A Novel and Convenient Conversion of 17-Keto-steroids into their 18-Nor Derivatives

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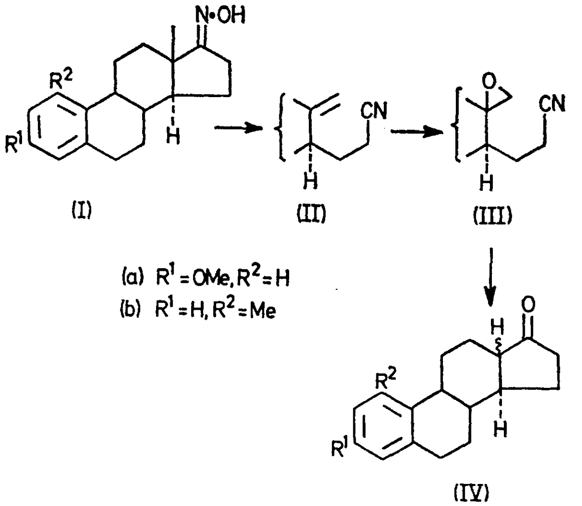
Summary Oestrone methyl ether and 1-methyloestra-1,3,5(10)-trien-17-one were converted into their 18-nor derivatives in 7—8% overall yield, the conversion proceeding *via* their oximes.

19-NORSTEROIDS have been studied extensively, but although a practical method[1] for the removal of the 19-methyl group from normal steroids has been developed, there has been little interest in their 18-nor isomers. Several routes to functionalisation of the 18-methyl group are now known, but no general method for the elimination of this group has been proposed although three conversions of 17-keto-steroids into 18-nor-20-keto-steroids have been described[2,3,4], one of which[4] does involve the eventual loss of the carbon atom originally present as the angular methyl group. It seemed however that the scheme recently described by Pinhey[5] for the removal of a 4-methyl group from tetracyclic triterpenoids should be applicable to this problem.

3-Methoxy-13,17-seco-oestra-1,3,5(10),13(18)-tetraen-17-onitrile (IIa), prepared[6] in 60% yield from the oxime (Ia) by an 'abnormal' Beckmann reaction with dimethylsulphoxide (DMSO) and dicyclohexylcarbodi-imide (DCC) in the presence of trifluoroacetic acid, was epoxidised with *m*-chloroperbenzoic acid (1·1 equiv.) in chloroform at 0° for 24 h. The product (90%) showed two adjacent spots of similar intensity (t.l.c.) and therefore probably consisted of similar amounts of the 13α,18- and 13β,18-epoxynitriles (IIIa). Without purification, this mixture (4·2 g) was boiled with dry toluene (1·2 l) containing boron trifluoride etherate (2·9 ml) for 50 h. After hydrolysis with 6N HCl, the toluene solution was washed with aqueous sodium hydroxide. Chromatography of the neutral material on a column of silica gel gave (IVa) (12·5%) from which pure 18-nor-13β-oestrone methyl ether, m.p. 163—164°, $[\alpha]_D$ $+188°$ ($CHCl_3$) (lit.[2] m.p. 161—163°, $[\alpha]_D + 188°$), M^+, 270·1613 (calc. for $C_{18}H_{22}O_2$: M^+, 270·1619) and 18-nor-13α-oestrone methyl ether, m.p. 120—122°, $[\alpha]_D - 69°$ ($CHCl_3$) (lit.[2] m.p. 121—122°, $[\alpha]_D - 66°$) M^+, 270·1615, were isolated by crystallisation from ethanol. It is not clear whether the mixture of epimers results from the epimeric nature of the epoxy nitriles (IIIa), because treatment of either 18-noroestrone methyl ether or its 13α-epimer with alkali yields a mixture containing 55% of the latter.[7]



In a similar fashion[8] 1-methyl-oestra-1,3,5(10)-trien-17-one[9] gave the oxime (Ib), m.p. 96—98°, M^+, 283·1936 ($C_{19}H_{25}ON$ requires M^+, 283·1938)† which on treatment with DMSO, DCC, and trifluoroacetic acid yielded the seco-nitrile (IIb) (67%) as an oil, $[\alpha]_D + 235°$ (EtOH), M^+, 265·1834 ($C_{19}H_{23}N$ requires M^+, 265·1830). The position of the isolated double bond was indicated by the presence of two, one-proton singlets in its n.m.r. spectrum at τ 5·04 and 5·28. Epoxidation gave the epimeric epoxynitriles (IIIb) (85%) again as an oil, $[\alpha]_D + 119°$ (EtOH), M^+ 281·1774 ($C_{19}H_{23}ON$ requires M^+, 281·1780) lacking these n.m.r. signals. Cyclisation with boron trifluoride led to 1-methyl-18-nor-13β-oestra-1,3,5(10)-trien-17-one (IVb) (14%), m.p. 85—88°, $[\alpha] + 67°$ (EtOH), M^+ 254·1665 ($C_{18}H_{22}O$ requires M^+, 254·1671). The 13β-configuration was assigned to this compound on comparison of its n.m.r. spectrum with those of the epimers of (IVa) of known stereochemistry. The 13-methine proton appeared as a well defined quartet (coupling constants 9 and 4 Hz, with evidence of further splitting > 1 Hz) in the spectrum of both 13β- (IVa) and (IVb), but as a multiplet in that of 13α-(IVa). Also two additional protons in the latter were shielded, a total of 7 resonating at fields higher than 8·2, compared with 5 protons in both the 13β-steroids. The energy required for inversion at C-13 in 18-norsteroids is known to be small, the configuration of the more stable epimer being critically dependent on the total structure.[7]

The yields in the cyclisation step (12·5, 14%) were considerably less than those obtained by Pinhey for recyclisation of the ring A. This probably reflects the greater difficulty associated with the formation of a five-membered, as opposed to a six-membered, ring. The reaction also proceeded much more slowly; possibly the yield could be improved by the use of even longer reaction times. Doubling the quantity of boron trifluoride did not increase the yield of (IVa) from (IIIa). The overall yield for the conversion of the 18-methyl-steroid into the 18-norsteroid was 7—8% which, although low, appears to offer a practical route to 18-nor-17-keto-steroids with structures otherwise compatible with the reagents (peracid, DCC, and BF_3) employed.

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† All new compounds gave satisfactory analytical data.

[1] A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Amer. Chem. Soc.*, 1962, **84**, 3204.

[2] W. F. Johns, *J. Amer. Chem. Soc.*, 1958, **80**, 6456.

[3] G. Stork, H. N. Khastgir, and A. J. Solo, *J. Amer. Chem. Soc.*, 1958, **80**, 6457.

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

[5] K. F. Cohen, R. Kazlauskas, and J. T. Pinhey, *J.C.S. Perkin I*, 1973, 2076.

[6] A. H. Fenselau, E. H. Hamamura, and J. G. Moffatt, *J. Org. Chem.*, 1970, **35**, 3546.

[7] N. L. Allinger, R. B. Hermann, and C. Djerassi, *J. Org. Chem.*, 1960, **25**, 922.

[8] C. W. Vose, Ph.D. Thesis, University of London, 1973.

[9] C. Burgess, D. Burn, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, A. P. Leftwick, J. S. Mills, and V. Petrow, *J. Chem. Soc. (C)*, 1962, 4995.