Acknowledgment.—The authors thank Dr. D. L. Aldous for a sample of his by-product identified by us as IIIa, Mrs. R. Kitai for assistance with some of the experimental work, and the South African Council for Scientific and Industrial Research for the grant of a bursary to one of them (P. P. E. S.).

Oxidation of Steroidal Ketones. III. Selenium Dioxide-Catalyzed Hydrogen Peroxide Oxidation of 4-En-3-ones[1]

E. CASPI[2] AND S. N. BALASUBRAHMANYAM

Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts

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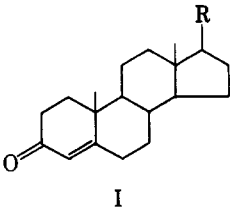
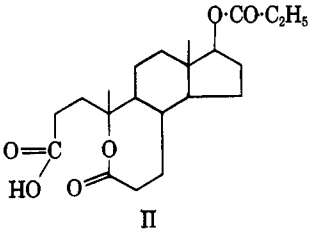
Oxidation of steroidal 4-en-3-ones with hydrogen peroxides in the presence of catalytic amounts of selenium dioxide yields products of structure II. The ϵ-lactones II can be easily rearranged to the more stable γ-lactones III. The resistence of 17β-acetyl moieties to the oxidation was confirmed.[1,3] The method is a facile and efficient route for the oxidative elimination of an α-carbon of an α,β-conjugated ketone and the formation of norseco acid lactones, II. Isolated Δ^5-bonds are converted to 5α,6β-diols.

The oxidation of cyclic stereoidal ketones to lactones with hydrogen peroxide in the presence of catalytic amounts of selenium dioxide was described in previous papers.[3-5] The acetyl moiety at C-17 resisted oxidation.[3,5] In further exploration of the reaction, the oxidations of 4-en-3-ones and of an isolated double bond at C-5 were investigated.

Oxidation of testosterone propionate (Ia) gave a syrupy residue from which the ϵ-lactone II was isolated. The lactone, m.p. 154–155°, had the formula $C_{21}H_{32}O_6$ and did not absorb ultraviolet light. Its infrared spectrum showed, among others, bands at 1750, 1730, and 1195 cm.$^{-1}$. On saponification the unstable lactone V was formed and, when recrystallized, gave the γ-lactone IIIa. Treatment of IIIa with propionic anhydride–pyridine yielded IIIb which was distinctly different from II. When IIIa was first treated with ethereal diazomethane, IIIc was obtained and on propionation gave IIId. Alternatively, IIId was prepared by esterification of IIIb with ethereal diazomethane. Attempts to prepare lactone II from V or the methyl ester analog of V failed and instead IIIb and IIIc were formed, respectively. Saponification of the syrupy mother liquor of II gave IIIa directly.



I

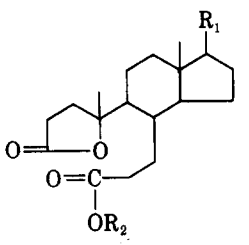


II

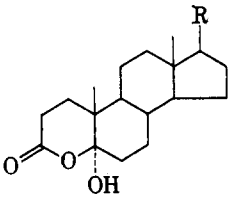
a, R = O·CO·C_2H_5

b, R = AcO—(CH$_3$)—H

c, R = CH_3·CO



III

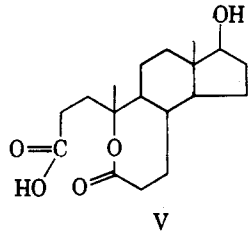


IV

a, R_1 = OH; R_2 = H
b, R_1 = O·CO·C_2H_5; R_2 = H
c, R_1 = OH; R_2 = CH_3
d, R_1 = O·CO·C_2H_5; R_2 = CH_3
e, R_1 = HO—(CH$_3$)—H; R_2 = H
f, R_1 = HO—(CH$_3$)—H; R_2 = CH_3
g, R_1 = AcO—(CH$_3$)—H; R_2 = CH_3
h, R_1 = CH_3·CO; R_2 = CH_3
i, R_1 = CH_3·CO; R_2 = H

a, R = O·CO·C_2H_5

b, R = AcO—(CH$_3$)—H



V

The structure of the seven-membered lactone II was proved by an independent synthesis. Lactol IVa was prepared by ozonolysis of testosterone propionate and then treated with acetic acid–hydrogen peroxide to yield II. Assignment of the structure rests on the documented observation that oxidation with peracids of saturated steroidal ketones in an acid medium proceeds *via* scission of the more substituted bond.[6,7] The carbonyl band[8] at 1750 cm.$^{-1}$ and the downfield shift of the C-10 methyl[9] to τ 8.64, are consistent for a seven-membered lactone and for the presence of an oxygen atom on the carbon bearing the methyl. Absence of a band in the n.m.r. ascribable to a methylene group bearing an oxygen atom supports structure II. Appearance of a carbonyl at 1770 cm.$^{-1}$

(1) This work was supported by grants CY-4663 and A-5326 from U. S. Public Health Service.

(2) Recipient of a Public Health Career Program Award CA-K3-16614 from National Cancer Institute.

(3) E. Caspi and S. N. Balasubrahmanyam, *Tetrahedron Letters*, 745 (1963).

(4) E. Caspi and S. N. Balasubrahmanyam, *Experientia*, **19**, 396 (1963).

(5) E. Caspi and S. N. Balasubrahmanyam, to be published.

(6) E. S. Rothman, M. E. Wall, and C. R. Eddy, *J. Am. Chem. Soc.*, **76**, 527 (1954); P. Bladon and W. McMeekin, *J. Chem. Soc.*, 3504 (1961).

(7) For leading references see E. Caspi, W. Schmid, and B. T. Khan, *J. Org. Chem.*, **26**, 3898 (1961); see also ref. 3.

(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, England, 1958, p. 178 and therein.

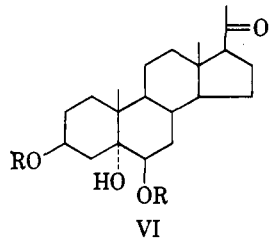
(9) L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, England, 1959, p. 53.

characteristic for a five-membered lactone[8] and the chemical shift of the C-10 methyl band to τ 8.69 are consistent with structure IIIa. The facile rearrangement of the seven-membered lactone to a five-membered one is in agreement with the known stability of five-membered lactones.

Similar results were obtained for 20β-acetoxypreg-4-en-3-one (Ib) and progesterone. Oxidation of Ib gave a syrupy residue which resisted crystallization and was saponified to yield the γ-lactone IIIe. Structure IIIe was assigned to the product because of its analysis, $C_{20}H_{30}O_5$, had a carbonyl band at 1750 cm.$^{-1}$, and had an n.m.r. peak at τ 8.68 for the C-19 methyl. Confirmation of the structure was provided by an alternative synthesis. Ozonolysis of Ib gave the lactol IVb, which was oxidized with peracetic acid and saponified to yield IIIe. Treatment of IIIe with ethereal diazomethane gave the methyl ester IIIf, which was acetylated to the methyl ester acetate IIIg.

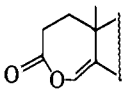
When progesterone (Ic) was oxidized, a syrupy acidic residue was formed. However, upon treating the syrup with ethereal diazomethane the γ-lactone ester IIIh was produced. Alternatively, chromic acid–acetone oxidation[10] of the 20β-hydroxy-γ-lactone IIIe provided the 20-keto-γ-lactone IIIi, which gave IIIh on treatment with diazomethane.

It was then of interest to assess the reaction for an isolated double bond. When pregnenolone was oxidized, 3β,5α,6β-trihydroxypregnan-20-one (VIa) was the sole product of reaction.

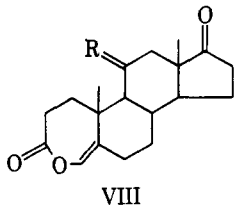


VI

a, R = H
b, R = CH_3·CO

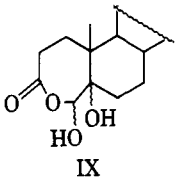


VII



VIII

a, R = OH (β)
b, R = O



IX

The formation of peroxides and hydroperoxides on treatment of ketones with hydrogen peroxides is well documented. Velluz, *et al.*,[11] have obtained relatively stable *gem*-hydroperoxides from the oxidation of steroidal 3, 17, and 20 carbonyls with hydrogen peroxides in the presence of mineral acids. In the case of 4-en-3-ones, the French authors isolated the *gem*-3,3-dihydroperoxide[11] which was rearranged[12] to 4-en-3-on-3a-oxa-A-homolactones, VII. Previously, we reported the preparation of 11β-hydroxy-3a-oxa-A-homoandrost-4-ene-3,17-dione (VIIIa) and 3a-oxa-A-homoandrost-4-ene-3,11,17-trione (VIIIb) on perchloric acid-catalyzed perbenzoic acid oxidation of 11β-hydroxyandrost-4-ene-3,17-dione and adrenosterone, respectively.[13] In addition to the preceding enol lactones, a 4,5-epoxy-3a-oxa-3-on-lactone also was obtained.

In considering the mechanism of the observed reactions two reasonable assumptions can be made: (a) lactols IV are intermediates in the formation of ϵ-lactones (II, V); (b) the initial attack of hydrogen peroxide on 4-en-3-one leads to *gem*-3,3-dihydroperoxides. That lactol IVa must be involved in formation of the ϵ-lactone was proved by its facile conversion to II with hydrogen peroxide in the presence of selenium dioxide. Observations of Velluz, *et al.*,[11,12] provide substance to the assumption that *gem*-hydroperoxides are the initial products of reaction. Should this be the case, a facile rearrangement of the hydroperoxides to enol lactones VII might be expected.[12] Such enol lactones could then form epoxides which would open α-hydroxyhemiacetal lactones, IX. Hydrolysis of IX could provide an α-hydroxyaldehyde which would be cleaved to the lactol, IV. The proposed sequence finds some support in the proven formation of 4,5-epoxy-3a-oxa-3-on lactones[13] from VIIIa. The alternative possibility whereby the 4-en-3-one was first converted to a 4,5-dihydroxy-3-one and then oxidized to IV, though less probable, cannot be excluded with certainty.

Pettit and Kasturi[14] have proposed a mechanism for the peracid oxidation of 4-en-3-ones to 3-on-4-oxa 3,5-lactones. The initial intermediate in their mechanism is also VII which is then hydrolyzed to a 3,4-seco-3-carboxylic acid 4-aldehyde. The latter on Baeyer–Villiger oxidation and ring closure yields the 3,5-lactone. This mechanism is not applicable to the present case, since such lactones would be stable to further oxidation.

The resistance of the 17β-acetyl moiety to oxidation is of interest. It has been pointed out already by Velluz, *et al.*, that while 4-en 3,3-dihydroperoxides rearrange with great ease to enol lactones VII, 20,20-dihydroperoxides require more vigorous conditions for conversion to 17β-acetoxy compounds.[12] Furthermore, the 20,20-dihydroperoxides when submitted to thermal rearrangement yield 20-ketones and C_{19}-17-desoxy compounds. It is possible that in our case the 20,20-dihydroperoxides, if formed, decompose thermally or otherwise to yield the 17β-acetyl products.

Experimental[15]

The oxidation of the steroids with hydrogen peroxide–selenium dioxide was carried out as previously described.[3-5]

The oxidation and especially the concentration step should be carried out behind an appropriate protective screen.[5]

17β-Propionoxy-3,5-seco-4-nor-10a-oxa-B-homoandrostan-5-on-3-oic Acid (II). A.—Testosterone propionate (660 mg.) was

(10) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(11) L. Velluz, G. Amiard, J. Martel, and J. Warnant, *Bull. soc. chim. France*, 879 (1957); J. Warnant, R. Joly, J. Mathieu, and L. Velluz, *ibid.*, 331 (1957).

(12) L. Velluz, G. Amiard, J. Martel, and J. Warnant, *ibid.*, 1485 (1957).

(13) E. Caspi, Y. W. Chang, and R. I. Dorfman, *J. Med. Pharm. Chem.*, **5**, 714 (1962).

(14) G. P. Pettit and T. R. Kasturi, *J. Org. Chem.*, **26**, 4557 (1961).

(15) Melting points were taken on a hot stage and are corrected. Infrared spectra were taken on solids incorporated in potassium bromide in paper blotters on a Perkin-Elmer Model 237 Infracord spectrometer. N.m.r. spectra were determined on a Varian Associates spectrometer Model V4300B in solvents indicated. Analyses by Dr. A. Schöller, Kronach, Germany.

oxidized to yield a sirupy acidic material which on trituration with ethyl acetate gave II (526 mg.).

B.—Testosterone propionate (2.0 g.) in ethyl acetate (150 ml.) was ozonized at −70°, and the ozonide decomposed with water. After partitioning of the residue with 2 *N* sodium carbonate, the lactol IVa was obtained and identified as previously described.[16] Hydrogen peroxide (6 ml., 50%) was added to a solution of the lactol (1.0 g.) in glacial acetic acid (10 ml.), and the mixture was stored at 37°. At the end of 72 hr. the solution was diluted with water (200 ml.), extracted with ethyl acetate, washed, dried, and concentrated to a residue (1.16 g.). The residue was crystallized from ethyl acetate–hexane to yield II.

C.—A mixture of the lactol IVa (255 mg.), *t*-butyl alcohol (10 ml.), 50% hydrogen peroxide (0.3 ml.), and selenium dioxide (50 mg.) was refluxed for 7 hr. After the usual work-up, II was obtained as the sole reaction product.

A sample was recrystallized from ethyl acetate–hexane; m.p. 154–155°; acid equivalent, 396 (required 380); ν_{max}^{KBr} 3450 (broad), 3150 (broad), 1750, 1730, 1195 cm.$^{-1}$; τ ($CDCl_3$) 5.42, 7.68 (quartet, J = 7.5 c.p.s.), 8.69, 8.88 (triplet, J = 7.1 c.p.s.), 9.19.

Anal. Calcd. for $C_{21}H_{32}O_6$: C, 66.30; H, 8.48. Found: C, 65.88; H, 8.44.

17β-Hydroxy-3,5-seco-4-nor-10a-oxa-B-homoandrostan-5-on-3-oic Acid (V).—The compound II (150 mg.) in methanol (15 ml.) containing 2 *N* sodium hydroxide (3 ml.) was refluxed in an atmosphere of nitrogen for 2 hr. The product V was recovered from the acidified solution in the conventional manner. A sample was recrystallized from ethyl acetate; m.p. 211–213°; ν_{max}^{KBr} 3475, 3125 (broad), 1750, 1720,1260 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.03; H, 8.37.

From the mother liquor after the isolation of V the lactone IIIa was obtained.

17β-Hydroxy γ-Lactone Acid (IIIa). A.—The second crop obtained after the isolation of V was IIIa.

B.—The dried mother liquor (180 mg.) from the isolation of II was dissolved in methanol (5 ml.) containing 2 *N* sodium hydroxide (2 ml.). The solution was refluxed for 1.5 hr. and processed as the preceding to yield IIIa (120 mg.).

A sample was crystallized from ethyl acetate; m.p. 211–212°; ν_{max}^{KBr} 3430 (sharp), 1770, 1705, 1190 cm.$^{-1}$; τ (in CD_3OD) 6.50, 7.25, 7.38, 7.55, 7.79, 8.65, 9.21.

Anal. Calcd. for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.13; H, 8.78.

17-Propionoxy γ-Lactone Acid (IIIb). A.—To a solution of the γ-lactone acid (IIIa, 10 mg.) in pyridine (1 ml.) was added freshly redistilled propionic anhydride (1 ml.). After 16 hr. at room temperature, ice was added and the volatile components were removed in a current of nitrogen to yield crystalline IIIb.

B.—The ε-lactone V (1 mg.) was propionated, and IIIb was isolated as previously described.

A sample was crystallized from ethyl acetate–neohexane; m.p. 170–174°; ν_{max}^{KBr} 3450 (broad), 2650 (broad), 1770, 1730, 1700, 1190 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{32}O_6$: C, 66.30; H, 8.48. Found: C, 66.16; H, 8.41.

17-Propionoxy γ-Lactone Methyl Ester (IIId). A.—Ethereal diazomethane was added to a solution of IIIb (20 mg.) in methanol (1 ml.). The residue left after the removal of solvent was crystallized from ether to yield IIId.

B.—The ε-lactone II (10 mg.) was esterified as previously described to yield IIId. A sample was recrystallized from ether; m.p. 149–152°; ν_{max}^{KBr} 1775, 1765, 1730, 1200 cm.$^{-1}$; τ (in $CDCl_3$) 5.29, 6.29 (OCH_3), 8.64 (19 Me), 8.82 (triplet, J = 7.2 c.p.s.), 9.13 (18 Me).

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 66.66; H, 8.69.

17-Hydroxy γ-Lactone Methyl Ester (IIIc). A.—The lactone V (209 mg.) in methanol (4 ml.) was treated with excess ethereal diazomethane. Removal of the solvents left the solid IIIc.

B.—The γ-lactone IIIa (113 mg.) was esterified as previously described to yield IIIc. A sample was recrystallized from hexane–ether; m.p. 151–152°; ν_{max}^{KBr} 3400 (broad), 1770, 1760, 1730, 1715, 1200 cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 3600, 1770, 1730, 1255 cm.$^{-1}$; τ (in $CDCl_3$) 6.33, 8.66, 9.19.

Anal. Calcd. for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.16; H, 9.10.

20-Hydroxy γ-Lactone Acid (IIIe). A.—20β-Acetoxypregn-4-en-3-one (Ib, 3 g.) was oxidized to yield a sirupy mixture of acids (2.66 g.), which resisted crystallization. A portion of the acidic fraction (662 mg.) in methanol (10 ml.) containing 2 *N* sodium hydroxide (5 ml.) was refluxed for 2 hr. in an atmosphere of nitrogen. The recovered products were crystallized from ethyl acetate–ether to yield IIIe.

B.—The lactol IVb (716 mg.) in glacial acetic acid (5 ml.) was treated with 50% hydrogen peroxide (3 ml.), and the mixture was stored at 40° for 72 hr. Water (500 ml.) was added and the products were extracted with ethyl acetate. The combined extracts were washed, dried, and concentrated to leave a residue (732 mg.). A portion of the syrup (146 mg.) was saponified in methanol (15 ml.) containing 2 *N* sodium hydroxide (3 ml.). The products were recovered in the usual manner to yield the solid IIIe.

A sample was recrystallized from ethyl acetate; m.p. 213–216° (softening at 206°); ν_{max}^{KBr} 3450, 3150, 2600, 1750, 1725–1710 (broad) cm.$^{-1}$; τ (in CD_3OD) 8.68, 8.91 (doublet, J = 6.6 c.p.s.), 9.21.

Anal. Calcd. for $C_{20}H_{30}O_5$: C, 68.15; H, 9.15. Found: C, 67.92; H, 9.10.

20-Hydroxy γ-Lactone Methyl Ester (IIIf).—An ethereal solution of IIIe (50 mg.) was esterified with diazomethane. The residue obtained after the removal of solvent was recrystallized from ether–ethyl acetate; m.p. 177–180°; ν_{max}^{KBr} 3500, 1775, 1765, 1730, 1250 cm.$^{-1}$; τ (in $CDCl_3$) 6.33 (3H), 8.68 (19 Me), 8.85 (doublet, J = 6.5 c.p.s.), 9.21.

Anal. Calcd. for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.65; H, 9.22.

20-Acetoxy γ-Lactone Methyl Ester (IIIg). A.—A portion of the syrupy acidic residue from the oxidation of Ib was treated with ethereal diazomethane. Removal of the solvent left crystalline IIIg.

B.—IIIf was acetylated with pyridine–acetic anhydride to yield IIIg after the usual procedure of isolation. A sample was recrystallized from ether–hexane; m.p. 164–165°; ν_{max}^{KBr} 1770, 1760, 1730, 1250 cm.$^{-1}$; τ (in $CDCl_3$) 5.20 (1H), 6.35 (OCH_3), 8.02 (acetate), 8.70, 8.85 (doublet, J = 6 c.p.s.), 9.33.

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.94; H, 8.87.

20-Keto γ-Lactone Methyl Ester IIIh. A.—A mixture of progesterone (Ic, 2 g.) in *t*-butyl alcohol (120 ml.), hydrogen peroxide (50%, 8 ml.), and selenium dioxide (100 mg.) was refluxed 7 hr. The solution was cooled to room temperature then diluted with water, and the steroids were extracted with ethyl acetate–methylene chloride (3:1). The extract was partitioned with 2 *N* sodium carbonate into neutral (negligible) and acidic fractions. The sirupy acidic fraction resisted crystallization and was treated with ethereal diazomethane to yield IIIh (657 mg.). The sirupy mother liquor resisted crystallization.

B.—Treatment of IIIi with ethereal diazomethane gave IIIh. A sample was recrystallized from ethyl acetate; m.p. 129–132°; ν_{max}^{KBr} 1770, 1760, 1730, 1700, 1175 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 68.41; H, 8.56.

20-Keto γ-Lactone Acid IIIi.—To a stirred solution of IIIe (200 mg.) in acetone (10 ml.) a standard solution of 8 *N* chromic acid (3.5 ml.) was added and the mixture was kept at room temperature for 20 min. Water was added, and the steroids were recovered with a mixture of ethyl acetate–methylene chloride (3:1). The extract was washed, dried, and concentrated to yield IIIi.

A sample was recrystallized from ethyl acetate–hexane; m.p. 141–142°; ν_{max}^{KBr} 2900 (broad), 1760, 1850, 1725–1695 (broad unresolved) cm.$^{-1}$; τ (in $CDCl_3$) 7.88 (CH_3CO), 8.68 (19 Me), 9.33 (18 Me).

Anal. Calcd. for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.58; H, 8.29.

3β,5α,6β-Trihydroxypregnan-20-one (VIa).—A mixture of pregnenolone (1.19 g.), *t*-butyl alcohol (60 ml.) hydrogen peroxide (50%, 5 ml.), and selenium dioxide (50 mg.) was refluxed for 7 hr. The solution was diluted with 2 *N* sodium carbonate (200 ml.), and the steroid was recovered with ethyl acetate–methylene chloride (3:1). The extract was washed with saline, dried, and concentrated to yield VIa (908 mg.).

(16) E. Caspi, B. T. Khan, and S. N. Balasubrahmanyam, *Tetrahedron*, **18**, 1013 (1962).

A sample was recrystallized from methanol–ethyl acetate; m.p. 249–252° (lit.[17] 252–255°); ν_{max}^{KBr} 3525, 3450, 1695, 1040, 1030, 1010 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{34}O$: C, 71.96; H, 9.78. Found: C, 72.00; H, 9.67.

(17) O. Mancera, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **16**, 192 (1951).

3β,6β-Diacetoxy-5α-hydroxypregnan-20-one (VIb).—The acetate was prepared by treatment of VIa with acetic anhydride and pyridine. The recovered VIb was recrystallized from ethyl acetate; m.p. 207–209° (lit.[17] 212–215°); ν_{max}^{KBr} 3480, 1730, 1720, 1705, 1235 cm.$^{-1}$; τ (in $CDCl_3$) 5.32 (1H), 7.90, 7.93, 7.98, 8.85, 9.37.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.24; H, 8.76.

Studies in Syntheses of Steroid Metabolites. II

M. HARNIK

Steroid Research Department, Zori Pharmaceutical and Chemical Industrial Company, Tel Aviv, Israel

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Hydrogenation of hydrocortisone acetate and of cortisone acetate in ethyl acetate in the presence of palladium on charcoal leads to the formation of appreciable amounts of 5β isomers. Raney nickel hydrogenation of IIb gives VIIa and a low yield of Reichstein's compound C acetate. Similarly hydrogenation of VIb leads to Xa and a small amount of Reichstein's 11-dehydro compound C acetate. Independent syntheses of Reichstein's compound C and 11-dehydro C diacetate are reported. Raney nickel hydrogenation of 3-keto-5β compounds furnishes a mixture of 3α and 3β epimeric derivatives and is the basis of a synthesis of tetrahydro compound F.

It was previously observed[1] that, when a solution of hydrocortisone in ethyl acetate was hydrogenated in the presence of palladium on charcoal, the two epimers 5α- and 5β-pregnane-11β,17α,21-triol-3,20-dione (IIa) and (IIIa) could be isolated by crystallization in 46 and 35% yield, respectively. Since the literature indicates that the saturation of the 4,5 double bond in hydrocortisone acetate and cortisone acetate leads to the predominant formation of the 5α isomers, it was decided to examine the problem in a little more detail. In this connection it is of interest that Caspi[2] obtained relatively large amounts of 5β compounds by hydrogenation of hydrocortisone in acetic acid in the presence of rhodium on alumina or platinum (Scheme I).

While Pataki, *et al.*,[3] found that hydrogenation of hydrocortisone acetate with palladium on barium sulfate in ethyl acetate afforded an 84% yield of the 5α-dihydro derivative IIb, it was now observed that with palladium on charcoal in ethyl acetate there was obtained an 80% yield of a solid which proved to be a mixture of the two epimeric acetates IIb and IIIb which, unlike the free alcohols IIa and IIIa, were inseparable by crystallization. This mixture of IIb and IIIb, on sodium borohydride–sodium periodate degradation, gave 5α-androstane-3β,11β-diol-17-one and 5β-androstane-3α,11β-diol-17-one (IX) in the ratio of 3:1. While the 5α isomer IIb could be purified by hydrolysis followed by crystallization, the 5β isomer IIIb was not easily isolated from the hydrolysis mixture.

Similarly, palladium-on-barium sulfate hydrogenation of cortisone acetate in ethyl acetate is reported[4] to lead to a 72% yield of the 5α-dihydro compound VIb, while palladium-on-charcoal hydrogenation in ethyl acetate gave[5] the same compound in 70% yield. Other workers report[6] that hydrogenation in the presence of potassium hydroxide gave VIb in 43% yield and also some 5β isomer Vb. In our hands the hydrogenation of cortisone acetate in ethyl acetate in the presence of palladium on charcoal afforded a 44–52% yield of VIb and a 26–30% yield of Vb, separable by fractional crystallization. Hydrogenation of cortisone under similar conditions gave a hard to separate mixture which appeared to contain the two dihydro compounds VIa and Va in the ratio of 4:1.

Next the Raney nickel hydrogenation of several 3-keto corticoids was studied. The Syntex group reported[3] that 5α-pregnane-11β,17α,21-triol-3,20-dione-21-acetate (IIb) was reduced in dioxane with this catalyst to Reichstein's compound V monoacetate (VIIa), isolated as the diacetate VIIb in 25% yield. A similar hydrogenation of the 11-keto analog VIb furnished[7c] Reichstein's compound D monoacetate (Xa) in 70% yield. In repeating the former, we have been able to isolate VIIa in 65–69% yield, and by chromatography of the acetylated filtrate a 2.7–3.2% yield of Reichstein's compound C diacetate (VIIIa), and also a small amount of VIIb. Reichstein's compound C was previously obtained by Caspi[2] together with several other compounds by hydrogenation of hydrocortisone with rhodium on alumina. Fukushima and Daum[8a] obtained it in 17% over-all yield from hydrocortisone by lithium–ammonia reduction of its bismethylenedioxy (BMD) derivative, formation of the tosylate at position 3, epimerization, and splitting off the BMD moiety. Confirmation of the identity of our sample of VIIIa was achieved by a synthesis which, like Fukushima and Daum's approach, involved epimerization at position 3. However we did not employ a BMD derivative for the protection of the corticoid side chain, having obtained Reichstein's compound V monoacetate (VIIa) from the hydrogenation experi-

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