86. *Studies in the Sterol Group. Part XXIX. The Constitution of the Isomeric Ethers of Cholesterol.*

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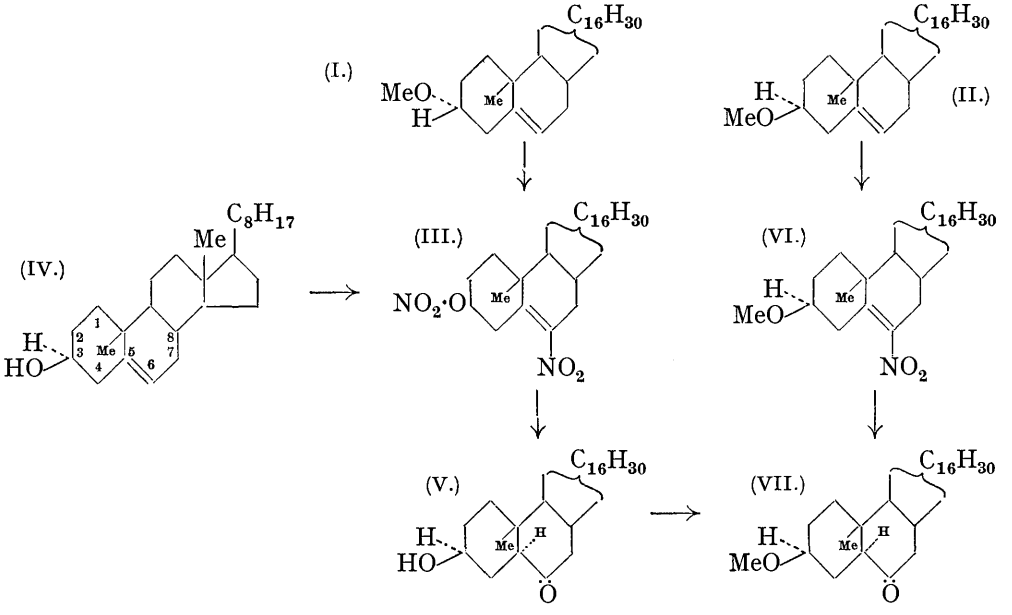
In Part XXV (J., 1936, 907) we reported that the isomeric pairs of cholesteryl methyl, ethyl, and benzyl ethers show remarkable differences in their reactions with the halogen acids and with bromine. For instance, the dextrorotatory or "*cis*" series of ethers yield

the corresponding cholesteryl halide and tribromocholestane respectively, whereas the lævorotatory or "*trans*" series fail to react with the halogen acids, and with bromine yield the corresponding ether 5 : 6-dibromides.

We now find that "*cis*"-cholesteryl methyl ether gives tribromocholestane with bromine in the presence of excess of potassium acetate, thus showing that the replacement of the methoxyl by bromine is not due to the catalytic influence of hydrogen bromide. Furthermore, "*cis*"-cholesteryl methyl ether is quantitatively converted into cholesteryl acetate on refluxing with potassium or zinc acetate in acetic acid, and into cholesteryl chloride with acetyl chloride in pyridine solution; the "*trans*"-ether is unchanged under these conditions.

In order to examine the constitutional features responsible for the reactivity of the "*cis*"-cholesteryl ethers, it was decided to study the reactions of the saturated *cis*- and *trans*-cholestanyl methyl ethers. Whereas the latter reacts neither with bromine nor with halogen acids at room temperature, it was not possible to apply these reactions to the *cis*-ether, as all attempts to prepare it were unsuccessful. Thus the methylation of *cis*-cholestanol (Ruzicka, Brüngger, Eichenberger, and Meyer, *Helv. Chim. Acta*, **1934**, **17**, 1407) by treatment of its potassium salt with methyl iodide was accompanied by epimerisation, with formation of *trans*-cholestanyl methyl ether. No reaction was observed when *cis*-cholestanol in benzene solution was heated under reflux with moist silver oxide and methyl iodide. With the same object, the hydrogenation of "*cis*"-cholesteryl methyl ether by the aid of a platinum catalyst was again studied, and contrary to the observations of Stoll (*Z. physiol. Chem.*, **1932**, **207**, 147) and Wagner-Jauregg and Werner (*ibid.*, **1932**, **213**, 119), gave in our hands a quantitative yield of cholestane, demethylation having accompanied the reduction process. The fact that the "*cis*"-ether gives cholestane and not coprostane provides further evidence in favour of the view previously expressed (Beynon, Heilbron, and Spring, *loc. cit.*) that the ethenoid linkage of the ether is situated between C_5–C_6 and not between C_4–C_5, as sterols of the latter (ψ-cholestene) type give coprostane derivatives on hydrogenation.

Further valuable information concerning the structural relationship of the two cholesteryl methyl ethers is obtained from an examination of their behaviour with nitric acid. Nitration of the "*cis*"-ether (I) yields 6-nitrocholesteryl nitrate (III), identical with that



prepared by the direct nitration of cholesterol (IV) (Windaus, *Ber.*, **1903**, **36**, 3752). Nitration of "*trans*"-cholesteryl methyl ether (II), on the other hand, yields 6-*nitro*-3-*methoxy*-

Δ^5-*cholestene* (VI), which on reduction with zinc dust and acetic acid is converted into 3-*methoxycholestan*-6-*one* (VII), identical with the ether prepared by methylation of 6-keto-cholestanol (V), which in its turn is obtained by reduction of (III) with zinc and acetic acid (Windaus, *loc. cit.*).

This series of reactions locates the ethenoid linkage in the two cholesteryl ethers at C_5–C_6, and it therefore follows that they differ only in the orientation of the groups associated with C_3, *i.e.*, that they are correctly named as "*cis*"- and "*trans*"-3-methoxy-Δ^5-cholestenes.*

Experimental.

Cholesteryl Acetate from "cis"-*Cholesteryl Methyl Ether.*—A solution of "*cis*"-cholesteryl methyl ether (1 g.) and zinc acetate (2 g.) in glacial acetic acid (50 c.c.) was refluxed for 8 hours. The solid separating on dilution with water was crystallised from ethyl acetate, from which cholesteryl acetate (1 g.) separated in needles, $[\alpha]_D^{19°}$ − 30·0° (l = 1, c = 2·4),† m. p. 115°, unchanged by admixture with an authentic specimen.

Cholesteryl Chloride from "cis"-*Cholesteryl Methyl Ether.*—The ether (1 g.) was refluxed for 7 hours with acetyl chloride (50 c.c.) in dry pyridine (50 c.c.). The mixture was diluted with water, and the separated solid crystallised from acetone (charcoal), yielding cholesteryl chloride (1 g.) in laminæ, m. p. 95°, showing no depression on admixture with an authentic specimen.

trans-*Cholestanyl Methyl Ether.*—*cis*-Cholestanol (2 g.) was refluxed for 1 hour with a suspension of "molecular" potassium (0·5 g.) in dry benzene (30 c.c.). Methyl iodide (6 c.c.) was added, and the mixture refluxed for a further 3 hours. After the addition of alcohol, the solvent mixture was removed under reduced pressure, and the residual oil extracted with ether. Removal of the ether from the dried extract, followed by crystallisation of the residue from methyl alcohol, gave *trans*-cholestanyl methyl ether (2 g.) as plates, m. p. 83°, unchanged by admixture with an authentic specimen; $[\alpha]_D^{20°}$ + 19·8° (l = 1, c = 1·78) (Found: C, 83·6; H, 12·4. Calc. for $C_{28}H_{50}O$: C, 83·5; H, 12·5%).

Hydrogenation of "cis"-*Cholesteryl Methyl Ether.*—A solution of the ether (5 g.) in glacial acetic acid (150 c.c.) was shaken with hydrogen for 4 hours at 65—70° in the presence of platinum oxide (1 g.). The solid (4·5 g.) separating from the filtered mixture was crystallised from methyl alcohol, giving cholestane (4 g.) in plates, m. p. 80°, not depressed by admixture with an authentic specimen; $[\alpha]_D^{19°}$ + 26·6° (l = 1, c = 0·9) (Found: C, 86·9; H, 12·6. Calc. for $C_{27}H_{48}$: C, 87·0; H, 13·0%).

Nitration of "cis"-*Cholesteryl Methyl Ether.*—A mixture of nitric acid (d, 1·53; 50 c.c.) and glacial acetic acid (20 c.c.) was added during 1 hour with stirring to a suspension of "*cis*"-cholesteryl methyl ether (5 g.) in glacial acetic acid (60 c.c.) maintained at 0°. The solid separating on dilution of the solution with water was crystallised from glacial acetic acid, from which 6-nitrocholesteryl nitrate (4 g.) separated in colourless needles, m. p. 128°, showing no depression on admixture with an authentic specimen (Found: C, 68·0; H, 9·4; N, 5·9. Calc. for $C_{27}H_{44}O_5N_2$: C, 68·0; H, 9·3; N, 5·9%).

6-*Nitro*-3-*methoxy*-Δ^5-*cholestene.*—Nitric acid (d 1·42; 30 c.c.) was added during ½ hour to a suspension of "*trans*"-cholesteryl methyl ether (10 g.) in glacial acetic acid at 0°. The mixture was stirred at room temperature until complete solution occurred (4 hours), and then set aside at − 10° overnight. The solid separating on dilution with water was well washed with water, and crystallised from methyl alcohol, giving 6-*nitro*-3-*methoxy*-Δ^5-*cholestene* (5 g.) in needles, m. p. 114° (Found: C, 75·4; H, 10·5; N, 3·1; OMe, 7·1. $C_{28}H_{47}O_3N$ requires C, 75·4; H, 10·6; N, 3·1; OMe, 7·0%).

3-*Methoxycholestan*-6-*one.*—(a) 6-Nitro-3-methoxy-Δ^5-cholestene (9 g.) was boiled under reflux for 12 hours with zinc dust (40 g.) and glacial acetic acid (100 c.c.). The solid separating on dilution with water was extracted with ether, the extract washed with water, and dried. Removal of the ether and crystallisation of the residue from methyl alcohol gave 3-*methoxycholestan*-6-*one* (7·5 g.) in needles, $[\alpha]_D^{19°}$ − 11·2° (l = 1, c = 1·4), m. p. 92° (Found: C, 80·6; H, 11·5. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%). The *oxime* separated as needles from methyl alcohol, m. p. 210° (Found: C, 78·0; H, 11·4; N, 3·3. $C_{28}H_{49}O_2N$ requires C, 77·9; H, 11·45; N, 3·2%).

* (*Note added in proof, March 9th*). Since the completion of this work Wallis, Fernholz, and Gephard (*J. Amer. Chem. Soc.*, 1937, **59**, 137) have described the preparation of an i-cholesterol, which they assert contains a *cyclo*propane bridge and not an ethylenic linkage. They further suggest that a close relationship exists between i-cholesterol and the "*cis*"-cholesteryl ethers. The possibility of such a relationship is being examined.

† All rotations recorded were measured in chloroform solution.

(b) A solution of 6-ketocholestanol (1 g.) in benzene (50 c.c.) was refluxed for 40 hours with moist silver oxide (5 g.) and methyl iodide (15 c.c.). After filtration, the solvent was removed under reduced pressure, and the residue crystallised from methyl alcohol, from which 3-methoxycholestan-6-one (0·8 g.) separated in needles, $[\alpha]_D^{19°} - 11{\cdot}2°$ ($l = 1$, $c = 0{\cdot}896$), m. p. 92° alone or in admixture with the specimen prepared by method (a).

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