

SYNTHESIS OF D-NORPROGESTERONE¹

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MODIFIED steroids have recently received considerable attention³ owing to the interesting biological properties that many of them exhibit. D-Norsteroids merit additional interest for stereochemical reasons since they contain a six- and four-membered fused ring system. A recent report⁴ on the synthesis of D-norsteroids, prompts us to communicate our findings to date.

Dehydroepiandrosterone (I) can be transformed to D-norprogesterone (XI) by the following route. Nitrosation of I to II⁵ followed by reaction with chloramine gave 16-diazo-5-androstene-3 β -ol-17-one (III),⁶ m.p. 196-197^o, in 72 per cent yield. Ultraviolet light irradiation of the latter in tetrahydrofuran-methanol gave upon chromatography 16-carbomethoxy-D-nor-5-androstene-3 β -ol (IV), m.p. 163-164^o, in 40 per cent yield (reported^{4b} m.p. 164-165^o). When the irradiation of III was carried out in the presence of water instead of methanol an acid, m.p. 175-177^o, was isolated (65 per cent) which proved to be a mixture of two acids, m.p. 212-214^o and m.p.

¹ Presented in part before the 33rd Meeting of the Colorado-Wyoming Academy of Science in Greeley, Colorado, 1962.

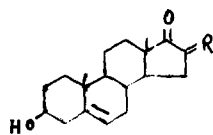
² National Science Foundation Summer Research Participation Fellow, 1960.

³ Cf. L.F. Fieser and M. Fieser, Steroids. Reinhold, New York (1959).

^{4a} M.P. Cava and E. Moroz, J. Amer. Chem. Soc. **84**, 115 (1962); ^bJ. Meinwald, G.G. Curtis and P.G. Gassman, Ibid. **84**, 116 (1962).

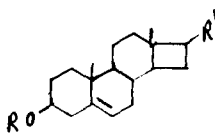
⁵ A. Hassner and I.H. Pomerantz, J. Org. Chem. **26**, 1760 (1962).

⁶ Satisfactory analyses for all compounds reported with melting points were obtained by A. Bernhardt, Max Planck Institut, Muelheim, Germany. All melting points are uncorrected.



I, R:H

II, R:NOH

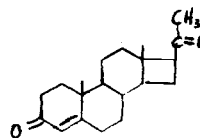
III, R:N₂IV, R:H, R':COOCH₃

V, R:H, R':COOH

VI, R:Ac, R':COOH

VII, R:Ac, R':COOCOCH₃

VIII, R:Ac, R':COCl

IX, R:Ac, R':COCH₃X, R:H, R':COCH₃

XI

262-263°. The acid, m.p. 212-214°, is interconvertible with the methyl ester IV by esterification and hydrolysis and therefore possesses structure V. Analogous reactions are observed for the 5,6-dihydroanalogs⁷ of I-V. These results are in agreement with a ketene intermediate in the rearrangement of III to IV (or V).

Acetylation with acetic anhydride effected quantitative conversion of V to the mixed anhydride VII, 1800 cm⁻¹, m.p. 253-256°, which is cleaved with difficulty by boiling methanol-water to 3β-acetoxy-16-carboxy-D-nor-5-androstene (VI), m.p. 210-212°. The slowness of hydrolysis of anhydride VII and of reaction of acid V with methyl lithium suggest a hindered carboxy function, i.e. 16-β-carboxy.⁸ The acid chloride VIII obtained from VI with thionyl chloride, was converted with dimethyl cadmium to the methyl ketone IX in good yield. Hydrolysis of IX gave D-nor-5-pregnene-3β-ol-20-one (X), m.p. 185-187°, which upon Oppenauer oxidation yielded D-norprogesterone

⁷ The properties of these compounds agree with those reported in ref. 4^b. The four-membered D-ring structure for the 5,6-dihydroanalog of IV and thus for IV has been established (see ref. 4^b).

⁸ On the assumption of a C/D trans junction in V.

(XI), m.p. 155-156°, γ_{\max} 1700 cm^{-1} , 1665 cm^{-1} , 1610 cm^{-1} ; λ_{\max} 2.41 μ
(ϵ 16,500). Biological screening of these compounds is under way and will
be reported separately.

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