11α-Deutero-17α-hydroxy Corticosterone[1]

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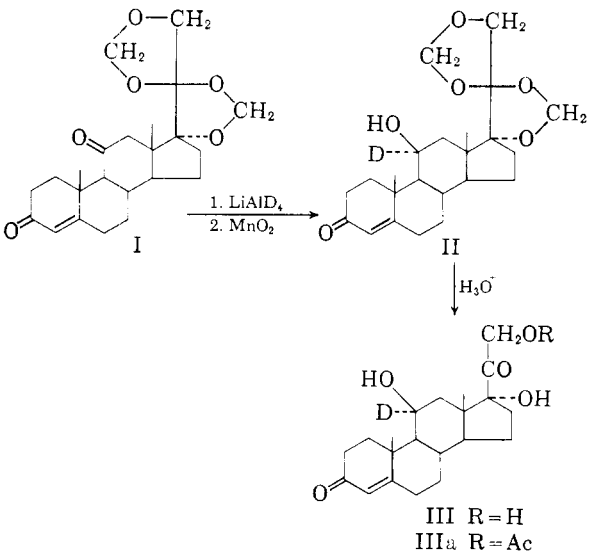
Received February 2, 1959

The role of the 11-oxygen function in steroid metabolism has been discussed in some detail recently by Bush.[2] This author emphasizes in particular the potential significance of the reversible oxidation-reduction of the 11-oxygen function in determining pharmacological properties. In view of these considerations together with the well recognized role of the isotope effect in the oxidation of alcohols,[3] it was of interest to synthesize 11α-deuterohydrocortisone and determine its biological activity relative to hydrocortisone itself.

Cortisone in the form of its 17,20:20,21-bismethylenedioxy(BMD) derivative I[4] was reduced with lithium aluminum deuteride followed by oxidation at C-3 with manganese dioxide to give the BMD derivative of 11α-deuterohydrocortisone (II). Hydrolysis of the latter with hot 50% aqueous acetic acid according to the published method gave 11α-deutero-17α-hydroxycorticosterone (III).



In the oral glycogen deposition test in mice and in the oral systemic granuloma assay in rats, the approximate potencies relative to hydrocortisone in the two tests were 0.7–1 and 1.5, respectively.

EXPERIMENTAL[5]

Reduction of 17,20:20,21-bismethylenedioxy-4-pregnene-3,11-dione with lithium aluminum deuteride. To a stirred solution of 3.0 g. of lithium aluminum deuteride (97% pure, 0.0693 mole) in 450 ml. of dry tetrahydrofuran under nitrogen was added a solution of 6.00 g. of 17,20:20,21-bismethylenedioxy-4-pregnene-11,20-dione in 150 ml. of tetrahydrofuran. The mixture was stirred and refluxed for 80 min. and then cooled to 5° and quenched by cautious addition of 60 ml. of ethyl acetate followed by 100 ml. of saturated sodium sulfate solution and finally 100 g. of anhydrous magnesium sulfate. The resulting mixture was filtered and the inorganic precipitate washed thoroughly with ethyl acetate. The combined filtrate and washings were taken to dryness *in vacuo* to yield 5.94 g. of product exhibiting no U.V. absorption maximum.

A solution consisting of 5.17 g. (12.7 millimoles) of the above crude reduction product was dissolved in 120 ml. of benzene and treated with 414 ml. of acetone and 62 g. of manganese dioxide. The mixture was stirred at room temperature (25°) overnight (16 hr.), filtered with the aid of Supercel, washed and the combined filtrate and washings taken to dryness *in vacuo*. The residue amounted to 4.96 g., λ_{max} 242 mμ, ε = 12,000. A sample crystallized from acetone-ether melted at 218–222°. Mixed m.p. with 17,20:20,21-bismethylenedioxy-11β-hydroxy-4-pregnen-3-one was not depressed.[3]

11α-Deuterohydrocortisone 21-acetate (IIIa). To a solution of 4.94 g. of 17,20:20,21-bismethylenedioxy-11α-deutero-11β-hydroxy-4-pregnen-3-one in 245 g. of glacial acetic acid was added 245 ml. of water. The system was flushed with nitrogen and heated on the steam bath for 5.5 hr. Water was added, the mixture extracted with chloroform, the chloroform extract was extracted with bicarbonate, water, and saturated salt solution. The chloroform extract was dried over magnesium sulfate and taken to dryness *in vacuo* to yield 4.43 g. of crude 11α-deuterohydrocortisone. The latter was acetylated in 100 cc. of pyridine with 500 g. acetic anhydride at room temperature for 18 hr. The product was worked up in the usual manner and crystallized from ethyl acetate and from acetone-ether. M.p. 218–221.5°, $\lambda_{max}^{CH_3OH}$ 242 mμ, ε = 16,200: λ_{max}^{Nujol} 2.94, 3.02, 5.75, 5.80, 6.12 and 8.09μ.

Anal. Calcd. for $C_{23}H_{31}DO_6$: C, 68.12; H, 8.20; D, 1 atom/molecule. Found: C, 68.38; H, 8.00; D, 0.92 atom/molecule.

A solution of 1.1 g. of the 21-acetate (IIIa) in 33 cc. of methanol under reflux in a nitrogen atmosphere was hydrolyzed by addition of a solution of 1.1 g. of potassium bicarbonate in 11 cc. of water. The mixture was stirred and refluxed for 10 minutes, cooled and neutralized with acetic acid and extracted with ethyl acetate. The product was chromatographed on Florisil and eluted with (1:1) ethyl acetate-chloroform and crystallized from ethyl acetate-acetone to give 0.55 g. of *11α-deuterohydro*-cortisone (III), m.p. 217–219°, $\lambda_{max}^{CH_3OH}$ 242, ε = 18,000; λ_{max}^{Nujol} 2.92, 5.84, 6.07, and 6.19μ.

Anal. Calcd. for $C_{21}H_{29}DO_5$: C, 69.39; H, 8.60; D, 1 atom/molecule. Found: C, 69.47; H, 8.88; D, 0.96 atom/molecule.

A mixed m.p. of III with an authentic sample of hydrocortisone was not depressed and the flow rate of the two samples on a paper chromatogram was identical.

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(1) Presented at the Meeting-in-Miniature of the North Jersey Section of the American Chemical Society on January 26, 1959.

(2) I. E. Bush, *Experientia*, **12**, 326 (1956).

(3) F. H. Westheimer, *Chem. Revs.*, **45**, 419 (1949).

(4) R. E. Beyler, R. M. Moriarty, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

(5) All melting points are corrected. The bioassays were carried out at the Merck Institute for Therapeutic Research by Dr. Silber and his collaborators.