105. *Partial Reduction of Steroid Hormones and Related Substances. Part II.* A New Synthetic Route to Steroidal* 20 : 21-*Ketols.*

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The 17-hydroxyl group is removed from 17α : 21-dihydroxy-20-oxo-steroids by zinc in aqueous acetic acid. The examples investigated include the conversion of cortisol into corticosterone.

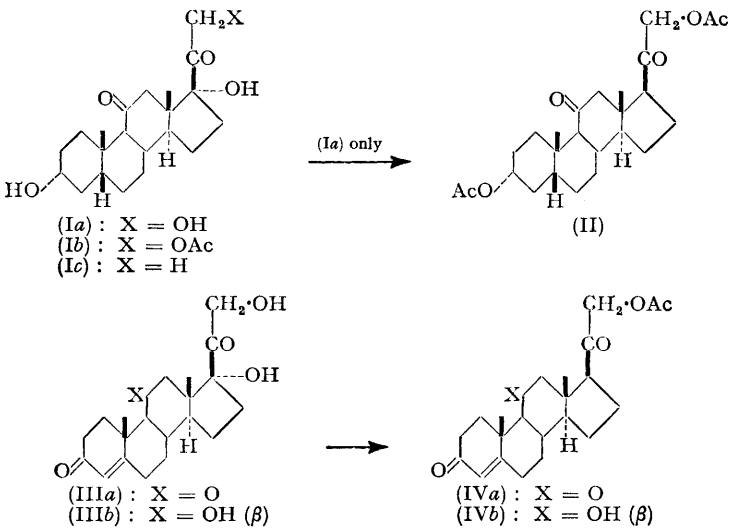
Although 11-oxygenated 17α : 21-dihydroxy-20-oxo-steroids have become readily available, their 17-deoxy-analogues are still difficult to obtain. The present work concerns the one-step conversion of compounds of the former into those of the latter class by a method capable of wide application.

Treatment of 3α : 17α : 21-trihydroxypregnane-11 : 20-dione (I*a*) with zinc in boiling aqueous acetic acid, followed by acetylation, gave 3α : 21-diacetoxypregnane-11 : 20-dione [1] (II) as the sole product. 21-Acetoxy-3α : 17α-dihydroxypregnane-11 : 20-dione (I*b*) and 3α : 17α-dihydroxypregnane-11 : 20-dione (I*c*) failed to react under identical conditions. Evidently the presence of a free 21-hydroxyl is necessary for the hydrogenolysis of the $C_{(17)}$–O bond, possibly because it facilitates the effective binding of the dihydroxyacetone (I*a*) on the zinc surface.

* Part I, *J.*, 1955, 3426.

[1] Sarett, *J. Amer. Chem. Soc.*, 1948, **70**, 1454.

It appears [2] that 4 : 5-unsaturated 3-ketones are resistant towards zinc in acetic acid and hence it seemed feasible to use this reagent for the selective removal of the 17-hydroxyl from cortisone (III*a*) and from cortisol (III*b*). In fact, the two compounds gave severally 11-dehydrocorticosterone acetate [3] (IV*a*) and corticosterone acetate [3] (IV*b*), though in



both reactions some reduction of the 4-en-3-one grouping was indicated by ultraviolet spectroscopy. In many respects the above conversions compare favourably with the known preparative routes to 11-dehydrocorticosterone [4] and corticosterone.[4b, 5]

Experimental

Specimens for analyses were dried in a high vacuum for 4—16 hr. at 80—100°. M. p.s were determined on a Kofler stage. Unless otherwise specified, rotations were measured in $CHCl_3$ (at 15—20°), ultraviolet absorption spectra in EtOH. For chromatography neutralised alumina [6] was used; elution was effected with benzene of gradually increasing content of ethyl acetate. Acetylations were performed with acetic anhydride in pyridine at room temperature.

Treatment with Zinc. General Procedure.—A 0·02—0·03M-solution of the steroid in aqueous acetic acid (50%; v/v) was treated under reflux with 40—80 mol. of zinc dust (" AnalaR ") for 60—90 min. The still hot solution was filtered and the zinc was washed with methanol. Ice was added to the filtrate and then enough 3N-sodium hydroxide to neutralise nine-tenths of the acetic acid. The mixture was extracted with ether–chloroform in the usual manner.

Treatment of 3α : 17α : 21-*Trihydroxypregnane*-11 : 20-*dione* (I*a*) *with Zinc.*—This compound (100 mg.) was treated by the general procedure, followed by acetylation and chromatography on alumina. 3α : 21-*Diacetoxypregnane*-11 : 20-*dione* (II) (88 mg., 74%) was eluted in the early fractions. Crystallisation from ether–light petroleum gave prisms (75 mg., 63%), m. p. 107—109°, $[\alpha]_D$ +127° (*c*, 2·15) (Found: C, 69·9; H, 8·15. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%). The compound was identified with authentic material by mixed m. p. and comparison of the infrared spectra.

[2] Fieser, *ibid.*, 1953, **75**, 4377; Amendolla, Rosenkranz, and Sondheimer, *J.*, 1954, 1226.
[3] Reichstein, *Helv. Chim. Acta*, 1937, **20**, 953.
[4] (*a*) Lardon and Reichstein, *ibid.*, 1943, **26**, 747; (*b*) von Euw, Lardon, and Reichstein, *ibid.*, 1944, **27**, 1287; (*c*) von Euw and Reichstein, *ibid.*, 1946, **29**, 1913; Sarett, *J. Amer. Chem. Soc.*, 1946, **68**, 2478; Wettstein and Meystre, *Helv. Chim. Acta*, 1947, **30**, 1262; von Euw and Reichstein, *ibid.*, 1948, **31**, 2076; Mattox and Kendall, *J. Biol. Chem.*, 1951, **188**, 287; Poos, Lukes, Arth, and Sarett, *J. Amer. Chem. Soc.*, 1954, **76**, 5031.
[5] Wendler, Huang-Minlon, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 3818; Lardon and Reichstein, *Helv. Chim. Acta*, 1954, **37**, 443; Taub, Pettebone, Wendler, and Tishler, *J. Amer. Chem. Soc.*, 1954, **76**, 4094; Bernstein and Lenhard, *ibid.*, 1955, **77**, 8331.
[6] Brooks and Norymberski, *Biochem. J.*, 1953, **55**, 371.

The authentic specimen was prepared by acetylation of 3α : 21-dihydroxypregnane-11 : 20-dione, kindly provided by Dr. W. Klyne from the M.R.C. Steroid Reference Collection. It had m. p. 107—109°, $[\alpha]_D$ +123° (*c*, 0·97) (Found : C, 68·9; H, 8·2. Calc. for $C_{25}H_{36}O_6$: C, 69·4; H, 8·4%). The compound has not been previously fully described. Sarett [1] reported m. p.s 100—110° and 82—90° for specimens crystallised from different solvents, in a patent [7] the m. p. 95—105° was recorded, and Colton and Kendall [8] gave m. p. 131°, $[\alpha]_D$ +127°.

Treatment of 21-*Acetoxy*-3α : 17α-*dihydroxypregnane*-11 : 20-*dione* (I*b*) *with Zinc*.—This compound (120 mg.) was treated as above. Crystallisation of the crude acetylated product first from methanol and then from acetone–hexane afforded pure 3α : 21-diacetoxy-17α-hydroxypregnane-11 : 20-dione (85 mg.) of m. p. and mixed m. p. 229—231°, $[\alpha]_D$ +112° (*c*, 1·31), +89° (*c*, 0·82 in acetone) (Found : C, 66·9; H, 8·2. Calc. for $C_{25}H_{36}O_7$: C, 66·9; H, 8·1%). Sarett [1] found m. p. 233—236°, $[\alpha]_D$ +93° (in acetone). The pronounced effect of solvent on the rotatory power of this compound is consistent with observations made on other 17 : 20-ketols.[9]

Treatment of 3α : 17α-*Dihydroxypregnane*-11 : 20-*dione* (I*c*) *with Zinc*.—This compound (100 mg.) was treated with zinc as above. Crystallisation from acetone–light petroleum gave starting material (70 mg.) of m. p. and mixed m. p. 200—202°, $[\alpha]_D$ +41° (*c*, 1·15), +63·5° (*c*, 1·12 in acetone). Sarett [1] reported m. p. 207—208°, $[\alpha]_D$ +68·5° (in acetone).

Treatment of Cortisol (III*b*) *with Zinc*.—Cortisol (300 mg.) was treated as above, and the crude acetylated product was chromatographed. An unidentified gum [100 mg.; $\lambda_{max.}$ 208 and 240 mμ ($E^{1\%}_{1\,cm.}$ 110 and 210)] was first eluted and was followed by corticosterone acetate (IV*b*) (160 mg., 50%). One crystallisation from acetone–hexane gave pure material (120 mg., 37%), m. p. 145—146° (solidifies on cooling and on re-heating melts at 152—153°), $[\alpha]_D$ +221° (*c*, 0·67), $\lambda_{max.}$ 241 mμ (ε 16,000) (Found : C, 70·9; H, 8·4. Calc. for $C_{23}H_{32}O_5$: C, 71·1; H, 8·3%). The compound was identified with authentic material {m. p.s 145—146° and 152—153°, $[\alpha]_D$ +220° (*c*, 1·05)} by mixed m. p. and comparison of infrared spectra. The physical constants found are in agreement with those recorded in the literature.[3,5]

Oxidation of the above product with chromic oxide [3] gave 11-dehydrocorticosterone acetate (IV*a*), m. p. 178—180°, $[\alpha]_D$ +247° (*c*, 0·78), $\lambda_{max.}$ 238 mμ (ε 17,000) (Found : C, 71·3; H, 8·0. Calc. for $C_{23}H_{30}O_5$: C, 71·5; H, 7·8%), in agreement with the properties recorded elsewhere.[3,4]

Treatment of Cortisone (III*a*) *with Zinc*.—Cortisone (250 mg) was treated as above. Chromatography of the crude acetylated product gave, first, gummy unidentified fractions (60 mg.) of which an earlier eluted part (20 mg.) had no specific absorption at or about 238 mμ. Crystalline 11-dehydrocorticosterone acetate (IV*a*) (95 mg., 35%) was next eluted. It gave prismatic needles (70 mg., 26%) (from acetone–hexane), m. p. 177—180° (undepressed on admixture with material obtained from oxidation of corticosterone acetate), $[\alpha]_D$ +242° (*c*, 0·57), $\lambda_{max.}$ 238 mμ (ε 18,000) (Found : C, 71·4; H, 8·0. Calc. for $C_{23}H_{30}O_5$: C, 71·5; H, 7·8%).

This work was done during the tenure of an Empire Rheumatism Council Research Fellowship. The author is much indebted to Dr. A. E. Kellie for infrared measurements and to Dr. W. Klyne for the facilities of the M.R.C. Steroid Reference Collection. Gifts of steroids from Messrs. Merck and Co., Inc. (Rahway), and from Messrs. I. V. Organon (Oss) are gratefully acknowledged.

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[7] Swiss P. 274,689/1951; cf. *Chem. Abs.*, 1952, **46**, 4582.
[8] Colton and Kendall, *J. Biol. Chem.*, 1952, **194**, 247.
[9] Norymberski, *J.*, 1954, 762.