Structure Reassignment of a Steriod Refuting the Isolation of Rotational Isomers Around the C(17)–(20) Bond. *X*-Ray Crystal and Molecular Structure of 3β-Acetoxy-17aα-(2-acetoxyethoxy)-17α,17aβ-dimethyl-D-homoandrost-5-en-17β-ol

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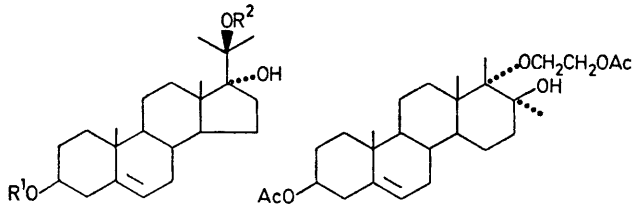
Summary The previously assigned structure of 20-methyl-20β-(2-hydroxyethoxy)pregn-5-ene-3β,17α-diol diacetate is reassigned, on the basis of an *X*-ray crystal structure analysis, to be 3β-acetoxy-17aα-(2-acetoxyethoxy)-17α,17aβ-dimethyl-D-homoandrost-5-en-17β-ol, thus disproving the isolation of the C-20 steroidal stereoisomers with asymmetry due to restricted rotation about the C(17)–(20) bond.

THE ready isolation of two rotamers of 20-methyl-20-(2-hydroxyethoxy)pregn-5-ene-3β,17α-diol (**1a**, $R^1 = H$; $R^2 = CH_2CH_2OH$) having different m.p., ^1H n.m.r., R_f and optical rotation data was reported by Kohen *et al.* in 1969.[1] In the course of our investigation on the stereomechanism of steroid hormone biosynthesis we have synthesized (20*S*)- and (20*R*)-[20-C^2H_3]-, -[20-C^3H_3]-, and [20-$^{13}CH_3$]-20-methylpregn-5-ene-3β,17α,20-triol (**1b**, $R^1 = R^2 = H$)[2] and observed that rotational isomers of (**1b**) and its 3-esters

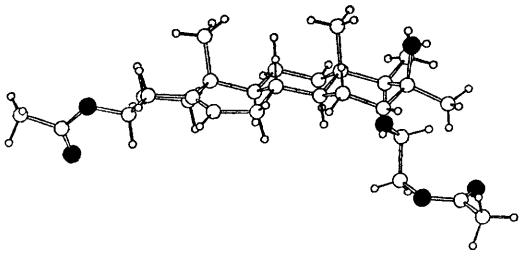


(1) (2)

a; $R^1 = H$; $R^2 = CH_2CH_2OH$
b; $R^1 = R^2 = H$

were not separable by t.l.c., h.p.l.c. counter-current distribution, or recrystallization. The observed sharp contrast in spite of the close structural relationship and our interests in the third isomer which, in theory, should be obtainable and in the equilibration of these rotamers prompted us to reinvestigate the synthesis and structure determination. In a recent review[3] Ōki also raised these questions on the original study. Nes and Varkey recently reported[4] conformational analysis results for the 17(20) bond of 20-ketosteroids, which supported the isolation of rotamers by Kohen *et al.*

Following the original procedure[1] methylmagnesium bromide in ether was added to the ethylene acetal of 3β,17α-dihydroxypregn-5-en-20-one in benzene and the mixture was heated under reflux for 90 h. Both the '20α' isomer, m.p. 275—278 °C, and the '20β' isomer, m.p. 200—203 °C, were isolated in yields corresponding to those originally reported. The diacetate of the '20β' isomer showed an m.p. of 162·5—165 °C; i.r. (KBr) 3490, 1730, 1710, and 1240 cm^{-1}; ^1H n.m.r. (60 MHz, $CDCl_3$) δ 1·02 (3H, s, 10- or 13-Me), 1·03 (3H, s, 13- or 10-Me), 1·15 (3H, s, Me), 1·23 (3H, s, Me), 2·02 (3H, s, OAc), and 2·05 (3H, s, OAc); shift in pyridine solution, Δ, −0·3 p.p.m. for 13-Me, +0·04 p.p.m. for 10-Me [ref. 1 gives m.p. 166·5—167·5 °C, δ 1·06 in $CDCl_3$ (13-Me) and Δ − 0·26 p.p.m. for 13-Me]. Equilibrium between the isomers could not be obtained by heating in solution or by melting.



FIGURE

Single crystals of the '20β' diacetate were grown from chloroform–methanol solution and the total structure of the '20β' diacetate was determined by single-crystal diffraction methods. The intensities of 3163 diffraction spectra having $\theta < 75°$ were measured using Cu-K_α radiation. The structure was solved by direct methods[5] and refined by full-matrix least-squares techniques. The final reliability index (R) was 9·9% for all data. The structure was shown to be 3β-acetoxy-17aα-(2-acetoxyethoxy)-17α,17aβ-dimethyl-D-homoandrost-5-en-17β-ol (**2**) with the D-ring in a chair conformation. A perspective view of this molecule is given in the Figure. Detailed crystal structure data will be published elsewhere.

The structure determination thus disproves the first reported isolation of rotamers with asymmetry due to restricted rotation around the steroidal C(17)–(20) bond. The shift of −0·3 p.p.m. observed for the 13-Me resonance in changing from a $CDCl_3$ to pyridine solution of (**2**) is attributable to the 1,3-diaxial effect[6] of the 17β-hydroxy group of the D-homo structure rather than to the postulated interaction[1,4] between the ether oxygen and the 13-Me group. The mechanism of this unusual D-homologation by the Grignard reagent and the contraction by formic acid to 3β-hydroxy-17β-methyl-pregn-5-en-20-one reported in the original paper is under investigation.

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