The Isolation of C-20 Steroidal Stereoisomers with Asymmetry due to Restricted Rotation about the C-17,20 Bond

By F. KOHEN, R. A. MALLORY, and I. SCHEER*

(*Division of Organic Chemistry, Ortho Research Foundation, Raritan, New Jersey* 08869)

Summary Methyl Grignard addition to 3β,17α-dihydroxypregn-5-en-20-one ethylene acetal gives two isomeric C-20 tertiary glycol ethers.

WE report the isolation of two stereoisomers which owe their separate identities to hindered rotation about a single bond joining two saturated carbon atoms.

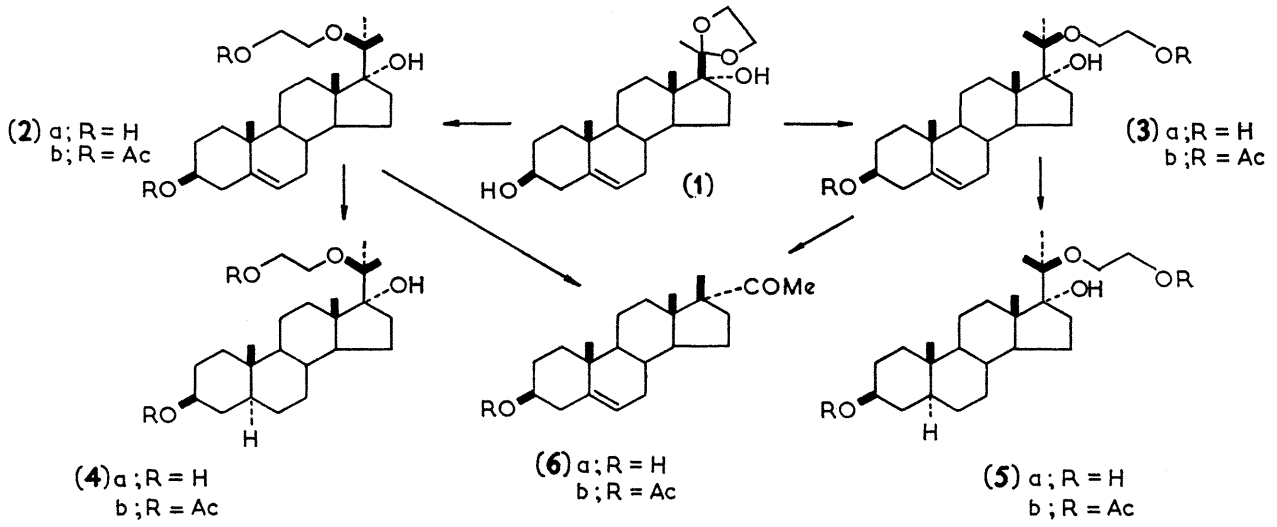
In the course of our investigation on the addition of Grignard reagents to steroidal acetals[1] we attempted the addition of methylmagnesium bromide to the hindered acetal 3β,17α-dihydroxypregn-5-en-20-one ethylene acetal (**1**). Cleavage of the dioxolan ring with formation of a tertiary glycol ether system was extremely slow. No significant amount of reaction occurred after 3 hr. under reflux in benzene,† and a maximum of 48% yield of products was obtained after 48 hr. Chromatography of the reaction mixture on silicic acid yielded starting material (41%) and two isomeric C-20 tertiary glycol ethers (48%), having the empirical formula $C_{24}H_{40}O_4$.

From the evidence presented below we suggest the structure 20-methyl-20β-(2-hydroxyethoxy)pregn-5-ene-3β,17α-diol (**2a**) for the glycol ether (R_F 0·27,‡ m.p. 200—203°, $[\alpha]_D$ −65°, 32·5% yield) that was eluted first. We suggest the structure 20-methyl-20α-(2-hydroxyethoxy)pregn-5-ene-3β,17α-diol (**3a**) for the more polar glycol ether (R_F 0·17,‡ m.p. 274—276°, $[\alpha]_D$ − 108·2°, 15·5% yield). The structures (**2a**) and (**3a**) are based on the following observations: (a) the chemical shift of the C-18 protons in the n.m.r. spectra of the derived diacetates (**2b**) (m.p. 166·5—167·5°, $[\alpha]_D$ − 27°) and (**3b**) (m.p. 103·5—104·6°, $[\alpha]_D$ − 47·5°) was quite different; in (**2b**), due to the proximity of the glycol chain, the C-18 methyl protons were deshielded and resonated at δ 1·06 in $CDCl_3$ solution and at δ 1·30 in pyridine solution (the pyridine-induced shift, Δ, being − 0·26 p.p.m.§) whereas in (**3b**) no deshielding effect of the C-18 protons was observed, and they appeared at δ 0·90 in $CDCl_3$ and at δ 0·85 in pyridine (the pyridine-induced shift, Δ, being +0·05 p.p.m.); (b) saponification of (**2b**) and (**3b**) gave back the starting diols (**2a**) and (**3a**); (c) catalytic hydrogenation of (**2a**) and (**3a**) gave the dihydro-isomers (**4a**) (m.p. 213—214°) and (**5a**) (m.p. 289—291°), and n.m.r. analysis of the dihydro-diacetates (**4b**) (m.p. 140—141°, $[\alpha]_D$ − 1·42° and (**5b**) (m.p. 149—150°, $[\alpha]_D$ − 18·3°) showed that in (**4b**) the C-18 protons, due to the proximity of the glycol chain, were deshielded and appeared at δ 1·00 in $CDCl_3$ solution and at δ 1·30 in pyridine solution

† With unhindered acetals, such as 3β-hydroxypregn-5-en-20-one ethylene acetal the reaction was complete within 3 hr. and about 80% of the desired glycol ether was obtained (ref. 1b).

‡ The glycol ethers (**2a**) and (**3a**) were examined by t.l. c., using chloroform-ethyl acetate (3 : 7) as developing solvent and silica gel G as adsorbent.

§ P. Demarco, *et al.* (*J. Amer. Chem. Soc.*, **1968**, **90**, 5480) have shown that in the n.m.r. spectra of hydroxylic steroids, protons occupying 1,3-diaxial position, vicinal or geminal to a hydroxy-group, are strongly deshielded in pyridine solution with respect to $CDCl_3$ solution; we suggest that a similar effect is operating in compounds (**2b**) and (**4b**) between the ether oxygen and the C-18 methyl group.



(Δ — 0·30 p.p.m.) while in (**5b**) they resonated at δ 0·85 in $CDCl_3$ and at δ 0·80 in pyridine (Δ +0·05 p.p.m.); (d) both isomers (**2a**) and (**3a**) upon treatment with formic acid were converted into the same compound, 3β-hydroxy-17β-methylpregn-5-en-20-one (**6a**)[2]¶ (m.p. 184—185°, $[\alpha]_D$ —78°, the C-18 protons appeared at δ 0·80 in $CDCl_3$ solution in the n.m.r.) by a pinacol rearrangement, through initial carbonium-ion formation at C-17, followed by migration of a methyl group from C-20 to C-17 with loss of the two carbon glycol side-chain; (e) mass-spectral analysis of the two isomers (**2a**) and (**3a**) revealed that identical fragments with approximately the same intensity were produced in both compounds after the initial loss of the C-20 tertiary glycol ether chain which occurred at *m/e* 330.

(*Received, March* 10*th*, 1969; *Com.* 328.)

[1] (a) R. A. Mallory, S. Rovinski, and I. Scheer, *Proc. Chem. Soc.*, 1964, **416**; (b) R. A. Mallory, S. Rovinski, F. Kohen, and I Scheer, *J. Org. Chem.*, 1967, **32**, 1419.
[2] (a) P. A. Plattner, H. Heusser and P. Th. Herzig, *Helv. Chim. Acta*, 1949, **32**, 270, (b) H. Heusser, Ch. R. Engel and P. A. Plattner, *ibid.*, 1950, **33**, 2242.

¶ Compound (**6a**) was further characterized by its derived acetate (**6b**) (m.p. 171—172°, $[\alpha]_D$ — 66·4° (ref. 2b) and Oppenauer oxidation of (**6a**) gave the known 17β-methylisoprogesterone (m.p. 152—153°, $[\alpha]_D$ + 74·8°) (ref. 2b).