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dl-18-NORTESTOSTERONE

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IN view of the therapeutic importance of 19-nor steroidal hormones, there has recently been considerable interest in examining the 18-nor compounds. To date 18-nor-estrone,[1] -progesterone,[2] and -cortisone[3] have been prepared, but no representative of the male hormone series has been reported. We disclose herewith a total synthesis of racemic 18-nortestosterone (VI).

The cis-anti-trans alcohol I,[4] on reduction with lithium and alcohol in ammonia followed by hydrolysis of the enol ether and catalytic reduction of the resulting unsaturated ketone, was converted stereoselectively into dl-3a-hydroxy-18-nor-D-homoetiocholane-17a-one (II).[5] Contraction of ring-D was effected by the following sequence. The hydroxy ketone II was converted into the 17-furfurylidene derivative[5] which, as the 3-acetate, m.p. 194-195°

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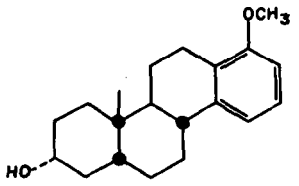
[1] K.H. Loke, G.F. Marrian, W.S. Johnson, W.L. Meyer and D.D. Cameron, Biochim. Biophys. Acta 28, 214 (1958).

[2] R. Anliker, M. Müller, M. Perelman, J. Wohlfahrt and H. Heusser, Helv. Chim. Acta 42, 1071 (1959).

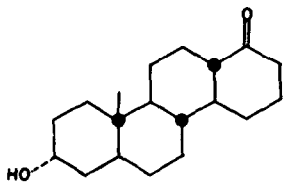
[3] L. Velluz, G. Amiand, R. Heymes and B. Goffinet, C.R. Acad. Sci. Paris 250, 371 (1960).

[4] W.S. Johnson, A.D. Kemp, R. Pappo, J. Ackerman and W.F. Johns, J. Amer. Chem. Soc. 78, 6312 (1956).

[5] W.S. Johnson, W.A. Vredenburgh and J.E. Pike, J.Amer.Chem.Soc. In press.



I



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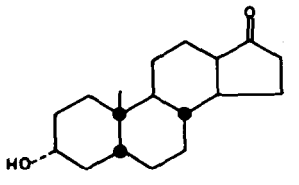
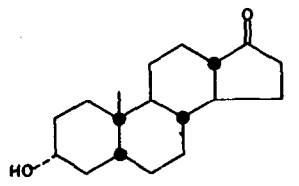
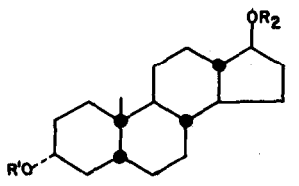


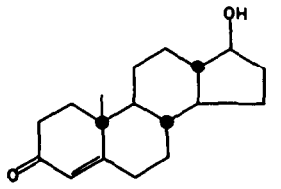
III



IV



V



VI

(C, 76.2; H, 8.3), was ozonolyzed to give dl-3α-acetoxy-18-nor-etiohomobilianic acid, m.p. 213-214° (C, 66.2; H, 8.2). This diacid was transformed, with diazomethane, into the dimethyl ester, m.p. 111-112° (C, 67.5; H, 8.8) which was cyclized with potassium t-butoxide in benzene.[6] Hydrolysis and decarboxylation of the resulting β-keto ester was effected by heating in triethylene glycol containing about 5% water which yielded a mixture of two epimeric

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[6] W.S. Johnson, B. Bannister and R. Pappo, J. Amer. Chem. Soc. 78, 6331 (1956).

(at C_{13}) hydroxy ketones: m.p. 150-151° (C, 78.2; H, 10.25), acetate, m.p. 144-145° (C, 75.5; H, 9.55); and m.p. 113-114° (C, 78.3; H, 10.3), acetate, m.p. 116-117° (C, 75.5; H, 9.6). The configurations of these substances were established by reduction experiments with pyridine-borane in acetic acid.[7] This regent, which was shown to reduce the 17-carbonyl group of epiandrosterone acetate in high yield, similarly effected complete reduction of the keto group of the 117° acetate, but was completely inert to the 145° acetate. The latter therefore corresponds to the 13-iso compound III with a hindered (axial to ring C) keto group, while the former corresponds to the isomer of natural configuration IV, and its reduction product is, accordingly, dl-3α-acetoxy-17β-hydroxy-18-noretiocholane (V,R^1 = Ac,R^2 = H). Benzoylation afforded the 17-benzoate V (R^1 = Ac, R^2 = COC_6H_5), m.p. 144-145° (C, 76.6; H, 8.7) which on mild saponification yielded the hydroxy benzoate V (R^1 = H, R^2 = COC_6H_5), m.p. 132-133° (C, 78.4; H, 9.0). Chromic acid oxidation to the 3-keto compound, m.p. 139-140° (C, 78.7; H, 8.3) followed by bromination and dehydrobromination afforded the benzoate of dl-18-nortestosterone, m.p. 151-152° (C, 79.3; H, 8.0), saponification of which gave dl-18-nortestosterone (VI), m.p. 165-167° (C, 79.2; H, 9.6). The results of physiological tests will be reported elsewhere.

The 18-nor-17-keto compounds III and IV are readily interconverted. The position of the equilibrium of the hydroxy ketones in dioxane and hydrochloric acid was estimated, by infrared spectroscopy, to be about 60-65% in favor of the cis isomer. The interconvertibility of these isomers make the above synthesis completely stereoselective, since pyridine-borane reduces only the trans isomer.[8]

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[7] R.P. Barnes, J.H. Graham and M.D. Taylor, J.Org.Chem. 23, 1516 (1958).

[8] This work was aided by grants from the U.S. Public Health Service and the National Science Foundation.