Formation of Polyoxymethylene Dicholesteryl Ethers in Preparation of Dicholesteryl Formal

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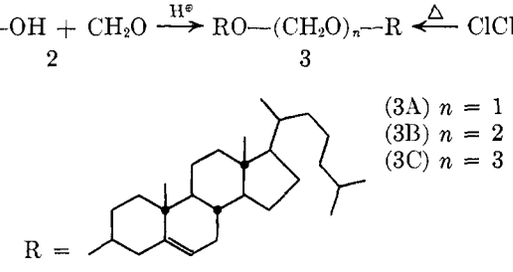
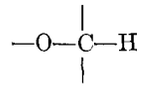
Dicholesteryl formal is formed during the recrystallization of cholesteryl chloromethyl ether and is a component of Montignie's "dicholesteryl formal"—a mixture containing unreacted cholesterol, as well as dioxymethylene and trioxymethylene dicholesteryl ethers.

Some years ago we became interested in the nature of the product which Montignie (*5*) described as dicholesteryl formal, 3A, when a substance which we obtained by recrystallizing cholesteryl chloromethyl ether (*6*), 1, from diisopropyl ether was identified as this compound and yet melted at a much higher temperature. Subsequently Kupchan et al. (*3*) isolated in low yield, from the condensation of cholesterol, 2, with formaldehyde in the presence of aqueous hydrochloric acid, a compound which was assigned the dicholesteryl formal, 3A, structure. They found that the infrared spectrum of this substance was similar to that of a small fraction, which they isolated by column chromatography, of the crude reaction product prepared by Montignie's (*5*) procedure. Their product appears to be identical with that which we had obtained from cholesteryl chloromethyl ether, 1, inasmuch as the melting points and specific rotations of the two products are in close agreement.

Since dicholesteryl formal, 3A, appeared to be but a minor component of the Montignie product, we investigated the latter's composition by a combination of crystallization and chromatographic techniques. It consists mostly of unreacted cholesterol, 2, admixed with smaller amounts of dicholesteryl formal, 3A, dioxymethylene dicholesteryl ether, 3B, and trioxymethylene dicholesteryl ether, 3C. Although the latter two substances are novel steroid derivatives, they belong to a well-known class of compounds, most of whose members are polyoxymethylene dialkyl ethers (*7*), 3. These compounds have usually been prepared by a similar acid-catalyzed reaction of an alcohol with formaldehyde, often conducted at elevated temperatures (*2*, *7*). Unlike the less volatile steroid derivatives, readily separated by chromatography, the individual dialkyl ethers have usually been isolated and purified by fractional distillation (*1*, *7*). The structures of our homologues were readily differentiated by comparing the areas of their —O—CH_2—O— signals with those of the olefinic and the





protons at the 6 and 3 positions, respectively, in each compound.

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EXPERIMENTAL

Melting points are uncorrected and were determined with a Fisher-Johns apparatus. Infrared spectra were recorded, using nujol mulls, with a Perkin-Elmer Model 137 Infracord spectrophotometer. Nuclear magnetic resonance spectra were measured on a Varian A-60 spectrometer using deuterochloroform as solvent and tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as an internal standard. Optical rotations were determined as 0.300% solutions in chloroform at 26°C with a Bendix Automatic Digital Polarimeter (Model 1140).

Thin-layer chromatography (tlc) was performed on silica gel G (Brinkmann); benzene–chloroform (1:4) was the developing solvent mixture. The chromatographic spots were detected by spraying the plates with methanol-concentrated sulfuric acid followed by heating at 110°C for 1–2 min. Thin-layer chromatography was a convenient way to follow the progress of the column chromatographic separation carried out on a 2.5 × 110-cm column (125 grams) of silica gel (Baker). Benzene–chloroform (1:4) was used in preparing the column and the same solvent mixture was employed in eluting the adsorbed products at the rate of 11 ml/7.5 min; 130 fractions, each measuring 11 ml, were collected. Yields are based on the original amount of cholesterol employed in the reaction and do not take into account the amount of the steroid recovered.

Elemental analyses (C and H), in agreement with theoretical values, were obtained and submitted for review.

Dicholesteryl Formal, 3A. To a stirred, chilled mixture of 6.00 grams (1.55 mmol) of cholesterol, dissolved in 28 ml of ether and 150 ml of 37% formalin was added dropwise over a period of 10 min and at a temperature below 25°C, 30 grams of concentrated sulfuric acid. The mixture was stirred in a closed system for an additional 60 hr at room temperature (25–30°C). A precipitate, which formed after about 20 hr of stirring, was removed at the end of the reaction and washed with ice-cold ether. Thin-layer chromatography of this crude material (2.51 grams) indicated that it was essentially unreacted cholesterol (41.8% recovered); its infrared spectrum was almost identical with that of the starting steroid.

The ether layer was separated from the aqueous acid solution in the filtrate and the solvent removed by distillation. The residue, crystallized from 95% ethanol, weighed 2.40 grams and melted at 168–79°C. A thin-layer chromatogram revealed that it was a mixture consisting of five components, the most polar of which was cholesterol. Part of the mixture (1.25 grams) was dissolved in a minimum volume of benzene–chloroform (1:4). The solution was then transferred to a column of silica gel subsequently eluted with the same solvent

mixture. Fractions 24–30 of the eluate were combined. Removal of the solvent left 421 mg (13.3%) of dicholesteryl formal, mp 190–2°C. After crystallization from hexane-acetone the product (308 mg) melted at 195–6°C; $[\alpha]_D^{26}$ −28.6°; λ 9.05 and 9.65 (C—O of ether) (no adsorption in the hydroxyl and carbonyl regions).

Proton magnetic resonance (pmr): 3.43 (broad multiplet, 3 —OCH—), 4.77 (s, —OCH$_2$O—), 5.33 (broad doublet, 6 = CH) ratio of integrations 1:1:1, respectively.

Kupchan et al. (*3*) reported an mp of 190.5°C, and $[\alpha]_D^{26}$ −30.8° (chloroform) for their dicholesteryl formal. Lunn (*4*) assigned a signal observed at δ 4.63 ppm in the pmr spectrum of 17β,17β′-oxymethylene-diandrost-4-ene-3-one to the —OCH$_2$O— hydrogens. The area of this peak, as in the case of 3A, was equal to that of the steroid

protons (at the 17 and 17′ positions). He also suggested that the —CH$_2$OCH$_2$OCH$_2$— structure in some of his compounds was responsible for the intense absorption bands observed at 8.62, 9.09, 9.81, and 10.87 μ in their infrared spectra.

Dioxymethylene Dicholesteryl Ether. On combining fractions 33–40 of the eluate and removing the solvent, there remained 295 mg (9.0%) of a white solid melting at 134–42°C. One recrystallization from hexane–ethanol afforded 222 mg of dioxymethylene dicholesteryl ether, mp 148–9°C; $[\alpha]_D^{26}$ −29.8°; λ 8.99, 10.04, and 10.12.

Pmr: 3.38 (broad multiplet, 3 —OCH—) 4.82 (s, —OCH$_2$O—), 5.33 (broad doublet, 6 = CH) ratio of integrations 1:2:1, respectively.

Trioxymethylene Dicholesteryl Ether. Fractions 44–55 were combined, evaporated to dryness, and the residue was crystallized from hexane–ethanol. There was obtained 79.0 mg (2.3%) of trioxymethylene dicholesteryl ether, mp 174–7°C; $[\alpha]_D^{26}$ −34.2°; λ 8.87, 9.01, 10.23, and 10.86.

Pmr: 3.38 (broad multiplet 3 —OCH—) 4.82 (s, —OC$_2$HO), 4.88 (s, central —OCH$_2$O—), 5.33 (broad doublet, 6 = CH) ratio of integrations 1:2:1:1, respectively.

When fractions 63–76 were combined and evaporated to dryness, 2–3 mg of a white solid remained. This material was not identified but, because of the relationship of its thin-layer chromatographic spot to those of the formal, the polyoxymethylene ethers and cholesterol (R_f of 3A > 3B > 3C > this fraction > 2), it is quite possible that this product may be the next higher homologue, tetraoxymethylene dicholesteryl ether. Cholesterol, identified by thin-layer chromatography, was isolated from subsequent eluates.

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Behavior of 4-β-Hydroxyethyl-6,7,8,9-tetrachloro-1-oxa-4-azaspiro[4.4]nona-6,8-diene in Diels-Alder Reaction

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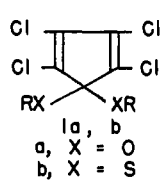
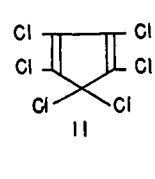
The formation of ketals (Ia) and mercaptals (Ib) of 1,2,3,4-tetrachlorocyclopentadienone from the condensation of hexachlorocyclopentadiene (II) with alcohols (*5*, *8*, *10*) or thiols (*9*) in the presence of strong bases has been known for some time. Although I and II add a variety of dienophiles



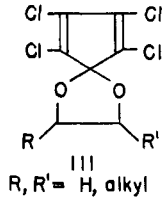
Ia, b
a, X = O
b, X = S



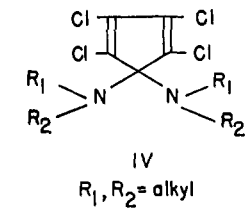
II

to afford typical Diels-Alder adducts, neither undergoes the Diels-Alder self-dimerization characteristic of related cyclic dienes such as cyclopentadiene, cyclopentadienone or 1,2,3,4-tetrachlorocyclopentadienone. The 5,5-bis(dialkylamino)-1,2,-3,4-tetrachlorocyclopentadienes (IV) also do not self-dimerize and in fact decompose under Diels-Alder reaction conditions (*7*).

Vicinal glycols condense with II in the presence of bases to form cyclic ketals (III) which, unlike their acyclic counterparts Ia and Ib or hexachlorocyclopentadiene itself, readily afford Diels-Alder adducts via the self-dimerization route (*1*, *2*).



III
R, R′ = H, alkyl



IV
R_1, R_2 = alkyl