fect is greater than the effect of resonance on the acid strengths of the activated complexes. It is not necessary to think of the addition of a proton and the attack by a water molecule as steps taking place in series; in a single attack by a hydronium ion, the same factors would affect the relative reactivities of disulfonate, N-alkyl and N-aryl sulfamates.

An uncatalyzed reaction with water like (III) would require the liberation of the unstable ion; $:\overset{H}{\underset{\cdot\cdot}{N}}—R$ and hence does not take place. If the activated complex for the acid catalyzed reaction were $HO_3S—\overset{H}{\underset{\cdot\cdot}{N}}—R$ the same unfavorable factor would affect the reaction.

Acknowledgment.—We are indebted to Professor Don M. Yost for proposing this problem to us. Professors N. Kharasch and S. Winstein of the University of Southern California and The University of California, respectively, have made stimulating suggestions as to the mechanism of the reaction.

Summary

The rate of the acid catalyzed hydrolysis of amine disulfonate ion, $HN(SO_3)_2^=$, in water solution has been studied over the temperature range 25–45°. The results at constant ionic strength conform to the rate equation

$$-d[HN(SO_3)_2^=]/dt = k[H^+][HN(SO_3)_2^=]$$

if the equilibrium between sulfate ion and hydrogen ion is taken into account. The uncatalyzed hydrolysis was found to have an undetectable rate compared to the rate of the acid catalyzed reaction.

The variation of the rate constant with ionic strength implies that the charge product of the ions involved in the rate determining reaction is −2.

The variation of the rate constant at zero ionic strength with temperature is described by the equation

$$k_0(\text{ml./mole} \times \text{sec.}) = 2.54 \times 10^{17} \exp.\ (-23{,}500/RT)$$

The relatively large value of the frequency factor (as compared with that expected on the basis of collision theory for a bimolecular reaction between uncharged molecules) is explained on the basis of a large positive entropy of formation of the activated complex, due to its electrostatic interaction with the solvent.

A mechanism involving an activated complex of amine disulfonate ion and hydronium ion may be invoked to explain these results. A hypothesis to explain the relative stability toward hydrolysis of methyl sulfamic acid as compared with phenyl sulfamic acid or amine disulfonate is advanced.

In addition, the ionization function (classical ionization constant) for the equilibrium: $HN(SO_3)_2^= = H^+ + N(SO_3)_2^{\equiv}$ in a sodium chloride solution at an ionic strength of 1.00 at 25° was measured as 3.2×10^{-9}.

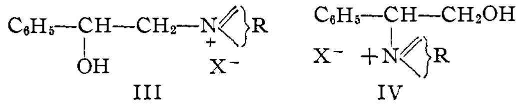
Pasadena, Calif. Received January 3, 1949

[Contribution from the Chemical Laboratories of Northwestern University]

Reactions of 1,2-Epoxides with Salts of Organic Bases. I. Styrene Oxide[1,2]

By L. Carroll King, Neil W. Berst and F. N. Hayes

Styrene oxide (I) reacts with strong acid salts of certain organic bases to give a mixture of quaternary salts. For example, I reacted with pyridine hydriodide (II) to give a mixture of 2-phenyl-2-hydroxyethylpyridinium iodide (IIIa) and 1-phenyl-2-hydroxyethylpyridinium iodide (IVa).



III IV

(a) $X = I^-$; (b) $X = Br^-$; (c) $X = ClO_4^-$; (d) $X = {}^-O_3SC_6H_4CH_3$; $R = C_5H_5$—

In a series of reactions between I and II the over-all yield of mixed salts was quite constant, with IVa the principal product. The yields of IIIa were consistently low, except in the case where I was in excess. The requisite reaction time was five to ten minutes. Prolonged heating had little effect on the total yield or distribution of isomers except when I was in excess. In this case the products became tarry and the isolable yield of IVa was smaller.

The structure of IIIa was determined by comparison with authentic 2-phenyl-2-hydroxyethylpyridinium iodide, prepared by the method of Krohnke.[3] Further proof was obtained by oxidizing[4] 2-phenyl-2-hydroxyethylpyridinium perchlorate (IIIc), prepared from IIIa, to the known phenacylpyridinium perchlorate.[5] The structure assigned to IVa follows from its non-identity with IIIa and from its formation from the reaction of 2-phenyl-2-iodoethanol[6] with pyridine.

The generality of the reaction was established by allowing I to react with a number of acid salts

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[1] Presented before the Organic Division of the American Chemical Society, San Francisco, April, 1949.

[2] This investigation was supported in part by a research grant from the National Cancer Institute, U. S. Public Health Service.

[3] Krohnke, *Ber.*, **66**, 607 (1933).

[4] Krohnke, *ibid.*, **67**, 659 (1934).

[5] King, This Journal, **66**, 894 (1944).

[6] Prepared by the method of Golumbic and Cottle, *ibid.*, **61**, 996 (1939).

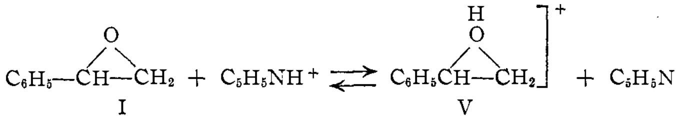
TABLE I[a]

Salt used in reaction	Yield, %		M. p., °C.		Formula of product	Carbon, %			Hydrogen, %		
							Found			Found	
	III	IV	III	IV		Calcd.	III	IV	Calcd.	III	IV
Pyridine hydriodide	6.7	68[e]	256–258	127–129	$C_{13}H_{14}ONI$	47.72	47.62	48.00	4.31	4.29[b]	4.40[d]
Pyridine hydrobromide	5.3[c]	73	230–232	134–135	$C_{13}H_{14}ONBr$	55.73	55.98	55.30	5.04	5.04	5.06
Pyridinium perchlorate	18[f]	56	217–218	[g]	....	...	...	...	..	...	..
Pyridinium tosylate	11	52	212–213	[g]	$C_{20}H_{21}O_4NS$	64.67	64.60	...	5.70	5.50	..
Picoline hydriodide	10[h]	88	175–177	133–134	$C_{14}H_{16}ONI$	49.28	49.23	48.98	4.73	4.82[i]	4.73
3-Picolinium perchlorate	15	62	180–184	123–125	$C_{14}H_{16}O_5NCl$	53.57	53.80	53.15	5.14	5.22	4.82
Isoquinolinium perchlorate	21	60	214–215	132–133	$C_{17}H_{16}O_5NCl$	58.37	58.03	58.10	4.61	4.36	4.67
Isoquinoline hydriodide	99[j]	86[j]	173–176	146–147	$C_{17}H_{16}ONI$	54.12	54.36	54.27	4.28	4.41	4.34

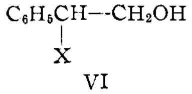
[a] In this table, III and IV refer to the generalized ion as shown in the text. R and X are determined by the salt used in the reaction. [b] Iodide: calcd. 38.9; found, 38.2. [c] This compound was also prepared from 1-phenyl-2-bromoethanol. [d] Iodide: calcd. 38.9; found, 38.4. [e] This compound was also prepared from 2-phenyl-2-iodoethanol. [f] Identical with 1-(2-phenyl-2-hydroxyethyl)-pyridinium perchlorate, synthesized by Krohnke, *Ber.*, 66, 607 (1933). [g] These salts were not isolated as such. The yields are based on the amount of IVa isolated after metathetical reactions with iodide ion (see experimental). [h] In the first run this compound was obtained in the yield shown by one of us, F. N. H. We were unable to repeat the experiment. The substance is readily obtained by action of β-picoline on 1-phenyl-2-bromoethanol followed by metathetical reaction with iodide ion. [i] Iodide: calcd. 37.2; found, 37.0. [j] When prepared by action of isoquinoline hydriodide on styrene oxide these compounds could not be separated. They were prepared in the yields shown by the reaction of isoquinoline with 1-phenyl-2-bromoethanol followed by metathetical reaction with iodide and from the reaction of isoquinoline with 2-phenyl-2-iodoethanol.

of pyridine and other heterocyclic tertiary amines. The results of these experiments along with the data for the products are listed in Table I. In the reactions employing pyridinium perchlorate and *p*-toluenesulfonate, IIIc and IIId were obtained in much larger yields than IIIa for the analogous reaction using II. Compounds IVc and IVd would not crystallize, but their identity was demonstrated, in each case, by a metathetical conversion to IVa.

Using the pyridinium ion as an example, an initial step in the over-all reaction may be envisioned as an equilibrium partition of a proton between generalized bases.

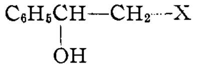


The ion (V)[7] could then react directly with the base present to form salts of types III and IV, or, V could react with the anion present to form compounds of types VI and VII.[8] Compounds VI and VII could subsequently react with the base to form salts of type III or IV.



$C_6H_5CH(X)—CH_2OH$

VI



$C_6H_5CH(OH)—CH_2—X$

VII

In connection with this study 2-phenyl-2-iodoethanol (VI, X = I) and 1-phenyl-2-bromoethanol (VII, X = Br) were prepared and their reactions with pyridine type bases were studied. 2-Phenyl-2-iodoethanol reacted with pyridine to give IVa in essentially quantitative yield. No trace of IIIa was observed. Similarly 1-phenyl-2-bromoethanol reacted with pyridine to give IIIb in excellent yield and no IVb could be detected in the reaction mixture. With both halides the time required for complete reaction with pyridine was longer than that required for the formation of the corresponding salts by means of the reaction between styrene oxide and pyridinium salts.

In view of these observations VI and VII are of minor importance in the above reactions. Furthermore when VI or VII react with pyridine-type bases the halogen is displaced without the formation of styrene oxide as an intermediate.

Experimental

Preparation of Starting Materials.—The styrene oxide was a commercial sample; b. p. 66–67° (7 mm.).[9]

The iodide, bromide and perchlorate salts were prepared by mixing the appropriate aqueous acid with a slight excess of the base and evaporating the mixture on the steam-bath. The resulting salt was washed with ether and recrystallized from a suitable solvent. The melting points of the salts and the crystallization solvents were as follows: pyridine hydriodide, m. p. 175–190° (dec.), alcohol; pyridinium bromide, m. p. 215°,[10] alcohol; pyridinium perchlorate, m. p. 289°, water; β-picoline hydriodide, m. p. 87–88°, alcohol; β-picolinium perchlorate, m. p. 40–50°[11]; isoquinolinium perchlorate, m. p. 165–170°, acetone–water.

Pyridinium *p*-toluenesulfonate was prepared directly from pyridine and *p*-toluenesulfonic acid monohydrate. The product was recrystallized from acetone–alcohol, m. p. 117°.[12]

Examples of Styrene Oxide Reactions with Salts. (a) **Pyridine Hydriodide.**—A mixture consisting of 6.0 g.

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[7] Kadesch, THIS JOURNAL, **68**, 43 (1946), has suggested that ions such as V undergo ring opening to give carbonium ions. If this should occur the resulting carbonium ions could react with the base present to give products of type III or IV.

[8] The formation of VI or VII, where X is perchlorate, may be assumed to be unimportant because of the poor nucleophilic character of the perchlorate ion. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., 1940, p. 301. However, because of some known additions of perchloric acid to 1,2-epoxide, an attack by perchlorate ion on V cannot be completely ruled out. Hoffmann, Zedwitz and Wagner, *Ber.*, **42**, 4390 (1909).

[9] We are indebted to the Dow Chemical Company for a generous sample of this substance.

[10] Dehn and Dewey, THIS JOURNAL, **33**, 1596 (1911).

[11] This substance was used without further purification.

[12] Rapoport, THIS JOURNAL, **68**, 341 (1946).

(0.05 mole) of styrene oxide, 8.0 g. (0.1 mole) of pyridine and 10.3 g. (0.05 mole) of pyridine hydriodide was heated on the steam-bath. Within two minutes, the pyridine hydriodide had dissolved and a vigorous reaction began. After the reaction subsided, the mixture was heated ten minutes more, cooled, layered with ether and rubbed with an applicator stick until the entire mass crystallized. The crude mixture of products weighed 13.2 g.

The solid material was leached three times with 75-cc. portions of boiling acetone and the 4.0 g. left was dissolved in 20 cc. of water containing a little alcohol. On cooling, 0.7 g. (4.2%) of a substance melting at 244–252° separated. After recrystallization from water, pure 1-(2-phenyl-2-hydroxyethyl)-pyridinium iodide (IIIa), melting at 252–255°, was obtained.

On cooling the acetone extracts from above, there separated out a compact crystalline product, 8.7 g. (52%),[13] m. p. 125–129°. Recrystallization from acetone gave pure 1-(1-phenyl-2-hydroxyethyl)-pyridinium iodide (IVa), m. p. 128–129°.

(b) **Pyridinium Perchlorate and *p*-Toluenesulfonate.**—As in the previous procedure, high melting acetone-insoluble salts were obtained. However, no crystalline material separated from the acetone extracts, even after concentration. Subsequently, each oil was treated with sodium iodide in acetone. At this point, the pyridinium perchlorate reaction started to deposit crystals. On long cooling of the acetone solution, followed by filtration, a 56% yield of IVa, melting at 128–129° was obtained. The sodium iodide treated acetone solution of the *p*-toluenesulfonate reaction immediately gave a precipitate of sodium *p*-toluenesulfonate. The mixture was heated and filtered. After long cooling, there separated from the filtrate a 52% yield of IVa, melting at 128–129°.

The Oxidation of IIIc to 1-Phenacylpyridinium Perchlorate.—According to the directions of Krohnke,[4] 0.15 g. of 1-(2-phenyl-2-hydroxyethyl)-pyridinium perchlorate (IIIc) in 1 cc. of water was heated under reflux for six hours with 0.5 cc. of 6 *N* sulfuric acid and 0.075 g. of sodium dichromate. On cooling, there separated out long yellow needles, which were filtered off and washed with ice-water. The yellow crystals weighing 0.1 g. (93%), were recrystallized from acetone-water, using norite, yielding white crystals melting at 189°. This material gave no depression in a mixed melting point with an authentic sample of 1-phenacylpyridinium perchlorate prepared in this Laboratory.[5]

Reactions Involving 1-Phenyl-2-bromoethanol.—By heating 1-phenyl-2-bromoethanol[14] with pyridine, on a steam-bath for twenty-four hours, and then washing the product with ether, an essentially quantitative yield of crude 2-phenyl-2-hydroxyethylpyridinium bromide was obtained. An aqueous solution of the bromide on treatment with 48% hydriodic acid gave the corresponding iodide (IIIa); yield 90%; m. p. 252–255°[15] after crystallization from alcohol-water. In a similar manner the following salts were prepared by action of the corresponding bases on 2-phenyl-2-bromoethanol; 1-(2-phenyl-2-hydroxyethyl)-3-picolinium iodide, m. p. 175–177°[15] crystallized from alcohol-water; and 2-(2-phenyl-2-hydroxyethyl)-isoquinolinium iodide, m. p. 173–176° crystallized from alcohol.

No compounds of type IV were observed in any of these reactions.

Reactions Involving 2-Phenyl-2-iodoethanol.—2-Phenyl-2-iodoethanol[6] was heated with pyridine, on a steam-bath for thirteen hours. The resulting reaction mixture was washed with dry ether and the crude crystalline product was recrystallized from acetone; yield, 82%, of 1-(1-phenyl-2-hydroxyethyl)-pyridinium iodide (IVa), m. p. 128–129°[15]; in a similar manner the reaction of 2-phenyl-2-iodoethanol with β-picoline and isoquinoline gave 83% of 1-(1-phenyl-2-hydroxyethyl)-3-picolinium iodide, m. p. 131–132°, and 86% of 2-(1-phenyl-2-hydroxyethyl)-isoquinolinium iodide, m. p. 146–147°.

Summary

1. The reaction of styrene oxide with pyridine hydriodide gives a mixture of salts consisting of 1-phenyl-2-hydroxyethylpyridinium iodide and 2-phenyl-2-hydroxyethylpyridinium iodide.

2. The generality of this reaction was established by allowing styrene oxide to react with a variety of strong acid salts of pyridine and by allowing it to react with salts of a number of pyridine-type bases.

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[13] By reworking all mother liquors including that from which the high melting compound separated, the total yield of IVa, the low melting compouud, was 75%.

[14] Read and Reid, *J. Chem. Soc.*, 1487 (1928).

[15] No depression in mixed melting point with the corresponding salt prepared from styrene oxide.

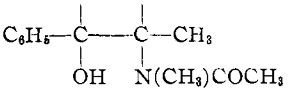
EVANSTON, ILLINOIS RECEIVED MAY 26, 1949

[CONTRIBUTION FROM THE CHEMICAL BRANCH, DIVISION OF MEDICINE, FOOD AND DRUG ADMINISTRATION, FEDERAL SECURITY AGENCY]

Mechanism and Stereochemical Course of Acyl Migrations in Derivatives of Ephedrine and ψ-Ephedrine

BY LLEWELLYN H. WELSH

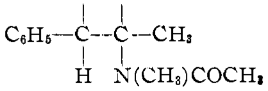
It has been reported[1] that treatment of N-acetyl-(−)-ephedrine, I, with hot 5% hydrochloric acid quantitatively yielded a mixture of (−)-ephedrine and its diastereomer, (+)-ψ-ephedrine, in the ratio of 38:62,[2] and that inversion took place at the number one carbon atom during an N → O shift of the acetyl group prior to hydrolysis of the ester salt so formed. Under the same conditions N-acetyl-(+)-ψ-ephedrine, II, gave a product in which complete retention of configuration was evident.



$C_6H_5-\overset{H}{\underset{OH}{C}}-\overset{H}{\underset{N(CH_3)COCH_3}{C}}-CH_3$

I[3]

erythro configuration



$C_6H_5-\overset{HO}{\underset{H}{C}}-\overset{H}{\underset{N(CH_3)COCH_3}{C}}-CH_3$

II[3]

threo configuration

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[1] Welsh, THIS JOURNAL, **69**, 128 (1947).

[2] When this reaction is carried out under temperature conditions more closely controlled than those formerly employed, a ratio of 33:67 results.

[3] The projection formulas are based on the work of Leithe, *Ber.*, **65**, 660 (1932), and of Freudenberg, *et al.*, THIS JOURNAL, **54**, 234 (1932); *Ann.*, **510**, 223 (1934). Jarowski and Hartung, *J. Org. Chem.*, **8**, 565 (1943), have misinterpreted the publication of Leithe, and are in error when they state that the relative configuration of the methylamino-bearing carbon atom is unsettled.