Steroidal Acetals of Formaldehyde

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The anodic oxidation of cholesterol yields 3β,3′β-(methylenedioxy)-dicholest-5-ene. A new method for the preparation of methoxymethyl ethers of steroids is described. The n.m.r. and mass spectra of these compounds is reported.

L'oxydation anodique du cholestérol conduit au (méthylènedioxy)-3β,3′β dicholestene-5. On décrit une nouvelle méthode pour la préparation des éthers méthoxyméthylés des stéroides. On rapporte les spectres de r.m.n. et de masse de ces composés.

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In order to confirm the identity of the main anodic oxidation product of cholesterol in aqueous acidic methanol as 3β,3′β-(methylenedioxy)-dicholest-5-ene (**1**) direct comparison with an authentic specimen was necessary.

Compound **1** was prepared by reaction of cholesterol and chloromethyl methyl ether in the presence of sodium hydride (1) and shown to be identical in all respects with the anodic oxidation product. Reaction of 5α-cholestan-3β-ol under the same conditions however gave a mixture of 3β,3′β-(methylenedioxy)-5α-cholestane (**2**) and 3β-(methoxymethoxy)-5α-cholestane (**3**) in poor yield.

As an alternative method for preparing compound **1**, the reaction of cholesterol and dimethoxymethane in the presence of acidic catalysts was investigated. The product thus obtained was 3β-(methoxymethoxy)-cholest-5-ene (**4**), the structure of which was confirmed by its n.m.r. (Table 1) and mass spectra (see below). This method was also used to prepare compound **3** and seems of general applicability. Methoxymethyl ethers have also been prepared by Kupchan *et al.* (1) by a modification of the method employing chloromethyl methyl ether.

The mass spectrum of compound **1** differs from that of cholesterol only in the greater abundance of the ions *m/e* 368 and 353 relative to 386 (the molecular ion of cholesterol). Higher mass ions cannot be detected and no metastable transition can be found in the first field-free region of the spectrometer (2) for the decomposition of the parent molecular ion (M^+, *m/e* 784) to either 386 or 368. Evidently a very ready fragmentation, either thermal or electron impact induced, results in the formation of the molecular ions of cholesterol and cholestadiene. The mass spectrum of 3β-(methoxymethoxy)-cholest-5-ene (**4**) is also very similar to that of cholesterol and shows no parent molecular ion (*m/e* 430). Higher mass ions are very weak in the spectrum of compound **2** but the decomposition 788 (M^+) → 402 can be detected in the first field-free region. The latter together with a fairly intense ion at *m/e* 386 suggests a fragmentation producing (nominally) the molecular ion of methoxycholestane and of cholestanone. The mass spectrum of 3β-(methoxymethoxy)-5α-cholestane is remarkable. The molecular ion (*m/e* 432) is one of the strongest in the spectrum while another (370) is derived from it by loss of methoxymethanol. Such an intense molecular ion appears to be without precedent for an acetal (3).

TABLE 1. Partial proton magnetic spectra of steroidal acetals of formaldehyde

Compound	—OCH_2O— δ, p.p.m.	CH_3O— δ, p.p.m.
1	4.81	—
2	4.79	—
3	4.70	3.40
4	4.66	3.77

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Experimental

The n.m.r. spectra were determined for deuteriochloroform solutions with tetramethylsilane as an internal reference using a Varian A-60 spectrometer. Mass spectra were determined using an A.E.I. MS9 instrument, samples being inserted directly into the ion source at the lowest possible temperature.

Anodic Oxidation of Cholesterol

Cholesterol (1 g) was partially dissolved in methanol (40 ml), water (40 ml), and 20% sulfuric acid (5 ml), and electrolyzed (4) for 5 h on a lead dioxide electrode (30 V, 2 A) with agitation and external cooling (ice–water). The mixture was extracted with methylene chloride and the extract washed free of acid. The residue on evaporation was crystallized several times from methylene chloride – acetone giving 3β,3′β-(methylenedioxy)-dicholest-5-ene, m.p. 191°, $[\alpha]_D$ −36° (lit. (1) m.p. 190.5°, $[\alpha]_D$ −30.8°).

Anal. Calcd. for $C_{55}H_{92}O_2$ (mol. wt. 785): C, 84.12; H, 11.81. Found (770 (Rast)): C, 83.93; H, 12.01.

Reaction of 5α-Cholestan-3β-ol with Chloromethyl Methyl Ether

5α-Cholestan-3β-ol (3.14 g) was added to a suspension of 50% sodium hydride (0.24 g NaH) in dry benzene (50 ml) and the mixture refluxed for 30 min. Chloromethyl methyl ether (1.1 g) was added dropwise to the cooled mixture which was then agitated for 18 h. Water was added and the organic layer separated and evaporated to dryness. The residue was separated on a dry silica gel column using methylene chloride as a solvent giving 3β-(methoxymethoxy)-5α-cholestane (243 mg), m.p. 61°, after crystallization from ethyl acetate – methanol, $[\alpha]_D$ +17° ($CHCl_3$).

Anal. Calcd. for $C_{29}H_{52}O_2$: C, 80.49; H, 12.11. Found: C, 80.64; H, 12.21.

Later fractions yielded 3β,3′β-(methylenedioxy)-di-5α-cholestane (100 mg), m.p. 206–207°, after crystallization from ethyl acetate, $[\alpha]_D$ +1° ($CHCl_3$).

Anal. Calcd. for $C_{55}H_{96}O_2$: C, 83.69; H, 12.36. Found: C, 83.47; H, 12.19.

3β-(Methoxymethoxy)-cholest-5-ene

To cholesterol (1 g), dimethoxymethane (10 ml), and dry tetrahydrofuran (10 ml) was added perchloric acid (70%, 5 drops). After agitation for 24 h at room temperature, solid Na_2CO_3 was added, the solids removed by filtration, and the filtrate evaporated to dryness. Chromatography of the residue on neutral alumina in hexane gave the title compound (265 mg), m.p. 76–78°, after crystallization from methylene chloride – methanol, $[\alpha]_D$ −23° (in $CHCl_3$) (lit. (1) m.p. 85–86°).

Anal. Calcd. for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.94; H, 11.70.

3β-(Methoxymethoxy)-5α-cholestane

This was prepared from 5α-cholestan-3β-ol and dimethoxymethane as described above. It was purified by chromatography on basic alumina (Bio Rad A 10) and crystallization from ethyl acetate – methanol, yield 41%, m.p. 62°, $[\alpha]_D$ +20° (in $CHCl_3$).

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