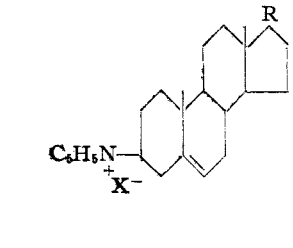
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Preparation and Structure of Cholesteryl Quaternary Salts

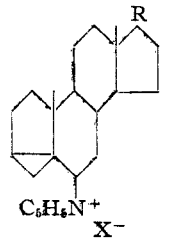
BY L. CARROLL KING, R. M. DODSON AND LEE A. SUBLUSKEY

Cholesterylpyridinium *p*-toluenesulfonate (I) was prepared in two ways: (a) by action of pyridine on cholesteryl *p*-toluenesulfonate and (b) by action of pyridine and *p*-toluenesulfonic acid on *i*-cholesteryl methyl ether. Cholesteryl isothiuronium *p*-toluenesulfonate (II)[1] was prepared (a) by action of thiourea on cholesteryl *p*-toluenesulfonate and (b) by action of thiourea and *p*-toluenesulfonic acid on *i*-cholesteryl methyl ether in alcoholic solution. Compound I was converted to the corresponding iodide on treatment with sodium iodide or on treatment with hydriodic acid. It was unchanged on refluxing twenty-four hours with pyridine and *p*-toluenesulfonic acid and displayed qualitative evidence for unsaturation. Compound II was converted to cholesteryl mercaptan and this in turn was converted to cholesteryl disulfide. These compounds were identical with the corresponding compounds reported by Wagner–Jauregg and Lennartz.[2]

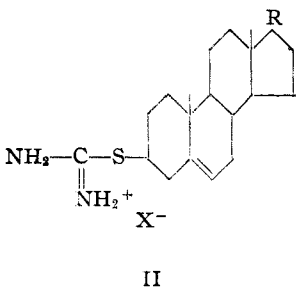
Of the structures considered for these quaternary salts, I and II are preferred over Ia and IIa.



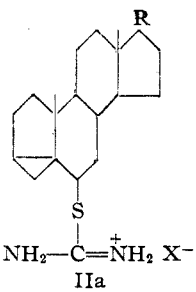
I



Ia



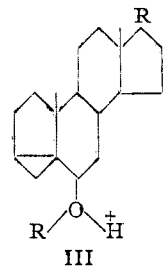
II



IIa

X = $CH_3C_6H_4SO_3^-$
R = $C_8H_{17}^-$

This preference is based on the fact that a single levorotatory salt is obtained from each of the reactions and on the fact that the salt when prepared from *i*-cholesteryl methyl ether is produced under conditions favoring rearrangement of the *i*-steroid structure. Structures Ia and IIa are further considered to be unlikely in view of their similarity to an oxonium structure such as III which may be involved when an *i*-steroid ether is rearranged to the normal steroid structure.[3]



III

Both cholesteryl *p*-toluenesulfonate and *i*-cholesteryl methyl ether are known to react readily with alcohol when a trace of acid is present. In the present paper they are shown to react selectively with thiourea in the presence of alcohol. A further study of this observation is in progress.

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Experimental[4]

Cholesterylpyridinium *p*-Toluenesulfonate (I).—(a) A solution of 5.4 g. (0.01 mole) of cholesteryl *p*-toluenesulfonate[5] in 40 cc. of pyridine was heated on the steam-bath for five and one-half hours. The solution was diluted with acetone, cooled in ice, the product separated by filtration and washed with acetone–hexane. From this reaction 4.0 g. of product, m. p. 227–229°, was obtained. Two crystallizations from a mixture of chloroform and carbon tetrachloride raised the melting point to 231–232°; $[\alpha]^{26}D$ −6.1° in chloroform.

Anal. Calcd. for $C_{39}H_{57}O_3NS \cdot H_2O$: C, 73.44; H, 9.01; N, 2.20. Found: C, 73.73, 73.34; H, 9.10, 9.44; N, 2.56.

This compound is slightly soluble in acetone, soluble in chloroform but insoluble in carbon tetrachloride. It forms a colloidal solution on heating with water and can be crystallized from dilute alcohol. In chloroform solution this compound reacts rapidly with bromine forming a light yellow solution. A suspension of this compound in water slowly decolorized permanganate.

(b) A solution consisting of 1.0 g. of *i*-cholesteryl methyl ether,[6] 1.0 g. of *p*-toluenesulfonic acid and 10 cc. of pyridine was refluxed for two hours, then cooled and diluted with acetone. The crystalline material which was isolated from this reaction mixture was identical in all respects with the compound I; m. p. 230–232°, $[\alpha]^{25}D$ −4.5° in chloroform, yield 0.9 g.

Cholesterylpyridinium Iodide.—(a) A solution of 1.4 g. of cholesterylpyridinium *p*-toluenesulfonate (I) in absolute alcohol was treated with 2 g. of sodium iodide in alcohol. The cholesterylpyridinium iodide precipitated

(1) Cholesteryl isothiuronium halides were prepared and converted to cholesteryl mercaptan: Rosenberg and Turnbull, U. S. 2,375,873; U. S. 2,375,874, *C. A.*, **39**, 5049 (1945).

(2) Wagner–Jauregg and Lennartz, *Ber.*, **74**, 27 (1941).

(3) R. M. Dodson and Byron Riegel, *J. Org. Chem.*, in press, (1948); E. W. Meyer, Ph. D. Thesis, Northwestern University, 1943, pp. 49, 54.

(4) All melting points were observed on a Fisher–Jones melting point block. All rotations were determined with 100–105 mg. of sample in 3 cc. of solvent using a 1-dcm. tube of 2.5 cc. capacity. Analysis by P. Craig.

(5) Freudenberg and Hess, *Ann.*, **448**, 128 (1926).

(6) Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).

at once. It was crystallized from alcohol; m. p. 260–261° dec., $[\alpha]^{27}D$ −7.4° in chloroform; yield 1.3 g.

Anal. Calcd. for $C_{32}H_{50}NI$: C, 66.75; H, 8.79; N, 2.44. Found: C, 66.59; H, 8.66; N, 2.12.

(b) A solution of 1.1 g. of I in absolute alcohol was treated with concentrated hydriodic acid. The iodide precipitated at once. It was crystallized from alcohol and was identical with that above, m. p. 260–261°; $[\alpha]^{25}D$ −7.8° in chloroform; yield 0.9 g.

Attempted Rearrangement of Cholesterylpyridinium *p*-Toluenesulfonate.—A solution consisting of 1.0 g. of cholesterylpyridinium *p*-toluenesulfonate and 1 g. of *p*-toluenesulfonic acid in 15 g. of pyridine was heated at the reflux temperature for twenty-four hours. The reaction mixture was worked up as described under the preparation of I. There was no evidence of decomposition and 0.9 g. of the starting substance was recovered unchanged; m. p. 229–231°. This was converted to the iodide, m. p. 260–261°; $[\alpha]^{24}D$ −7.5° in chloroform.

Cholesterylisothiuronium *p*-Toluenesulfonate (II).—(a) A solution of 5.4 g. (0.01 mole) of cholesteryl *p*-toluenesulfonate, 9.0 g. of thiourea and 5 cc. of pyridine in 50 cc. of absolute ethanol was heated under reflux for three hours. The resulting solution was diluted with water until a precipitate started forming, cooled and filtered. The residue was then suspended in acetone, the acetone heated to boiling, and the insoluble product filtered from the solution; yield 4.0 g. (65%) of salt; m. p. 230–234°. Recrystallization from alcohol raised the melting point to 233–235°; $[\alpha]^{24}D$ −27.1° in pyridine.

Anal. Calcd. for $C_{35}H_{56}N_2O_3S_2$: C, 68.15; H, 9.15; N, 4.54. Found: C, 68.26; H, 9.16; N, 4.31.

(b) From a similar reaction using 0.01 mole of cholesteryl *p*-toluenesulfonate, 0.02 mole of thiourea and 50 cc. of 95% alcohol, 2.26 g. (40%) of II, m. p. 231–233°, was obtained. This reaction mixture was acid to litmus and contained some cholesteryl ethyl ether, m. p. and mixed m. p. 89.0–89.5°.

(c) A reaction mixture consisting of 2.0 g. of *i*-cholesteryl methyl ether,[6] 2.0 g. of *p*-toluenesulfonic acid, 4.0 g. of thiourea in 50 cc. of ethyl alcohol was refluxed four hours. Compound II was isolated as described above; m. p. 233°; yield 1.3 g. (42%); $[\alpha]^{24}D$ −26.9° in pyridine. From this reaction mixture 0.3 g. of unchanged *i*-cholesteryl methyl ether, m. p. 75–77°, was also obtained.

Cholesteryl Mercaptan.—A solution of 2.46 g. (0.004 mole) of II and 0.68 g. (0.012 mole) of sodium hydroxide in 50 cc. of ethyl alcohol was heated under reflux. After the solution became homogeneous 5 cc. of water was added and the heating continued for two hours. The reaction mixture was then poured into 100 cc. of ice water and the resulting suspension acidified with 1 cc. of glacial acetic acid and stirred until the precipitate coagulated. The compound was separated and crystallized from acetone–methanol; m. p. 94–96°; yield 1.5 g. (93%). Recrystallization from acetone raised the melting point to 97.0–97.5°; $[\alpha]^{25}D$ −26.6° in chloroform.[7]

Anal. Calcd. for $C_{27}H_{46}S$: C, 80.53; H, 11.51. Found: C, 80.25; H, 11.80.

Cholesteryl Disulfide.—A solution consisting of 0.50 g. (0.00125 mole) of cholesteryl mercaptan in 10 cc. of hexane was oxidized with 0.32 g. (0.00125 mole) of iodine. Ten cubic centimeters of 5% potassium hydroxide was added and the mixture shaken. The mixture was then diluted and extracted with hexane. The hexane was then evaporated and the residue crystallized from benzene–ethyl alcohol and from acetone–benzene; m. p. 141–143°.[7]

Summary

Cholesterylpyridinium *p*-toluenesulfonate was prepared from cholesteryl *p*-toluenesulfonate and from *i*-cholesteryl methyl ether. Cholesterylisothiuronium *p*-toluenesulfonate was prepared from the same substances. The evidence indicates that these salts are derivatives of the normal cholesteryl structure.

(7) Wagner–Jauregg and Lennartz (ref. 2) reported for cholesteryl mercaptan m. p. 99.5°, $[\alpha]D$ −23.85°; and for cholesteryl disulfide; m. p. 144.5°.

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Substituted Styrenes. III. The Preparation of Some *m*- and *p*-Substituted α-Methylstyrenes

BY DEXTER SEYMOUR AND KATHERINE B. WOLFSTIRN

In connection with some studies undertaken in this laboratory on the effect of ring substituents in styrenes on their reactivity toward certain types of free radicals,[1a,b] it was necessary to synthesize a series of substituted α-methylstyrenes. *p*-Bromo, *p*-chloro and *p*-methoxy-α-methylstyrenes were synthesized by known methods. Some peculiarities in the preparation of the last mentioned were noted and are discussed further in the experimental part.

p-Fluoro-α-methylstyrene was prepared in a straightforward way from *p*-fluorobromobenzene and acetone through the Grignard reagent. *p*-Cyano-α-methylstyrene was prepared by taking advantage of the rather large difference in reactivity toward the Grignard reagent between a nitrile and a ketone grouping. A somewhat obscure paper[2] which came to our attention later records this fact also. Methylmagnesium bromide was added to a stoichiometric amount of *p*-cyanoacetophenone and the crude alcohol was dehydrated with acetic anhydride. Careful fractionation of the product gave 44% of *p*-cyano-α-methylstyrene, 20% of unreacted *p*-cyanoacetophenone and about 25% of non-volatile polymeric material. *m*-Bromo-α-methylstyrene was prepared in 54% yield by addition of two moles of methylmagnesium bromide to methyl *m*-bromobenzoate followed by dehydration with acetic anhydride.

Although the reaction is reported in the literature,[3] we were unable to prepare the Grignard reagent from *p*-dimethylaminobromobenzene even

(1) (a) Walling, Seymour and Wolfstirn, THIS JOURNAL, in press; (b) Walling, Seymour and Wolfstirn, *ibid.*, submitted for publication.

(2) Carter, *Iowa State Coll. J. Sci.*, **15**, 63 (1940); *cf. British Chem. Abs.*, **AII**, 254 (1941).

(3) Ehrlich and Sachs, *Ber.*, **36**, 4297 (1903).