

Demethylation of a Steroid Methyl Ether with Concomitant Ring Expansion

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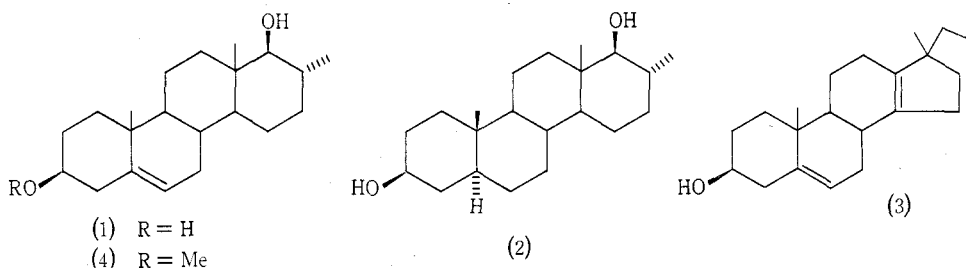
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Abstract

Demethylation of pregn-5-ene-3 β ,20 β -diol dimethyl ether with ferric chloride/acetic anhydride is shown to form the ring-expanded steroid 17 α -methyl-D-homoandrost-5-ene-3 β ,17 $\alpha\beta$ -diol (1) in 75% isolated yield.

Demethylation has been accomplished for a variety of steroid methyl ethers by employing the reagent combination of a Lewis acid and acetic anhydride.¹ In particular cholest-5-en-3 β -ol methyl ether has been reported to yield the respective 3 β -acetate in 87% yield.² The yields obtained from other steroid methyl ethers, however, were shown to be very dependent on their position and stereochemistry. In this communication we report the results of a demethylation study involving a 20 β -methoxy group.



When pregn-5-ene-3 β ,20 β -diol dimethyl ether was treated with ferric chloride/acetic anhydride followed by metal hydride reduction of the crude acetate mixture, one major component was formed in >95% relative yield. Comparison of its physical and spectral data with that of pregn-5-ene-3 β ,20 β -diol suggested its identity was 17 α -methyl-D-homoandrost-5-ene-3 β ,17 $\alpha\beta$ -diol (1). Confirmation of this structure was obtained by hydrogenation of (1) to form the known 5 α -D-homo diol (2), commonly called 'uranediol'. The only other product (<5%) formed in the demethylation reaction was a monoalcohol, tentatively identified as (3), on the basis of its mass

¹ Bruce, S. E., and Gall, R. E., *J. Chem. Soc., Perkin Trans. 1*, 1972, 2319, and references cited therein.

² Ganem, B., and Small, V. R., Jr, *J. Org. Chem.*, 1974, 39, 2738.

spectrum [trimethylsilyl derivative, m/z 372 (M), 357 (M-CH₃), 343 (100%, M-C₂H₅), 253 (95, M-C₂H₅-Me₃SiOH)] and previous work in this area.³ Substitution of boron trifluoride for ferric chloride gave a similar product profile. When the reaction was conducted at -20°, however, an appreciable amount of the alcohol (4) was formed with no trace of the corresponding 20 β -methoxypregn-5-en-3 β -ol.

A similar ring expansion has been previously documented for the solvolysis of 20 β -tosyloxy⁴ and sulfate⁵ pregnanes and the boron-trifluoride-promoted rearrangement of 20 β -acetoxy pregnanes.³ In contrast 20 α -pregnane derivatives yield complex product mixtures.³ The propensity for σ -bond rearrangement is quite marked and from the experiment at -20° appears more facile than the corresponding π -bond participation at C3. Presumably relief of steric interactions must also be a major driving force in the former process.

In conclusion it is apparent that while cleavage of 20 β -methoxy groups is a facile reaction, it is accompanied by total rearrangement to form ring-expansion products. The high yield in the cleavage reaction must be directly attributed to the σ -bond participation. Previous work has established that lack of π - or σ -bond participation in other steroid methyl ethers results in poor yields of the respective hydroxy products.⁶ The present results also suggest that the use of 20 β -methoxy groups as protecting groups is severely limited, since most alcohol regeneration processes rely on C-O bond cleavage to generate the most stable carbocation.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Steroid precursors were purchased from Steraloids Inc. (Wilton, U.S.A.). Thin-layer chromatography was carried out on Eastman precoated silica-gel sheets. N.m.r. spectra were obtained on a Varian T60 spectrometer. Rotations were run on a Perkin-Elmer 141 instrument operating at the sodium D line. Mass spectral data were obtained on an A.E.I. MS30 mass spectrometer interfaced to a Pye 104 gas chromatograph (column 30 m by 0.5 mm i.d., SE-30 SCOT, temperature 240°). Elementary analyses were performed by the Australian Microanalytical Service, Melbourne.

Pregn-5-ene-3 β ,20 β -diol Dimethyl Ether

Sodium hydride (0.8 g) was added to a solution of pregn-5-ene-3 β ,20 β -diol (1 g) in 1,2-dimethoxyethane (30 ml), and the mixture heated under reflux for 0.5 h. After the reaction mixture had been cooled to room temperature, methyl iodide (4.5 g) was added and stirring continued for a further 5 h, at which time the reaction was quenched by addition of water. The solvent was evaporated and the residue extracted with ether. The ethereal extract was washed with brine, dried and evaporated.

Chromatography of the crude product on Sorbsil (50 g) and elution with light petroleum/ether (20 : 1) gave pregn-5-ene-3 β ,20 β -diol dimethyl ether (1 g, 95%) as a white solid, pure by t.l.c. and g.c. Recrystallization of a portion from methanol/water gave crystalline plates, m.p. 103–105° (Found: C, 79.7; H, 10.9. C₂₃H₃₈O₂ requires C, 79.7; H, 11.0%). Mass spectrum m/z 346 (M), 314 (M-CH₃OH), 59 (100%, CH₃CHO⁺Me).

17 α -Methyl-D-homoandrost-5-ene-3 β ,17 α -diol (I)

A mixture of pregn-5-ene-3 β ,20 β -diol dimethyl ether (0.08 g) and anhydrous ferric chloride (0.006 g) in acetic anhydride (1 ml) was stirred for 0.5 h at room temperature, followed by dilution with water. The reaction mixture was then extracted with ether, and the ethereal extract was washed,

³ Aoyama, S., Kazus, K., and Komeno, T., *Chem. Pharm. Bull.*, 1971, **19**, 1329.

⁴ Hirschmann, H., Hirschmann, F. B., and Zala, A. P., *J. Org. Chem.*, 1966, **31**, 375.

⁵ Hirschmann, H., and Williams, J. S., *J. Biol. Chem.*, 1963, **238**, 2305.

⁶ Narayanan, C. R., and Iyer, K. N., *J. Org. Chem.*, 1965, **30**, 1734.

dried and then evaporated. The crude product was then dissolved in tetrahydrofuran and added to a refluxing solution of lithium aluminium hydride in tetrahydrofuran. After 0.5 h reaction time the reaction mixture was worked up in the usual manner. Chromatography on Sorbsil and elution with light petroleum/ether (2 : 1) gave the required *diol* (1) (0.055 g, 75%), m.p. 223–225° (recrystallized from ethyl acetate) (Found: C, 79.1; H, 10.8. $C_{21}H_{34}O_2$ requires C, 79.1; H, 10.8%). $[\alpha]_D^{23} -70.9^\circ$ (EtOH). Mass spectrum (as ditrimethylsilyl ether) m/z 462 (M), 372 (M–Me₃SiOH), 73 (100%, Me₃Si⁺). The trimethylsilyl derivative was found to be homogeneous by g.c., and not identical with an authentic sample of pregn-5-ene-3 β ,20 β -diol. N.m.r. δ [(CD₃)₂SO] 0.8, 3H, s, 18-Me; 0.88, 3H, m, C17-Me; 0.97, 3H, s, 19-Me; 4.03, 1H, m, C17a-H; 4.51, 1H, m, C3-H; 5.36, 1H, m, CH=C.

17 α -Methyl-D-homo-5 α -androstane-3 β ,17 $\alpha\beta$ -diol (2)

A solution of the diol (1) (0.1 g) in ethyl acetate was hydrogenated in the presence of Adams catalyst (0.005 g) for 2 h. Workup in the usual manner gave the product (0.09 g, 89%) which was recrystallized from ethyl acetate to give white needles, m.p. 215–216°, $[\alpha]_D^{23} +1^\circ$ (CHCl₃) [lit.⁷ m.p. 216–219°, $[\alpha]_D^{25} +3.7^\circ$ (CHCl₃)]. Mass spectrum (ditrimethylsilyl derivative) m/z 464 (M), 374 (M–Me₃SiOH), 75 (100%, Me₂SiO⁺H). Homogeneous by t.l.c. and g.l.c.

3 β -Methoxy-17 α -methyl-D-homoandrost-5-en-17 $\alpha\beta$ -ol (4)

A mixture of pregn-5-ene-3 β ,20 β -diol dimethyl ether (0.1 g) and ferric chloride (0.008 g) in acetic anhydride (2 ml) was stirred at –20° for 0.5 h. After workup as previously described, the crude product was chromatographed on Sorbsil (5 g). Elution with light petroleum/ether (20 : 1) gave starting material (0.05 g). Elution with light petroleum/ether (10 : 1) gave the required *product* (4) (0.022 g, 20%), m.p. 140–142° (Found: C, 79.5; H, 10.7. $C_{22}H_{36}O_2$ requires C, 79.5; H, 10.9%). Mass spectrum (trimethylsilyl derivative) m/z 404 (M), 372 (M–CH₃OH), 314 (M–Me₃SiOH), 75 (100%, Me₂SiO⁺H). Homogeneous by t.l.c. and g.l.c.

The absence of any 20 β -methoxypregn-5-en-3 β -ol was readily ascertained from the mass spectrum, which did not show m/z 59, a dominant and characteristic fragment in the spectra of all 20 β -methoxy steroids.

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⁷ 'Merck Index' 8th Edn, p. 1093 (Merck: Rahway, N.J., 1968).