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Molecular Rearrangements in the Sterols. II.[7] The Constitution of the Isomeric Ethers of Cholesterol

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In a recent article by Beynon, Heilbron and Spring[1] on the constitution of the isomeric ethers of cholesterol the conclusion was reached that the abnormal dextrorotatory ethers, first discovered by Stoll,[2] are ethers of *epi*-cholesterol, and that, therefore, the constitution of the two series differs only in the orientation of the groups associated with the C_3 position of the cholesterol molecule. This conclusion, which is in agreement with an earlier interpretation by Stoll,[2] but which has since been abandoned by him,[3] is based upon certain results obtained by them from hydrogenation experiments carried out on the two series of ethers, and from an examination of their behavior with nitric acid.

It is also to be noted that Butenandt and Grosse[4] seem to hold to this same point of view, for in their description of the preparation of dehydroandrosteryl chloride from dehydroandrosterone *p*-toluenesulfonate by the action of methyl alcohol, and then of concentrated hydrochloric acid on the methyl ether so obtained, they named this strongly dextrorotatory intermediate compound, *epi*-dehydroandrosterone methyl ether.

The high positive rotatory power of this ether, however, has led Ruzicka, Goldberg and Bosshard[5] to question this assumed constitution. These authors point out that if one takes into consideration the values of the normal and of the *epi* forms of cholesterol, dehydroandrosterone, and androstenediol, and also of the corresponding saturated compounds, cholestanol, coprostanol, androsterone and androstanediol, the methyl ether of *epi*-dehydroandrosterone should exhibit a much lower rotation. Following the more recent opinion of Stoll,[3] who has suggested that the strongly dextrorotatory ethers prepared from cholesterol may be allocholesteryl ethers, these authors suggest that the liquid dehydroandrosterone methyl ether may also belong to the *allo* series.

Beynon, Heilbron and Spring,[6] however, object to the point of view that during the formation of these abnormal ethers the Δ^5-ethylenic linkage has migrated to the Δ^4-position. Their reason is based upon the fact that these compounds fail to give with antimony trichloride the deep pink color reaction which has been observed to take place with *allo*-cholesterol, and with pseudocholestene.

In the first article of this series[7] certain experimental results were reported on the action of anhydrous potassium acetate on cholesteryl *p*-toluenesulfonate in acetic anhydride solution. The preparation of a new isomer of cholesterol, called *i*-cholesterol, m. p. 74–75°, $[\alpha]^{20}D$ +23.9, was described. Some important chemical properties of this new compound were also recorded. From the chemical behavior of this new substance the authors concluded that this reaction is accompanied by a molecular rearrangement—a fact

(1) Beynon, Heilbron and Spring, *J. Chem. Soc.*, 406 (1937).
(2) Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).
(3) Stoll, *ibid.*, **246**, 14 (1937).
(4) Butenandt and Grosse, *Ber.*, **69**, 2776 (1936).
(5) Ruzicka, Goldberg and Bosshard, *Helv. Chim. Acta*, **20**, 541 (1937).
(6) Beynon, Heilbron and Spring, *J. Chem. Soc.*, 907 (1936).
(7) I, Wallis, Fernholz and Gephart, THIS JOURNAL, **59**, 137 (1937).

which could be expected on the basis of the electronic conception of molecular rearrangements. A formulation of the constitution of this new isomer was also tentatively suggested, based upon a type of rearrangement which is known to take place in certain terpenes, but which hitherto has been unobserved in sterol chemistry.

From a study of the chemical properties of this compound there also emerged the fact that a close relationship exists between it and the "abnormal" ethers of Stoll.[2] Both types of compounds are strongly dextrorotatory. Catalytic hydrogenation under certain conditions gives the same hydrocarbon, cholestane.

This close relationship has been investigated further and we are now able to report that the so-called "*cis*-cholesteryl ethers" are in reality ethers of *i*-cholesterol. For, if one methylates *i*-cholesterol by treating its potassium salt with methyl iodide, an ether is obtained which melts at 78–78.5°, and when intimately mixed with an authentic specimen of the methyl ether prepared by Stoll's[2] method gives no depression of the melting point. This methyl ether is also dextrorotatory, $[\alpha]^{22}D$ +54°. The recorded rotation[2] for "*cis*-cholesteryl methyl ether is $[\alpha]^{19}D$ +55.

In order to further prove beyond any question of doubt that this dextrorotatory methyl ether is not the methyl ether of *epi*-cholesterol, some *epi*-cholesterol prepared according to the method of Marker[8] was methylated by the action of methyl iodide on its potassium salt. This methyl ether melts at 89° and in chloroform solution is strongly levorotatory, $[\alpha]^{20}D$ −46.5.

In conclusion, our experiments also seem to establish the fact that these "abnormal" ethers are not of the *allo*-cholesterol series, since the parent substance, *i*-cholesterol, is neither *allo*-cholesterol nor *epi-allo*-cholesterol. Therefore, until evidence is forthcoming to the contrary we are of the belief that the constitution and properties of these highly interesting compounds can be described best by a formulation which involves a molecular rearrangement, and which was tentatively suggested in Part I of this series.

(8) Marker, Oakwood and Crooks, THIS JOURNAL, **58**, 481 (1936); see also Marker, Kamm, Oakwood and Laucius, *ibid.*, **58**, 1948 (1936).

Experimental Part

Preparation of the Methyl Ether of *i*-Cholesterol.—To an anhydrous benzene solution of 51 milligrams of *i*-cholesterol, m. p. 74–75°, $[\alpha]^{20}D$ +23.9, there was added an excess of finely divided potassium and the contents of the flask were refluxed for forty-five minutes. An excess of methyl iodide (3 cc.) was then added and the refluxing was continued for three hours. On working up the products an oil was obtained which was taken up in boiling methyl alcohol. An appreciable amount of oily material remained undissolved. The contents of the flask were allowed to cool to room temperature and the supernatant liquid was removed. On further cooling at lower temperature, crystals separated which melted unsharply at 73°; yield 35 mg. One recrystallization from methyl alcohol gave well-defined crystals which melted sharply at 78–78.5°, $[\alpha]^{22}D$ +54° (10.2 mg. in 1.00 cc. $CHCl_3$ gave $\alpha^{22}D$ +0.55° in a 1-dm. Fischer micro tube). When mixed with an authentic specimen of the methyl ether of m. p. 78.5° prepared by Stoll's[2] method, no depression of the melting point was observed.

Preparation of the Methyl Ether of *epi*-Cholesterol.—This ether was prepared essentially by the same method as described above. The *epi*-cholesterol used in this experiment was prepared according to the method of Marker, Oakwood and Crooks.[8] The refluxing with methyl iodide was continued for two hours. On working up the product, crystals were obtained which after recrystallization from either methyl alcohol or acetone melted at 88–89°; $[\alpha]^{20}D$ −46.3° (31.5 mg. in 2 cc. of $CHCl_3$ gave $\alpha^{20}D$ − 0.73°).

Anal. Calcd.: C, 83.92; H, 12.08. Found: C, 84.04, 83.70; H, 11.75, 11.94.

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Summary

The methyl ethers of *i*-cholesterol and *epi*-cholesterol have been prepared and certain of their physicial properties have been characterized.

Evidence is submitted which shows that the "abnormal" dextrorotatory ethers of cholesterol, first discovered by Stoll, and recently referred to in the literature as "*cis*-cholesteryl ethers," are in reality ethers of *i*-cholesterol, and that consequently their formation by the action of anhydrous potassium acetate on cholesteryl *p*-toluenesulfonate in methyl alcohol solution is accompanied by a molecular rearrangement.

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