[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Reaction of Cholesteryl *p*-Toluenesulfonate and Cholesteryl Halides with Pyridine Type Bases

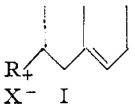
BY L. CARROLL KING AND BERNARD M. REGAN

RECEIVED JULY 2, 1952

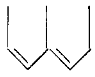
Cholesteryl *p*-toluenesulfonate reacts with pyridine-like bases to give a mixture consisting of 3,5-cholestadiene and a quaternary salt. The reactions of cholesteryl iodide and bromide with these bases are similar. The ratio of the amount of elimination reaction to replacement reaction depends on the nature of the entering group and on the group expelled. The elimination product is produced by a simultaneous competitive reaction and not by decomposition of the quaternary salt.

In a recent paper from this Laboratory[1] it was demonstrated that cholesteryl *p*-toluenesulfonate reacted with pyridine to give 3-β-cholesterylpyridinium *p*-toluenesulfonate (Ia) in 63% yield. This reaction has now been further investigated to identify products other than the quaternary salt, and to provide additional examples using bases other than pyridine.

In general, cholesteryl *p*-toluenesulfonate reacts with pyridine-like bases to give the quaternary salt similar to I, and a diene II melting at 78–79° and $[\alpha]_D$ −114° (presumably 3,5-cholestadiene).



I



II

Ia, R = C_5H_5N-, X^- = $C_7H_7SO_3^-$

In Table I the results of a number of these reactions are summarized.[2]

Inspection of the yield data in Table I indicates that the amount of the elimination reaction to produce the diene II, is increased at the expense of the replacement reaction when the attacking base is of a type where considerable steric strain might develop in the transition state required for replacement.

Cholesteryl iodide, bromide and chloride were prepared and compared with cholesteryl *p*-toluenesulfonate in the reactions with pyridine-like bases. The results of these experiments are summarized in Table I. With similar bases both cholesteryl iodide and bromide give a mixture of quaternary salt I and diene II but the elimination reaction to form II is far more extensive than when cholesteryl *p*-toluenesulfonate was used. Cholesteryl chloride did not react with either pyridine or isoquinoline under the conditions used in these experiments but was recovered unchanged.[3]

In connection with these experiments it was of interest to determine whether the diene II which is

TABLE I

REACTION OF PYRIDINE-LIKE BASES WITH CHOLESTERYL DERIVATIVES AT 120° FOR FIVE HOURS

		Quaternary salt			3,5-Cholestadiene		
3-β-Cholesteryl derivative	Base used	Yield, %	M.p., °C.[o]	$[\alpha]_D$[p]	Yield, %	M.p., °C.[o]	$[\alpha]_D$[p]
Chloride	Pyridine	...	.....	....	...	...	...
Bromide	Pyridine	27[a]	293–295	....	48[l]	...	...
Iodide	Pyridine	31[b]	260–261	− 7.0°	55	78–79	−116°
Tosylate	Pyridine	71[c]	231–232	− 5.7	21	78–79	−114
Tosylate	α-Picoline	23[d]	234–235	−18.0	60[l]	...	...
Tosylate	β-Picoline	66[e]	215–217	− 3.9	19	78–79	−113
Tosylate	γ-Picoline	47[f]	211–213	0.0	33[l]	...	...
Tosylate	4-*n*-Amyl-pyridine	...	.....	....	42(55)[m]	77–79	...
Tosylate	Quinoline	50[g]	246–247	−47.0	34	78–79	...
Tosylate	Quinaldine	1[h]	190–196	....	54(69)[m]	78–79	−110
Tosylate	3-Methylisoquinoline	47[i]	276–277	24.0	27	78–79	...
Tosylate	Isoquinoline	65[j]	207–208	5.8	20	78–79	−115
Tosylate	Isoquinoline[n]	53[n]	207–208	5.8	19[n]	78–79	−115
Iodide	Isoquinoline	25[k]	264–265	8.9	60	78–79	−114

[a] Crystallized from pyridine, this compound was converted to the corresponding iodide for identification of the cation. [b] Crystallized from alcohol, see reference 1. [c] For analytical data see reference 1. [d] Crystallized from alcohol–benzene. *Anal.* Calcd. for $C_{40}H_{59}O_3NS{\cdot}H_2O$: C, 73.69; H, 9.43; N, 2.12. Found: C, 72.90; H, 9.12; N, 2.17. [e] Crystallized from benzene. *Anal.* Calcd. for $C_{40}H_{59}O_3NS$: C, 75.94; H, 9.38; N, 2.20. Found: C, 75.78; H, 9.38; N, 2.44. [f] Crystallized from benzene. *Anal.* Calcd. for $C_{40}H_{59}O_3NS{\cdot}{}^1/_2H_2O$: C, 74.75; H, 9.40; N, 2.18. Found: C, 74.48; H, 9.11; N, 2.18. [g] Crystallized from alcohol. *Anal.* Calcd. for $C_{43}H_{59}O_3NS{\cdot}{}^1/_2H_2O$: C, 76.05; H, 8.91; N, 2.06. Found: C, 76.22; H, 9.34; N, 1.94. [h] Identity of compound questionable. [i] Crystallized from alcohol. *Anal.* Calcd. for $C_{44}H_{61}O_3NS{\cdot}{}^1/_2H_2O$: C, 76.25; H, 9.03; N, 2.02. Found: C, 76.43; H, 9.38; N, 2.12. [j] Crystallized from alcohol–acetone. *Anal.* Calcd. for $C_{43}H_{59}O_3NS{\cdot}{}^1/_2H_2O$: C, 76.05; H, 8.91; N, 2.06. Found: C, 75.98; H, 9.10; N, 2.63. [k] Crystallized from acetone–chloroform. *Anal.* Calcd. for $C_{36}H_{52}NI$: C, 69.14; H, 8.38; N, 2.24. Found: C, 68.79; H, 8.80; N, 2.18. [l] Compound was an oil, assumed to be 3,5-cholestadiene or a mixture of cholestadienes. [m] Yield in parentheses was estimated by isolation of the *p*-toluenesulfonate salt of the base. [n] Reaction mixture heated at 175° for 10 hours. [o] All melting points observed on a Fisher–Johns block. [p] All rotations in chloroform at 24–32°.

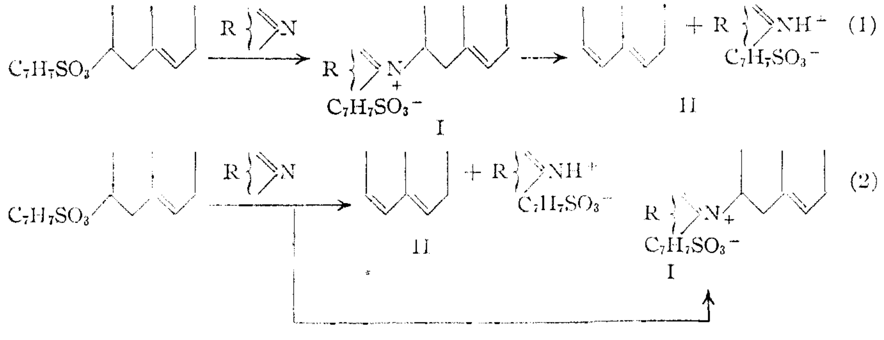
---

(1) L. C. King, R. M. Dodson and L. A. Subluskey, THIS JOURNAL, **70**, 1176, 2685 (1948).

(2) The analytical data and crystallization solvent data for new compounds in Table I are included in the footnotes. Each of the new quaternary salts described in Table I was converted by metathetical means, to the corresponding iodide. These compounds are described in Table II.

(3) J. Mauthner and W. Suida, *Monatsh.*, **17**, 29 (1896), reported the preparation of "cholesterylene" by heating cholesteryl chloride with quinoline at 237°.

formed in each reaction is produced by breakdown of the quaternary salt I, as shown in reaction sequence 1, or whether the II was formed by an independent process as shown in 2.

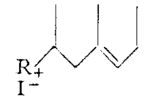


The experimental data indicate that sequence 1 does not describe the process. Thus cholesterylisoquinolinium *p*-toluenesulfonate on heating 12 hours at 120° with isoquinoline, was recovered unchanged and no diene II could be detected in the reaction products. It was further shown, Table I, that the amounts of diene and quaternary salt formed by action of isoquinoline on cholesteryl *p*-toluenesulfonate at 120° for five hours was essentially the same as the amounts formed by the same reactants when heated at 175° for 10 hours.

In a recent paper the 3-β-structure for cholesterylpyridinium *p*-toluenesulfonate (Ia) was established in detail.[4] The structures of all the quaternary salts described in this paper are assumed to have the 3-β-configuration. Both dextrorotatory and levorotatory compounds were found among the quaternary salts, Tables I and II, regardless of the nature of the anion. It is evident that the sign of the optical rotation cannot be used as a criterion to distinguish between 3-β-cholesteryl and *i*-cholesteryl structures for these compounds.

Table II

Iodides Prepared from Cholesteryl Quaternary Salts Described in Table I



R	M.p., °C.	Quaternary iodide		Nitrogen, %	
		[α]D	Formula	Calcd.	Found
β-Picoline[a]	269–271	−6.3°	$C_{33}H_{52}NI$	2.37	2.03
γ-Picoline[b]	271–272	0.0	$C_{33}H_{52}NI$	2.37	2.24
Quinoline[c]	287	−57.0	$C_{36}H_{52}NI$	2.24	1.93
3-Methylisoquinoline[d]	276–277	50.0	$C_{37}H_{54}NI$	2.19	2.13
Isoquinoline[e]	265–266	8.9	$C_{36}H_{52}NI$	2.24	2.18

[a] Crystallized from alcohol. [b] Crystallized from acetone. [c] Crystallized from alcohol. *Anal.* Calcd. for $C_{36}H_{52}NI$: C, 69.14; H, 8.38. Found; C, 69.10; H, 8.42. [d] Crystallized from absolute ethanol. [e] See footnote *k* in Table I.

Experimental

Preparation of Starting Materials.—Cholesteryl *p*-toluenesulfonate, m.p. 132–133°, was prepared by the method of Freudenberg and Hess.[5] Cholesteryl iodide, m.p. 105–106°, was obtained in 73% yield by action of sodium iodide on cholesteryl *p*-toluenesulfonate in acetone.[6] Cholesteryl bromide, m.p. 97–98°, [α]D −25.9°, was obtained in 70% yield by the action of lithium bromide on cholesteryl *p*-toluenesulfonate in acetone solution. Cholesteryl chloride, m.p. 96°, $[\alpha]^{24}$D −28.9°, was prepared by the treatment of cholesterol with thionyl chloride in pyridine solution.[7] The bases used were commercially available materials.

Preparation of Quaternary Salts; Separation and Identification of 3,5-Cholestadiene.—All reactions were carried out in about the same way. The reaction of cholesteryl *p*-toluenesulfonate with pyridine will serve as an example.

A solution of 8.8 g. (0.02 mole) of cholesteryl *p*-toluenesulfonate in 16 ml. of pyridine was heated at 118° for five hours. The solution was cooled, diluted with petroleum ether and filtered. The solid material was crystallized from benzene and from 50% alcohol to give 3-β-cholesterylpyridinium *p*-toluenesulfonate (Ia); yield 8.8 g. (71%), m.p. 231–232°, $[\alpha]^{23}$D −5.7° (in chloroform).

The pyridine-petroleum ether mother liquor was diluted to 200 ml. with more petroleum ether and extracted four times with 100-ml. portions of water. In the washing process any stable emulsions formed were dispelled by addition of warm salt water and shaking vigorously. The petroleum ether layer was then evaporated and the oily substance remaining was taken up in hot methanol. Long needles, m.p. 70–73°, separated on cooling. The 3,5-cholestadiene was recrystallized from methanol; yield 1.8 g. (21%), m.p. 78–79°, $[\alpha]^{29}$D −114° (in chloroform). Yield data for this and similar experiments are summarized in Table I.

Action of Isoquinoline on Cholesterylisoquinolinium *p*-Toluenesulfonate.—A solution of 2.1 g. of cholesterylisoquinolinium *p*-toluenesulfonate was heated with isoquinoline at 120° for 12 hours. From the reaction mixture 1.8 g. of the salt was isolated unchanged. No 3,5-cholestadiene could be isolated from the reaction mixture.

Preparation of Iodide Salts (Table II).—All these compounds were prepared in the same manner. For example, 1.5 g. of 3-β-cholesterylquinolinium *p*-toluenesulfonate was dissolved in a minimum volume of hot alcohol, and concentrated, aqueous hydriodic acid was added. The 3-β-cholesterylquinolinium iodide separated at once. It was recrystallized from alcohol; m.p. 287°, $[\alpha]^{32}$D −57° in chloroform, analysis in Table II.

Evanston, Illinois

---

[4] L. C. King and M. J. Bigelow, This Journal, **74**, 3338 (1952).

[5] K. Freudenberg and H. Hess, *Ann.*, **448**, 121 (1926).

[6] Burckhardt and Helferich, French Patent 846,380, Sept. 15, 1939; *C. A.*, **35**, 1186 (1941).

[7] O. Diels and E. Abderhalden, *Ber.*, **37**, 3102 (1904).