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A DIRECT ANGULAR ALKYLATION IN THE PREGNANE SERIES

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Alkylation of enolate ions at the angular positions of the steroid nucleus has been carried out in position 9α by Jones and co-workers[1] starting from a Δ^{7}-11-ketone[2], and in position 14α by Woodward[3], from a $\Delta^{8\text{-}14}$-15 ketone, with methyl iodide-potassium t-butoxide.

Attempted alkylation, by this procedure, of 16-dehydropregnenolone acetate, in order to obtain the valuable[4] 17α-methyl pregnane derivatives gave, in our hands, a complex crystalline mixture, resolved by thin layer chromatography into seven substances. Six of them still exhibited the U.V. spectrum of a conjugated ketone, indicating that the desired angular methylation did not occur to an appreciable extent.

When, however, 16-dehydropregnenolone acetate in tetrahydrofuran solution was alkylated in lithium liquid ammonia by the method of Stork et al.[5] with excess methyl iodide, followed by reacetylation and chroma-

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[1] E.R.H. Jones, G.D. Meakins and J.S. Stephenson, J.Chem.Soc. 2156 (1958).

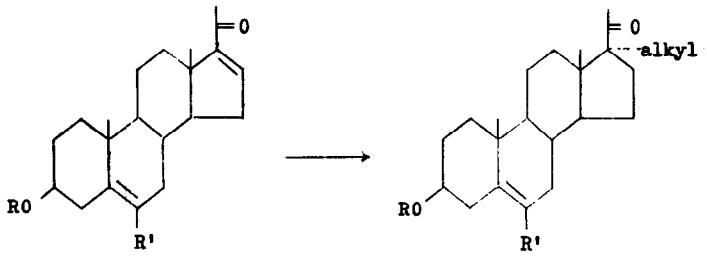
[2] R.E. Beyler, F. Hoffman, L.H. Sarett and M. Tishler, J.Org.Chem. 26, 2426 (1961) obtained paper strip evidence for methylation in 9α of an 11-ketone, in trace amount.

[3] R.B. Woodward, A.A. Patchett, D.H.R. Barton, D.A.J. Ives and R. B. Kelly, J.Am.Chem.Soc. 76, 2852 (1954).

[4] R. Deghenghi and R. Gaudry, J.Am.Chem.Soc. 83, 4668 (1961).

[5] G. Stork, P. Rosen and N.L. Goldman, Ibid. 83, 2965 (1961).

tography, 17α-methyl pregnenolone acetate[6] was isolated in 25% yield. The structure was established by comparison with an authentic sample and by its conversion to the known[6] 17α-methylprogesterone. Thin layer chromatography data on the crude alkylation product showed that a small amount of the less polar 17β-methyl epimer also formed. As expected, the presence of the axial angular methyl group at C_{18} did not favour the approach of the alkyl iodide from the β-side, thus leading to the desired α orientation of the incoming group at C_{17}. When 6-methyl-16-dehydropregnenolone acetate[7] was subjected to this alkylation procedure, a 40% yield of the corresponding 6,17α-dimethyl pregnenolone acetate, m.p. 137-138°C, $[\alpha]_D$ -65 ($CHCl_3$), (Found: C, 78.03; H, 10.01%) was recovered after chromatography of the reacetylated product; the acetate was hydrolized to the alcohol, m.p. 185-187°C, $[\alpha]_D$ -61.5 ($CHCl_3$), (Found: C, 79.84; H, 10.24%) and converted to the known[4] 6α,17α-dimethylprogesterone by oxidation and alkaline treatment.



Alkylation of 16-dehydropregnenolone acetate with ethyl iodide gave the corresponding 17α-ethyl pregnenolone [m.p. 200-202°C, $[\alpha]_D$ -65 ($CHCl_3$), (Found: C, 80.05; H, 10.33%)], which was converted to the new hormone analogue 17α-ethyl progesterone [m.p. 148-150°C, $[\alpha]_D$ +93 ($CHCl_3$),

[6] Pl. A. Plattner, H. Heusser and P.Th. Herzig, Helv.Chim.Acta 32, 270 (1949).

[7] D. Burn, B. Ellis, V. Petrow, I.A. Stuart-Webb and D.M. Williamson, J.Chem.Soc. 1957, 4092.

(Found: C, 80.20; H, 9.96%)]. O.R.D. and N.M.R. data[8] confirmed the assigned structure of the new compounds.

Biological data[9] of the new alkylated progesterones will be reported shortly elsewhere.

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[8]We are indebted to Professor K. Wiesner, University of New Brunswick, for these measurements.

[9]Performed by Dr. C. Revesz of these laboratories.