[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Preparation, Structure and Configuration of Some Salts Derived from Δ^6-*i*-Cholestadiene and *i*-Cholesten-6-one[1a]

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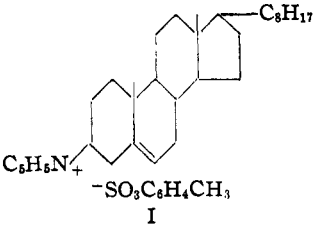
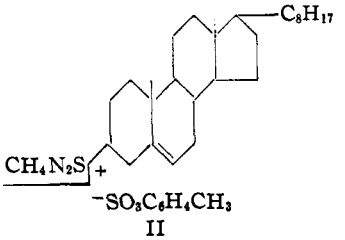
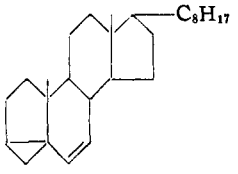
In a recent paper from this Laboratory[1b] it was demonstrated that *i*-cholesteryl methyl ether reacted with pyridine and *p*-toluenesulfonic acid to give cholesterylpyridinium tosylate (I) and with thiourea and *p*-toluenesulfonic acid in alcoholic solution to give cholesterylisothiuronium tosylate (II). This type of reaction has now been applied



I



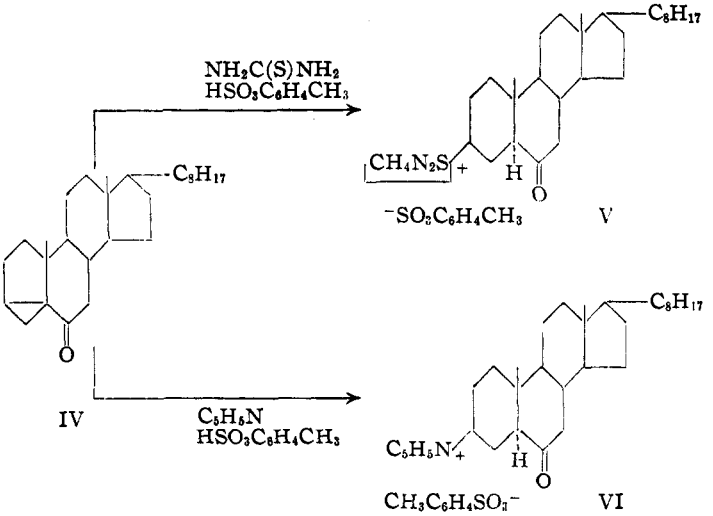
II



III

to two other molecules having the *i*-steroid structure.

The Δ^6-*i*-cholestadiene (III) described by Riegel[2] when it reacted with thiourea and *p*-toluenesulfonic acid in alcoholic solution gave compound II, identical with the corresponding substance obtained from similar treatment of *i*-cholesteryl methyl ether.[1b] Compound III, unlike *i*-cholesteryl methyl ether,[1b] would not react with pyridine and *p*-toluenesulfonic acid to give I.



IV V VI

i-Cholesten-6-one (IV) reacted with thiourea and *p*-toluenesulfonic acid in alcoholic solution to give 6-ketocholestanylisothiuronium tosylate (V) and with pyridine and *p*-toluenesulfonic acid to give 6-ketocholestanylpyridinium tosylate (VI).[3] These reactions may be formulated as shown.

When *i*-cholesteryl ethers react with reagents such as the halogen acids, or acetic acid containing a trace of sulfuric acid,[4] or with various alcohols in the presence of acids,[5] the products are invariably 3-β-substituted derivatives.[6] It was shown by Riegel[2] that in acidic media nucleophilic reagents reacted with Δ^6-*i*-cholestadiene at position 3 to give derivatives with the β-configuration. In view of these observations the cholesterylisothiuronium tosylate (II) described in this paper and in ref. 1 should be a 3-β-substituted compound. By a similar argument the cholesterylpyridinium tosylate I (described in ref. 1) should be a 3-β-substituted compound.

Wallis and co-workers[9] reported that *i*-cholesten-6-one (IV) reacted with dilute sulfuric acid to give 3-β-hydroxy-6-ketocholestane and with hydrochloric acid or hydrobromic acid to give a 3-α-halo-6-ketocholestane. Now the corrected configurations of the 3-substituted cholestyl and cholesteryl halides[6] can be directly related to the 3-halo-derivatives of

(1a) Presented before the Organic Division of the American Chemical Society, Chicago meeting, April, 1948.

(1b) King, Dodson and Subluskey, THIS JOURNAL, **70**, 1176 (1948).

(2) Riegel, Hager and Zenitz, *ibid.*, **68**, 2562 (1946).

(3) Isolated only as the iodide.

(4) Benyon, Heilbron and Spring, *J. Chem. Soc.*, 907 (1936); 406 (1937); Wallis, Fernholz and Gephart, THIS JOURNAL, **59**, 137 (1937).

(5) The acid catalyzed conversion of *i*-cholesteryl methyl ether to the normal cholesteryl ether, isopropyl or *t*-butyl ether, according to the nature of the alcohol used as solvent, was reported by E. W. Meyer, Ph.D. Thesis, Northwestern University, 1943, p. 55 and pp. 96–101. A similar reaction wherein *i*-cholesteryl methyl ether is converted to normal ethers was recently reported by McKennis, *ibid.*, **69**, 2565 (1947); *J. Biol. Chem.*, **172**, 313 (1948). See also Hey and Hook, British Patent 591,955 [*C. A.*, **42**, 1028 (1948)].

(6) Previous to 1937 an incorrect formulation for the configuration of the 3-halogen substituted steroids existed. This inconsistency was apparent in the papers of Marker and co-workers, THIS JOURNAL, **59**, 619 (1937), and was corrected by Bergman, *Helv. Chim. Acta* **20**, 600 (1937). Recent papers by Shoppee[7] and by Dodson and Riegel[8] have reviewed the corrected formulation of cholesteryl and cholestyl halides in detail.

(7) Shoppee, *J. Chem. Soc.*, 1138, 1147 (1946).

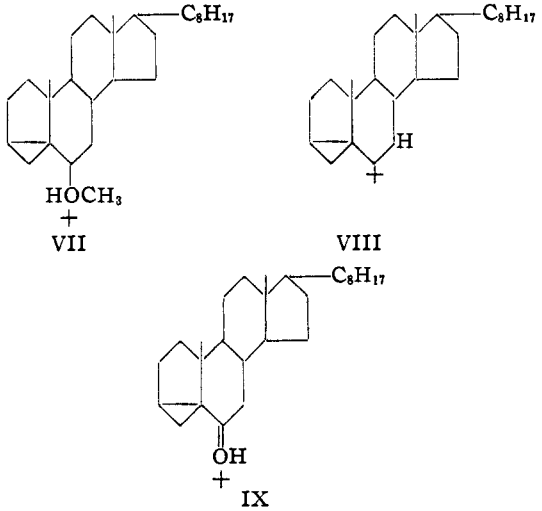
(8) Dodson and Riegel, *J. Org. Chem.*, **3**, 424 (1948).

(9) Ford, Chakravorty and Wallis, THIS JOURNAL, **60**, 413 (1938); Ladenburg, Chakravorty and Wallis, *ibid.*, **61**, 3483 (1939); Heilbron, Hodges and Spring, *J. Chem. Soc.*, 759 (1938).

6-ketocholestane. In view of this the compounds formulated as 3-α-halo-6-ketocholestanes by Wallis and co-workers and by Heilbron and co-workers,[9] should be 3-β-halo-6-ketocholestanes.[10] Since all these known reactions of *i*-cholesten-6-one with nucleophilic groups of the type HX result in 3-substitution with β-configuration, it seems likely that compounds V and VI described in this paper are 3-β-substituted-6-ketocholestanes.

In the formation of compounds I, II, V and VI, it seems evident that a proton is first added to the *i*-steroid with formation of an intermediate such as VII, VIII or IX. The intermediate so formed then is attacked at the 3-position by the nucleophilic group. Thus *i*-cholesteryl methyl ether could form VII, compound III could form VIII, and compound IV could form IX. VII could then react with the appropriate reagents to give I or II, VIII could form II, and IX could react with the appropriate reagents to form V or VI.

Our failure to obtain I from III is due to the limited availability of protons in pyridine solution so that VIII is not formed under these conditions.



In each of the reactions reported in this paper and in ref. 1 a change in the ionic nature of the solution takes place as the reaction proceeds. Hence it is possible to make a kinetic study of these reactions by electrical conductivity methods. Such a study is in progress in this Laboratory.

Experimental[11]

Δ^6-*i*-Cholestadiene.—This substance was prepared according to the directions of Riegel, Hager and Zenitz.[2] The use of chromatography on alumina was absolutely necessary to accomplish purification; m. p. 72.5–73°, $[\alpha]^{22}D$ −45.8° in chloroform.

***i*-Cholestene-6-one.**—This substance was prepared according to the direction of Windaus and Dalmer[12]; m. p. 95–97°, $[\alpha]^{22}D$ 47.9° in chloroform.

Cholesterylisothiuronium Tosylate (II).—A solution consisting of 0.50 g. of Δ^6-*i*-cholestadiene (III), 0.50 g. of *p*-toluenesulfonic acid monohydrate and 1.0 g. of thiourea in 20 cc. of methanol was refluxed for five hours. The methanol was partially removed and the product isolated as described in a previous paper[1]; yield 0.74 g. (88%), m. p. 234–235°, $[\alpha]^{22}D$ −27.4° in pyridine.

Attempted Preparation of Cholesterylpyridinium Tosylate (I) from Δ^6-*i*-Cholestadiene (III).—A solution consisting of 0.50 g. of III, 0.50 g. of *p*-toluenesulfonic acid monohydrate and 3.0 cc. of pyridine was refluxed for five hours. No product corresponding to I was obtained, but III was recovered unchanged. A twenty-hour heating period gave similar results.

6-Ketocholestanylisothiuronium Tosylate (V).—A solution consisting of 1.0 g. of *i*-cholesten-6-one (IV), 2 g. of thiourea and 1.0 g. of *p*-toluenesulfonic acid monohydrate in 20 cc. of methanol was refluxed for two hours and then allowed to stand overnight. The methanol was then removed by evaporation and the product thoroughly washed with water. The compound was crystallized from absolute alcohol; yield 1.5 g. (90%), m. p. 204–206°, $[\alpha]^{21}D$ −18.8° in chloroform.

Anal. Calcd. for $C_{35}H_{56}N_2S_2O_4$: C, 66.41; H, 8.91; N, 4.43. Found: C, 66.07; H, 8.47; N, 4.10.

This substance is insoluble in water and soluble in alcohol. It forms a very stable gel in water–alcohol solution.

6-Ketocholestanylpyridinium Iodide (VI).—A solution of 0.5 g. of *i*-cholesten-6-one, and 0.5 g. of *p*-toluenesulfonic acid in 3 cc. of pyridine was refluxed for twelve hours, then heated on the steam-bath for twenty-four hours, cooled and diluted with ether. The solid material which separated was taken up in absolute alcohol and hydroiodic acid was added. The crystalline solid which separated weighed 0.58 g. (75%) and melted at 285–295°. After crystallization from alcohol the melting point was 293–296°; $[\alpha]^{21}D$ 5.5° in chloroform.

Anal. Calcd. for $C_{32}H_{50}ONI$: C, 64.93; H, 8.51; N, 2.36. Found: C, 64.46; H, 8.43; N, 2.75.

Summary

Cholesterylisothiuronium tosylate was prepared from Δ^6-*i*-cholestadiene. Cholesterylpyridinium tosylate could not be prepared from this substance.

i-Cholesten-6-one reacted with thiourea and *p*-toluenesulfonic acid to give 6-ketocholestanylisothiuronium tosylate, and with pyridine and *p*-toluenesulfonic acid to give 6-ketocholestanylpyridinium tosylate.

A consideration of the reactions and steric relations involved indicates these compounds are all 3-β-substituted cholesteryl or cholestyl derivatives.

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(10) In the paper by Dodson and Riegel[8] the corrected configuration of this class of compounds is considered in detail.

(11) All rotations were determined with 100–105 mg. of sample in 3.0 cc. of solvent using a 1-dm. tube of 2.5 cc. capacity. All melting points were observed on a Fisher–Johns melting point block.

(12) Windaus and Dalmer, *Ber.*, **52**, 162 (1919).