Synthesis and 14-Methylation of 3-Methoxy-14β-estra-1,3,5(10),8-tetraen-15-one

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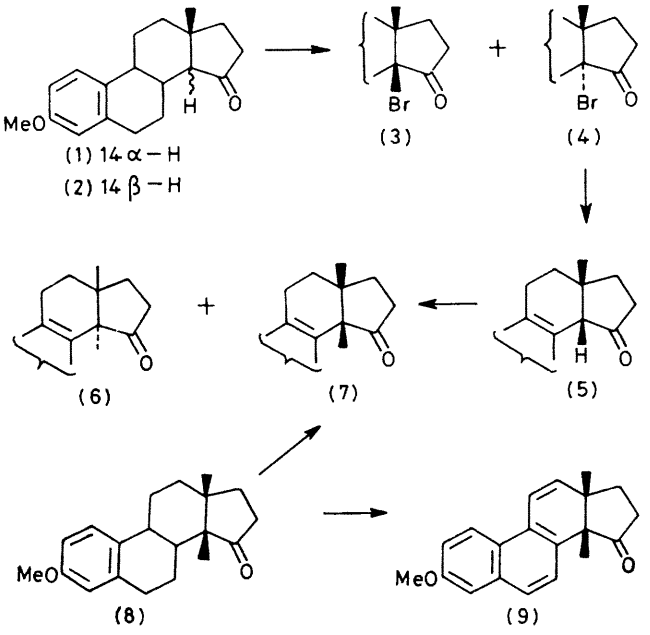
Summary The preparation of 3-methoxy-14β-estra-1,3,5(10),8-tetraen-15-one is described, base-catalysed methylation of which compound affords the corresponding 14α- and 14β-methyl compounds in a ratio of *ca.* 5:1.

THE recent finding,[1] that 3-methoxyestra-1,3,5(10)-trien-15-one (**1**), and related compounds having additional functionality in ring D undergo highly stereoselective 14β-methylation in the presence of base and methyl iodide, is at variance with the stereoselectivity encountered[2] upon alkylation of a steroidal $\Delta^{8(14)}$-15-ketone. As part of an effort to synthesise 14α-methyl-19-norsteroids and, incidentally, to identify the stereochemical influence of peripheral structural features upon the course of 14-en-15-olate alkylation, the synthesis and base-catalysed methylation of 3-methoxyestra-1,3,5(10),8(14)-tetraen-15-one was undertaken.



Treatment of the 15-ketone (**1**) [or its 14β-epimer (**2**)] with pyridinium hydrobromide perbromide in acetic acid at 15 °C afforded a chromatographically separable mixture of the 14β- and 14α-bromo-15-ketones (**3**) (31%; m.p. 116—118 °C, $[\alpha]_D$ +118°) and (**4**) (28%; m.p. 109—111 °C, $[\alpha]_D$ −59°);† although the proportion of isomers is similar to that found upon bromination of 5α-androstan-15-one,[3] some competitive aromatic bromination appears to be responsible for the modest overall yield.[4] The isomers were readily differentiated with the aid of c.d. spectroscopy in methanol; thus, the Cotton effect of (**3**) ($\Delta\epsilon_{317}$ +3·5), compared with that of the corresponding parent ketone (**2**) ($\Delta\epsilon_{302}$ −2·4), displayed a positive contribution ($\Delta\Delta\epsilon$ +5·9), whereas a comparison of those of (**4**) ($\Delta\epsilon_{314}$ −4·3) and the 14α-H-15-ketone (**1**) ($\Delta\epsilon_{296}$ +2·9) displayed a negative contribution ($\Delta\Delta\epsilon$ −7·2). Both of these increments are consistent with the given assignments.

The 14α-bromo-compound (**4**) underwent dehydrobromination in lithium bromide–lithium carbonate–dimethylformamide at 100 °C, and concomitant isomerisation gave, instead of the expected $\Delta^{8(14)}$-15-ketone, the Δ^{8}-isomer (**5**) {71%; m.p. 117—118 °C, $[\alpha]_D$ −49°, λ_{max} 275 nm (log ε 4·22)}. Analogy and c.d. spectroscopy ($\Delta\epsilon_{312}$ −2·4) indicated the 14β-configuration. The unexpected structural features of (**5**) have no bearing upon the succeeding reaction, mediated by a 8,14-dien-15-olate species.

Treatment of (**5**) in t-butyl alcohol with potassium t-butoxide followed by methyl iodide gave, after 1 h at 30 °C, a mixture of the 14α- and 14β-methyl-Δ^{8}-15-ketones (**6**) (57%; m.p. 127—129 °C, $[\alpha]_D$ +14°) and (**7**) (12%; m.p. 149·5—150 °C, $[\alpha]_D$ −246°). The structure of the minor isomer (**7**) was unequivocally established through correlation with 3-methoxy-14-methyl-14β-estra-1,3,5(10)-trien-15-one[1] (**8**), treatment of which with dichlorodicyanobenzoquinone in refluxing dioxan gave the Δ^{8}-compound (**7**) accompanied by an artefact (**9**) of further dehydrogenation. Accordingly, the structure of the major isomer (**6**) was readily inferred and was further supported by spectroscopic data. The c.d. spectrum of (**6**) ($\Delta\epsilon_{307}$ −1·1) is compatible with 14α-configuration and, interestingly, that of the 14β-methyl-Δ^{8}-15-ketone (**7**) ($\Delta\epsilon_{313}$ −21·5) is suggestive of a geometric arrangement most favourable for the mutual perturbation of the orbitals of the Δ^{8}-bond and the 15-carbonyl group.[5] Models reveal that such an arrangement is possible only in the 14β-isomer (**7**).

The remarkable change in stereoselectivity of 14-alkylation, attendant upon the introduction of an olefinic bond into ring c provides the key to a synthetic approach to 14α-methyl-19-norsteroids. Although an explanation based upon stereoelectronic considerations is not obvious, further work is in progress in order to delineate those structural features which influence stereoselectivity.

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† Satisfactory C and H combustion analyses and spectral data were obtained for all new compounds.

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[4] W. S. Johnson and W. F. Johns, *J. Am. Chem. Soc.*, 1957, **79**, 2005.
[5] P. Crabbé, 'Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry,' Holden-Day, San Fransisco, 1965, ch. 9-7, and references cited therein.