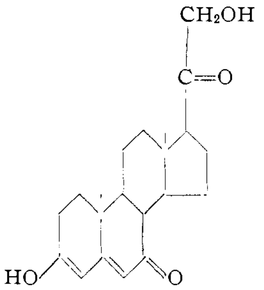
IV



Va, R = H
b, R = Ac



VIa, R = H
b, R = Ac



VII

IIa.[11] Acetylation furnished the known $\Delta^{4,6}$-pregnadiene-21-ol-3,20-dione 21-acetate (Vb).[3,12]

Our attention was finally directed to the synthesis of 7-ketodesoxycorticosterone (VII). Accordingly, a solution of Δ^5-pregnene-21-ol-3,7,20-trione 21-acetate 3,20-bis-ethylene ketal (IIIb) in methanol was refluxed with an aqueous solution of potassium bicarbonate. Unexpectedly, this treatment gave two products, one of which was Δ^5-pregnene-21-ol-3,7,20-trione 3,20-bis-ethylene ketal (IIIa) (14% yield). The major product of saponification, which could be obtained in 73% yield, was a compound in which not only was the 21-acetate group saponified but also it appeared that the 3-ketal group underwent ring fission to afford an enol-ether grouping. On the basis of analytical, ultraviolet absorption (λ_{max} 309–310 mμ, ε 32,800),[7,8b,13] infrared absorption and optical rotation ($[\alpha]^{27}_D$ −281°)[8b] data, the compound was assigned the structure VIa, namely, $\Delta^{3,5}$-pregnadiene-3-(β-hydroxy)-ethoxy-21-ol-7,20-dione 20-ethylene ketal. Acetylation furnished a diacetate VIb; this fact corroborated the assigned structure. Moreover, hydrolysis of VIa in acetone with perchloric acid gave 7-keto-desoxycorticosterone in its enol form, $\Delta^{3,5}$-pregnadiene-3,21-diol-7,20-dione (VII) (80% yield). The structure was supported by examination of the ultraviolet absorption spectrum, $\lambda_{max}^{abs.\ alc.}$ 320–321 mμ (ε 23,600) and 391–392 mμ (ε 3,800); $\lambda_{max}^{1\%\ KOH\ in\ abs.\ alc.}$ 390–391 mμ (ε 74,400).[7,8b,13]

Bioassays.[14]—In the electrolyte assay (K/Na ratio) on adrenalectomized rats, 7-ketodesoxycorticosterone (VII) exhibited a slight (if any) activity at 16.8-μg. dose level. In the same assay, desoxycorticosterone at a 6-μg. dose level gave a significantly positive result.

In the rat anti-inflammatory and thymus involution assays, 7-ketodesoxycorticosterone (VII) appeared inactive at a 1-mg. dose level whereas hydrocortisone gave significantly positive results.

Acknowledgment.—We wish to thank Messrs. Louis M. Brancone, Samuel S. Modes and Gerald P. McTernan for the microanalyses, and Messrs. William Fulmor and George Morton and Miss Anne Callaghan for the optical rotation data and the infrared absorption spectra.

Experimental

Melting Points.—All melting points are uncorrected, and were determined with uncalibrated Anschütz thermometers.

Optical Rotation.—The rotations are for chloroform solutions, unless otherwise noted.

Absorption Spectra.—The ultraviolet spectra were determined in absolute alcohol (unless otherwise noted) with a Beckman spectrophotometer (model DU). The infrared spectra (Nujol mull or pressed potassium bromide as indicated) were determined with a Perkin–Elmer spectrophotometer (model 21).

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

All evaporations were carried out under reduced pressure.

Δ^5-Pregnene-7α,21-diol-3,20-dione 21-Acetate 3,20-Bis-ethylene Ketal (IIb).—A mixture of the bis-ethylene ketal I of desoxycorticosterone acetate (2.0 g.), N-bromosuccinimide (0.97 g.) and anhydrous potassium carbonate (0.4 g.) in carbon tetrachloride (60 ml.) and petroleum ether (b.p. 62–64°) (20 ml.) was refluxed and irradiated for 4 minutes by the heat and light of a photospot lamp (Type RSP-2A,

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(11) A more thorough investigation of the hydrolysis of the two epimeric diol bis-ketals is warranted. However, it was decided to set this aside in view of the facile synthesis of 7α-hydroxy-Δ^4-3-ketones by microbiological methods (footnote 3, and unpublished results of this Laboratory).

(12) A. Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940).

(13) J. Barnett, B. E. Ryman and F. Smith, *J. Chem. Soc.*, 526 (1946).

(14) The bioassays were carried out under the direction of Dr. Ralph I. Dorfman at the Worcester Foundation for Experimental Biology, Shrewsbury, Mass. We are pleased to acknowledge this collaboration on the biological phase of the work.

General Electric Co.). The filtered solution was stirred at room temperature for 2.5 hours with ethyl acetate washed alumina (16 g.), filtered and evaporated to dryness. The residue was crystallized twice from ether–petroleum ether to yield 0.42 g. of crude product, m.p. 133–143° with previous softening. The alumina was stirred for 30 minutes with approximately 300 ml. of acetone, filtered and evaporated to dryness. Crystallization of the residue from ether–petroleum ether gave 0.61 g., m.p. 138–146° with previous softening. Five additional crystallizations of the latter fraction from ether–petroleum ether afforded 0.38 g. of pure IIb, m.p. 158–160°; $\lambda_{\max}$ none; $\nu_{\max}^{\text{Nujol}}$ 3534, 3460, 1748, 1674, 1242 and 1099 cm.$^{-1}$; $[\alpha]^{24}\text{D}$ $-55°$ (c 0.770).

Anal. Calcd. for $C_{27}H_{40}O_7$ (476.59): C, 68.04; H, 8.46. Found: C, 67.75; H, 8.82.

Δ^5-Pregnene-7α,21-diol-3,20-dione 3,20-Bis-ethylene Ketal (IIa).—A solution of IIb (100 mg.) in ethanol (5 ml.) was treated with anhydrous potassium carbonate (33 mg.) in water (0.25 ml.) and refluxed for 1.75 hours. The addition of water and chilling gave 88 mg. (97% yield) of the diol, m.p. 199–203° with previous softening. Four crystallizations from acetone–petroleum ether gave 57 mg. of pure IIa, m.p. 203–204°, $\nu_{\max}^{\text{Nujol}}$ 3460, 1672 and 1096 cm.$^{-1}$; $[\alpha]^{24}\text{D}$ $-49°$ (c 0.695).

Anal. Calcd. for $C_{25}H_{38}O_6$ (434.55): C, 69.09; H, 8.81. Found: C, 68.90; H, 9.08.

Δ^5-Pregnene-21-ol-3,7,20-trione 21-Acetate 3,20-Bis-ethylene Ketal (IIIb).—The acetate bis-ketal (IIb, 200 mg.) in pyridine (4 ml.) was added to a slurry of chromic anhydride (150 mg.) and pyridine (2 ml.). The reaction mixture, after standing for 17 hours at 27–30°, was poured into ice-water, and the precipitate was collected and washed with water. The crude product was dissolved in ethyl acetate, washed with saturated saline and water, dried and evaporated. Crystallization of the residue from ether–petroleum ether gave 177 mg. (89% yield) of IIIb, m.p. 141–145°. One crystallization from acetone–petroleum ether and two from ether–petroleum ether gave 110 mg. of pure product, m.p. 148–149.5° with previous softening; $\lambda_{\max}$ 240–241 mμ (ε 12,700); $\nu_{\max}^{\text{Nujol}}$ 1754, 1681, 1650, 1233 and 1109 cm.$^{-1}$; $[\alpha]^{24}\text{D}$ $-46°$ (c 0.585).

Anal. Calcd for $C_{27}H_{38}O_7$ (474.57): C, 68.33; H, 8.07. Found: C, 68.09; H, 8.39.

Δ^5-Pregnene-7α,21-diol-3,20-dione Bis-ethylene Ketal (IIa) and Δ^5-Pregnene-7β,21-diol-3,20-dione 3,20-Bis-ethylene Ketal (IV).—A solution of 500 mg. of IIIb in 200 ml. of anhydrous ether was treated with 300 mg. of lithium aluminum hydride and the mixture was refluxed for 2.75 hours. The excess hydride was decomposed cautiously with water and the inorganic solid was removed by filtration. The solid was triturated several times with ether and the combined washed and dried extracts were evaporated. The residue was dissolved in ether and adsorbed on 35 g. of silica gel (ether washed and dried at 110°). Elution with ether, 10% acetone–ether, and 25% acetone–ether gave fractions A, B and C, respectively. Fraction B was crystallized from acetone–petroleum ether to yield 175 mg. (29% yield) of IV, m.p. 173.5–174.5° with previous softening (product gels out, becomes crystalline on standing). Recrystallization from acetone–petroleum ether did not alter the melting point; $\lambda_{\max}$ none; $\nu_{\max}^{\text{Nujol}}$ 3425, 1681 (very weak?), 1639 and 1096 cm.$^{-1}$; $[\alpha]^{24}\text{D}$ $+29°$ (c 0.515).

Anal. Calcd. for $C_{25}H_{38}O_6$ (434.55): C, 69.09; H, 8.81. Calcd. for $C_{25}H_{38}O_6 \cdot CH_3COCH_3$ (492.63): C, 68.26; H, 9.00. Found: C, 68.36; H, 9.22.

Fraction C was crystallized from acetone–petroleum ether to afford 94 mg. of crude IIa, m.p. 185–194° with previous softening. Five crystallizations from acetone–petroleum ether gave 66 mg. (13% yield) of pure IIa, m.p. 203–204°; $\lambda_{\max}$ none (end absorption only); $\nu_{\max}^{\text{Nujol}}$ 3497, 1672 and 1098 cm.$^{-1}$; $[\alpha]^{24}\text{D}$ $-49°$ (c 0.510). Mixed melting point with the analytical sample above showed no depression.

Fraction A (65 mg., m.p. 158–175°) was rechromatographed on 4 g. of silica gel. Elution with 25% ether–benzene gave 59 mg. of material with m.p. 170–173° with previous softening. Four crystallizations from acetone–petroleum ether gave 24 mg. of material which was not further investigated; m.p. 178–181° with previous softening; $\nu_{\max}^{\text{Nujol}}$ 3390, 1658 and 1099 cm.$^{-1}$.

$\Delta^{4,6}$-Pregnadiene-21-ol-3,20-dione (Va).[15]—The diol bis-ketal (IV, 125 mg.) in methanol (10 ml.) and 8% (v./v.) sulfuric acid (1 ml.) was refluxed under an atmosphere of nitrogen for 40 minutes. The addition of water and cooling gave 63 mg. (67% yield) of the diene, m.p. 136.5–137.5° with previous softening. One crystallization from acetone–petroleum ether afforded 54 mg. of Va, m.p. 136.5–138° with previous softening; $\lambda_{\max}$ 283 mμ (ε 25,500); $\nu_{\max}^{\text{Nujol}}$ 3559, 3448, 1717, 1658, 1621 and 1587 cm.$^{-1}$; $[\alpha]^{24}\text{D}$ $+163°$ (c 0.405).

Anal. Calcd. for $C_{21}H_{28}O_3$ (328.44): C, 76.79; H, 8.59. Found: C, 76.11; H, 8.84.

B.—The diol bis-ketal (IIa, 40 mg.) in methanol (3 ml.) and 8% (v./v.) sulfuric acid (0.3 ml.) was treated in the same manner as above to yield 21 mg. (70% yield) of the diene, m.p. 136–137°. The product was identical with that obtained above as confirmed by melting point, admixture melting point, ultraviolet and infrared absorption data.

$\Delta^{4,6}$-Pregnadiene-21-ol-3,20-dione 21-Acetate (Vb).[16]—The diene-ol Va (20 mg.) was acetylated in the usual manner to yield 15 mg. (67% yield) of pure Vb, m.p. 112–114°. Recrystallization from acetone–petroleum ether did not alter the melting point; $\lambda_{\max}$ 282 mμ (ε 27,500); $\nu_{\max}^{\text{Nujol}}$ 1751, 1732, 1672, 1629, 1595 and 1245 cm.$^{-1}$; $[\alpha]^{24}\text{D}$ $+150°$ (c 0.240, abs. alc.).

Δ^5-Pregnene-21-ol-3,7,20-trione 3,20-Bis-ethylene Ketal (IIIa).—A solution of 647 mg. of IIIb in 45 ml. of methanol was treated with 170 mg. of potassium bicarbonate in 1.7 ml. of water and refluxed for 45 minutes under a nitrogen atmosphere. The reaction mixture was worked up as above and the residue was crystallized from acetone–petroleum ether to yield 380 mg. of VIa, m.p. 196.5–200° with previous softening. Evaporation of the mother liquor gave 80 mg. (14% yield) of crude IIIa, m.p. 164–169° with previous softening. Three crystallizations from acetone–petroleum ether gave 53 mg. of product, m.p. 171–173° with previous softening; $\lambda_{\max}$ 240 mμ (ε 12,400); $\nu_{\max}^{\text{KBr}}$ 3425, 1672, 1626 and 1103 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 68.85; H, 8.74.

The trione bis-ketal IIIa was readily acetylated to give pure IIIb, as confirmed by melting point, admixture melting point and infrared absorption data.

$\Delta^{3,5}$-Pregnadiene-3-(β-hydroxy)-ethoxy-21-ol-7,20-dione 20-Ethylene Ketal (VIa).—A solution of IIIb (150 mg.) in methanol (10 ml.) was treated with potassium bicarbonate (40 mg.) in water (0.4 ml.) and refluxed for 1 hour under a nitrogen atmosphere. The methanol, under nitrogen, was evaporated, and ethyl acetate and saturated saline were added to the residue. The aqueous phase was extracted several times with ethyl acetate, and the washed and dried extract evaporated. Crystallization of the residue from acetone–petroleum ether gave 100 mg. (73% yield) of product, m.p. 195–199.5° with previous softening. Five crystallizations from acetone–petroleum ether afforded 68 mg. of pure VIa, m.p. 202–203° with previous softening; $\lambda_{\max}$ 309–310 mμ (ε 32,800); $\nu_{\max}^{\text{KBr}}$ 3413, 3311, 1742, 1626, 1587 and 1088 cm.$^{-1}$; $[\alpha]^{27}\text{D}$ $-281°$ (c 0.235).

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 68.86, 68.92; H, 8.42, 8.45.

In another run (1.5 hr. reflux), 75 mg. of IIIb gave 10 mg. of VIa, m.p. 199–201°, $\lambda_{\max}$ 310 mμ (ε 30,000).

Anal. Found: C, 69.36, 69.74; H, 8.52, 8.52.

$\Delta^{3,5}$-Pregnadiene-3-(β-acetoxy)-ethoxy-21-ol-7,20-dione 21-Acetate-20-Ethylene Ketal (VIb).—Compound VIa (80 mg.) in pyridine (2 ml.) was treated with acetic anhydride (1 ml.) (22 hours at room temperature). The reaction mixture was poured into ice-water and collected; 85 mg. (89% yield), m.p. 165–170° with previous softening. Two crystallizations from acetone–petroleum ether gave 66 mg. of pure VIb, m.p. 172–173.5° with previous softening; $\lambda_{\max}$ 308 mμ (ε 28,000); $\nu_{\max}^{\text{KBr}}$ 1751, 1650, 1610, 1590 (shoulder), 1227 and 1075 (weak) cm.$^{-1}$; $[\alpha]^{25}\text{D}$ $-251°$ (c 0.531).

Anal. Calcd. for $C_{29}H_{40}O_8$ (516.61): C, 67.42; H, 7.80; OAc, 16.66. Found: C, 67.36; H, 8.09; OAc, 15.78.

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(15) Literature[3] m.p. 134–135°, $[\alpha]^{23}\text{D}$ $+139.5° \pm 4°$ (alc.).

(16) A. Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940); m.p. 115–116°; $\lambda_{\max}^{\text{alc}}$ 283 mμ, log ε 4.53; $[\alpha]^{18}\text{D}$ $+151.5°$ (alc.); footnote 3: m.p. 111–114°; $\lambda_{\max}^{\text{alc}}$ 284 mμ, ε 27,300; $[\alpha]^{23}\text{D}$ $+159.5 \pm 4°$ (alc.).

$\Delta^{3,5}$-Pregnadiene-3,21-diol-7,20-dione (VII).—A solution of VIa (100 mg.) in acetone (20 ml.) was treated with 3 *N* perchloric acid (1 ml.) and allowed to stand at room temperature for 2 hours. The greenish-yellow fluorescent solution was poured into ice-water, and the precipitate was collected; 63 mg. (80% yield), m.p. 227–232° with previous softening, browning and decomposition; λ_{max} 320–321 mμ (ε 23,500) and 389–392 mμ (ε 2,700). Two crystallizations from acetone–petroleum ether gave 39 mg., m.p. 232–235° with previous softening, browning and decomposition; λ_{max} 320–321 mμ (ε 23,600) and 391–392 mμ (ε 3,800), $\lambda_{max}^{1\%\ \mathrm{KOH\ in\ abs.\ alc.}}$ 390–391 mμ (ε 74,400); ν_{max}^{KBr} 3448, 3135, 1704, 1600 and 1546 cm.$^{-1}$; $[\alpha]^{27}\mathrm{D}$ −267° (*c* 0.487).

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 73.38; H, 8.43.

PEARL RIVER, NEW YORK

[CONTRIBUTION FROM THE BAKER LABORATORY OF CORNELL UNIVERSITY]

Cyclizations Accompanying the Hydration and the Dehydration of β-Methylheptenone

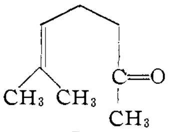
BY J. MEINWALD AND R. F. GROSSMAN

RECEIVED AUGUST 1, 1955

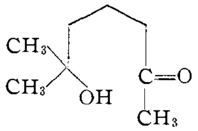
The hydration of β-methylheptenone (I) to the corresponding ketol II was observed to give some crystalline product on one occasion. This product, previously considered to be a pure sample of II, is now shown to be 1,3-dimethylcyclohexane-1,3-diol (IIIc). In connection with this structural assignment, it became necessary to reinvestigate the acid-catalyzed dehydration of I, reported by Verley to yield the "dihydro-*m*-xylene" IV. Verley's claim was discredited by Wallach, who adduced evidence in favor of the hydrocarbon consisting chiefly of a mixture of *m*-xylene and the "tetrahydro-*m*-xylene" VI. New chemical and physical evidence now supports the following conclusions regarding the disputed hydrocarbon: 1, the initial dehydration product is 1,3-dimethylcyclohexadiene-1,3 (IV); 2, under a variety of conditions, IV partially disproportionates to *m*-xylene and 1,5-dimethylcyclohexene (VI); 3, using strong sulfuric acid, the final product consists solely of IV and VI, while zinc chloride yields *m*-xylene in addition to these two components. Some rationalizations for these findings are offered.

The Hydration of β-Methylheptenone.—While carrying out Rupe's synthesis of α-cinenic acid,[1] a curious observation was made in the first step. β-Methylheptenone (I) was hydrated with 35% sulfuric acid to give the corresponding tertiary ketol II; on distillation of the ketol a crystalline material appeared as a slightly higher boiling fraction.[2] This material showed a melting range of 50–60°, but after purification it melted at 90–91°. Elementary analysis showed it to be isomeric with the normal hydration product II. Further quantities of the abnormal product were obtained from the residue remaining after the distillation of α-cinenic nitrile, formed by treating the crude ketol II with anhydrous hydrogen cyanide.[3]

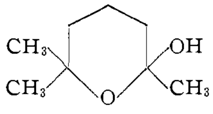
Although this abnormal product was not mentioned by Rupe, reference to its formation in one instance may be found in an early study of the action of sulfuric acid on β-methylheptenone published by Verley in 1897.[4] It was Verley's opinion that this material was simply a very pure sample of II. This hypothesis, however, is untenable. The abnormal hydration product shows no absorption in the carbonyl region of the infrared, although it does have strong hydroxylic absorption. The spectrum might be reconciled with Verley's view if we presume that the unknown is the hemiketal IIa. This possibility can be eliminated, however, by the observation that the compound fails to form a 2,4-dinitrophenylhydrazone, indicating the absence of even a potential carbonyl group.



I



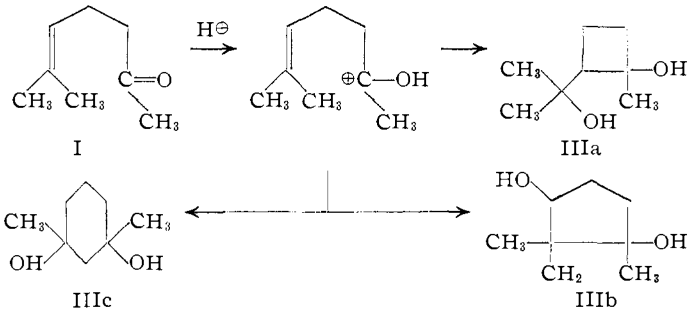
II



IIa

The following structures and modes of formation (eq. 1) for the abnormal hydration product were considered: IIIa appeared unlikely on steric grounds, while IIIb would require anti-Markownikoff addition and is not in accord with the fact that the compound is not acetylated by pyridine and acetic anhydride. IIIc, therefore, seemed most likely, even though its formation would require preliminary migration of the double bond into a terminal position. The dehydration of the diol to 1,3-dimethylcyclohexadiene-1,3 (IV) (discussed below) provides further evidence that the assignment of structure IIIc to the "anormal hydration product" is actually correct.

(1)



The Dehydration of β-Methylheptenone.—Verley's study of the β-methylheptenone–sulfuric acid reaction included a series of experiments in which the effect of acid concentration on product composition was investigated. The most interesting of his results was the finding that in 75% sulfuric acid, the chief product was a hydrocarbon, C_8H_{12},

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[1] H. Rupe and P. Schlochoff, *Ber.*, **38**, 1502 (1905); H. Rupe and C. Liechtenhan, *ibid.*, **41**, 1298 (1908).

[2] The formation of this product was first noticed in this Laboratory by R. Burrows.

[3] J. Meinwald, THIS JOURNAL, **77**, 1617 (1955). See especially footnote 25 in this reference.

[4] A. Verley, *Bull. soc. chim. Paris*, [3] **17**, 175 (1897).