zinc sulfide from sodium mercuric sulfide solutions which are undersaturated with mercuric sulfide. Such a postprecipitation occurs only when the mercuric sulfide is soluble in the primary precipitate, and the speed of separation of the latter from solution is greater than the speed of dissociation of the $HgS_2^{=}$ ion into HgS and $S^{=}$.

2. The distribution coefficient of mercuric sulfide between aqueous solution and solid has been determined at 25 and 80°. The solid solution does not behave as an ideal solution, but the values of the distribution coefficient are of the same order of magnitude as the value calculated upon the basis of formation of ideal solutions. This calculated value is independent of the nature of the solid, as long as the latter acts as a solvent for mercuric sulfide.

3. The speed of attainment of distribution equilibrium between sodium mercuric sulfide solution and zinc sulfide is a good indicator of the degree of perfection and the progress of aging of the latter. It is shown that zinc sulfide precipitated at a *p*H of 1.15 is more perfect and ages more rapidly at this *p*H than the sulfide formed and aged at a *p*H of 5 and the latter more so than the sulfide formed and aged in alkaline medium.

MINNEAPOLIS, MINN. RECEIVED APRIL 14, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

Hydroxyalkyl Ethers of Basic Phenols. The Antipneumococcic Activity of Some 8-Quinolyl Ethers

BY C. L. BUTLER AND ALICE G. RENFREW

It appeared to be of considerable general interest to extend the application of the hydroxyalkylation method used in the cinchona alkaloid field[1] to other types of basic phenolic substances. More specifically, it was hoped that studies carried out on simpler basic phenols would give a partial explanation, at least, of the low yields obtained in attempts to hydroxyethylate phenolic cinchona alkaloids with ethylene chlorohydrin.[2] Further, the preparation of simpler substances, related structurally to these alkaloids, was of interest in the chemotherapeutic study of pneumonia. Experiments undertaken with these considerations in view are described in the present report.

Phenol, aniline, *p*-aminophenol, *p*-acetaminophenol, *m*-diethylaminophenol and 8-hydroxyquinoline were chosen as suitable starting materials for the investigations. The compounds were alkylated in the usual way with benzyloxyalkyl *p*-toluenesulfonates[3] and the resulting aminoaryl benzyloxyalkyl ethers were hydrolyzed in dilute hydrochloric acid to hydroxyalkyl derivatives.[1] Yields were high in nearly all cases. The reaction with *p*-aminophenol was complicated by nitrogen alkylation. *p*-Acetaminophenol, however, gave with benzyloxyethyl *p*-toluenesulfonate, a high yield of the benzyloxyalkyl ether, which was readily converted to β-hydroxyphenetidine. Hydroxyalkylation of *m*-diethylaminophenol and 8-hydroxyquinoline was accomplished without difficulty.

It seemed possible that the failure of ethylene chlorohydrin to hydroxyethylate phenolic cinchona alkaloids[2] might be due to the presence in the cinchona structure of basic groups, with which this substance reacted with greater ease than with the phenolic group; or by which it was destroyed before it could react. Several alkylations with ethylene chlorohydrin were carried out in attempts to get further information on this point. According to Rindfusz[4] a 50% yield of hydroxyethyl phenyl ether is obtained on alkylation of sodium phenolate with this reagent. In the present work the reaction was carried out in the presence of one molecular equivalent of triethylamine. Only 13% of the theoretical quantity of hydroxyethyl phenyl ether was obtained in this experiment. The presence of triethylamine, however, did not decrease the yield of alkylation product when benzyloxyethyl *p*-toluenesulfonate was used as alkylating reagent. 8-Hydroxyquinoline, on alkylation with ethylene chlorohydrin, gave only 19% of the theoretical amount of

(1) Butler and Renfrew, THIS JOURNAL, **60**, 1473 (1938).
(2) Butler, Renfrew, Cretcher and Souther, *ibid.*, **59**, 227 (1937).
(3) Butler, Renfrew and Clapp, *ibid.*, **60**, 1472 (1938).
(4) Rindfusz, *ibid.*, **41**, 669 (1919); see also Bentley, Haworth and Perkin, *J. Chem. Soc.*, **69**, 164 (1896).

TABLE I

ANTIPNEUMONIC ACTIVITY AND TOXICITY OF 8-QUINOLYL ETHERS

Substance	Bactericidal power *in vitro*[a] Growth	Dilution	Toxicity[a] 20 g. mice; deaths at dosages of 1 mg.	2 mg.	3 mg.	7 mg.	8 mg.	10 mg.
8-Hydroxyquinoline sulfate	Complete inhibition	1:400000	8/30	30/30	30/30			
8-Quinolyl Ether Hydrochlorides								
Ethyl	Slight inhibition	1:50000					2/10	13/30
β-Hydroxyethyl	Slight inhibition	1:100000			0/30	0/10	0/30	
γ-Hydroxypropyl	No inhibition	1:50000					0/10	
α-Methyl β-hydroxyethyl	No inhibition	1:50000			0/30	0/10	0/10	2/30

[a] Detailed results will be published by the medical staff associated with the Mellon Institute in the chemotherapeutic study of pneumonia.

hydroxyethyl 8-quinolyl ether, as compared with the 50% yield obtained by Rindfusz[4] in the hydroxyethylation of phenol, where there could be no question of complication with basic nitrogen groups. Hydroxyethyl 8-quinolyl ether was obtained in 67% yield, using benzyloxyethyl *p*-toluenesulfonate. *m*-Diethylaminophenol gave practically identical quantities of hydroxyethyl ether with the two reagents. It is believed that these results confirm the opinion that the unfavorable yields reported in the earlier work on hydroxyalkylation of cinchona alkaloids with ethylene chlorohydrin[2] were due to complications involving the two nitrogen atoms of the alkaloids. The difficulty can be avoided to a very large extent by the use of the benzyloxyalkyl aromatic sulfonates for alkylations of this type.

The preparation of the quinoline derivatives had an added interest because of the structural relationship of these compounds to the cinchona alkaloids, and because of the marked germicidal activity of many substances of this type.[5] Hirschfelder and co-workers[6] found that 8-hydroxyquinoline sulfate was highly active *in vitro* against the pneumococcus. In spite of this observation the possibility of the usefulness of simpler quinoline derivatives as antipneumococcic agents has received very little attention. More recently, a series of eighteen quinoline derivatives was investigated by Bührmann[7] and several substances derived from 2-phenyl-4-amino- and 4-amino-6-hydroxyquinolines, were found which inhibited the growth of pneumococci. In view of Hirschfelder's results,[6] it seemed advisable to have further tests run on 8-hydroxyquinoline and the 8-quinolyl ethers prepared in the course of this work. Interest in these compounds was enhanced by the suggestion that 8-hydroxyquinoline may stimulate the defense mechanism of the body[5] (p. 33). In Table I, both the mouse toxicity and the pneumococcicidal activity are seen to be reduced sharply by alkylation of the phenolic hydroxyl group. Some pneumococcicidal activity is maintained in the ethyl and hydroxyethyl derivatives. Further biological examination of these substances would appear to be desirable, especially in view of their very low toxicities.

(5) Von Oettingen, "Therapeutic Agents of the Quinoline Group," The Chemical Catalog Company, Inc., New York, 1933.

(6) Hirschfelder, Jensen and Swanson, *Proc. Soc. Exptl. Biol. Med.*, **20**, 402 (1923).

(7) Bührmann, *Z. Immunitätsforschung*, **84**, 300 (1935).

Experimental

Half molecular quantities of the compounds to be alkylated were converted to potassium salts with the calculated amount of potassium hydroxide in about 300 cc. of absolute alcoholic solution. The alkylating reagent was then added and the mixture was refluxed for two to two and one-half hours on a water-bath. When ethylene chlorohydrin was used as alkylating reagent, the reaction mixtures were worked up directly in the usual way for hydroxyethyl ether. The crude reaction products from the benzyloxyalkyl *p*-toluenesulfonate alkylations were isolated by evaporating the solvent from the filtered alcoholic solution and separating from alkali-soluble material. The benzyl derivatives were hydrolyzed in dilute hydrochloric acid to hydroxyalkyl ethers as previously described[1] and the products were worked up and purified by the usual methods.

Phenoxyethyl Benzyl Ether.—The ether was obtained as an oil on alkylation of phenol with benzyloxyethyl *p*-toluenesulfonate. The product was purified by fractional distillation; yield 67%; b. p. 175° at 3 mm.

In a second experiment, conditions were altered by adding to the alkylation mixture one equivalent of triethylamine. The presence of this base did not interfere with the desired reaction, as was evidenced by the high yield (78% of the theoretical) of ether obtained.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1. Found: C, 79.05; H, 6.9.

β-Hydroxyethyl Phenyl Ether.[4]—The alkylation of phenol with ethylene chlorohydrin was carried out in the usual way except that one equivalent of triethylamine was added to the reaction mixture. The yield of β-hydroxyethyl phenyl ether was only 12.5%, as compared with the 50% yield obtained by Rindfusz.[4]

β-Hydroxyethylaniline.—Aniline was alkylated with benzyloxyethyl *p*-toluenesulfonate and the crude benzyl-

oxyethylaniline was hydrolyzed in 11% hydrochloric acid[1] to β-hydroxyethylaniline; yield 50%; b. p. 157–158° at 13 mm.

A portion of the hydroxyethylaniline was converted to N-benzoxyethyl benzanilide with benzoyl chloride, in 80% yield. The melting point was 91–92°, which agrees with the figure found by Schorigin and Below.[8]

Alkylation of *p*-Aminophenol with Benzyloxyethyl *p*-Toluenesulfonate.—The only product which could be isolated in this experiment was a crude trialkylated substance of probable structure $C_6H_5CH_2OCH_2CH_2OC_6H_4N(CH_2CH_2OCH_2C_6H_5)_2$. A small amount of this material was converted to a crystalline sulfate and analyzed.

Anal. Calcd. for $C_{35}H_{37}O_4N \cdot 0.5\,H_2SO_4$: SO_4, 8.5. Found: SO_4, 7.7.

The main portion of the reaction product was hydrolyzed in dilute hydrochloric acid to remove benzyl groups. The yield of hydrolysis product was very low. Since the crude substance formed only mono-acyl derivatives with *p*-toluenesulfonyl chloride and acetyl chloride, it consisted probably of phenylmorpholine *p*-hydroxyethyl ether.

Anal. Amorphous *p*-toluenesulfonyl derivative. Calcd. for $C_7H_7SO_3CH_2CH_2OC_6H_4N(CH_2CH_2)_2O$: $C_7H_7SO_3K$, 55.7. Found: $C_7H_7SO_3K$, 55.4.

Crystalline acetyl derivative from alcohol; m. p. 118–119°. Calcd. for $CH_3CO_2CH_2CH_2OC_6H_4N(CH_2CH_2)_2O$: CH_3CO, 16.2. Found: CH_3CO, 16.4, 16.7.

Benzyloxyethyl *p*-Acetaminophenyl Ether.—*p*-Acetaminophenol was readily alkylated with benzyloxyethyl *p*-toluenesulfonate. The solid ether was purified by crystallization from absolute alcohol; yield 88%; m. p. 88°.

Anal. Calcd. for $C_{17}H_{19}O_3N$: C, 71.6; H, 6.7. Found: C, 71.3; H, 7.0.

β-Hydroxyphenetidine.—Benzyloxyethyl *p*-acetaminophenyl ether was hydrolyzed in 11% hydrochloric acid in the usual way[1] to β-hydroxyphenetidine; yield 80%. A sample recrystallized from alcohol melted at 73°.

Anal. Calcd. for $C_8H_{11}O_2N$: N, 9.15. Found: N, 9.2.

A small sample was converted to a crystalline diacetyl derivative with acetyl chloride. The melting point was 128°, which was in fair agreement with the figure found by Katrak.[9]

β-Hydroxyethyl *m*-Diethylaminophenyl Ether.—*m*-Diethylaminophenol, on alkylation with ethylene chlorohydrin, gave a 62% yield of β-hydroxyethyl *m*-diethylaminophenyl ether. An identical over-all yield was obtained when the hydroxyalkylation was carried out through the intermediate benzyloxyethyl derivative. There is, therefore, no advantage in the use of benzyloxyethyl *p*-toluenesulfonate in this case; b. p. 148° at 3 mm., m. p. 41°.

Anal. Calcd. for $C_{12}H_{19}O_2N$: N, 6.7; C, 68.9; H, 9.1. Found: N, 7.9; C, 69.3; H, 9.6.

An acetyl derivative was obtained as a viscous liquid with acetic anhydride and sodium acetate.

Anal. Calcd. for $C_{14}H_{21}O_3N$: CH_3CO, 17.1. Found: CH_3CO, 16.9, 17.4.

(8) Schorigin and Below, *Ber.*, **68**, 833 (1935).

(9) Katrak, *J. Indian Chem. Soc.*, **13**, 334 (1936).

β-Hydroxyethyl 8-Quinolyl Ether.—8-Hydroxyquinoline was alkylated with benzyloxyethyl *p*-toluenesulfonate, and the crude benzyloxyethyl 8-quinolyl ether was hydrolyzed to β-hydroxyethyl 8-quinolyl ether in dilute hydrochloric acid. The substance was purified by crystallization of its hydrochloride from absolute alcohol; yield 70%; m. p. 199–200°.

Anal. Calcd. for $C_{11}H_{11}O_2N \cdot HCl$: Cl, 15.7. Found: Cl, 15.8.

The base was recovered from the hydrochloride and crystallized from alcohol; m. p. 83–84°.

Anal. Calcd. for $C_{11}H_{11}O_2N$: C, 69.8; H, 5.9; N, 7.4. Found: C, 69.5; H, 6.1; N, 7.3.

β-Acetoxyethyl 8-quinolyl ether was obtained by acetylation of the hydroxyethyl ether with acetyl chloride. It was purified by crystallization of its hydrochloride from alcohol; m. p. 153°.

Anal. Calcd. for $C_{13}H_{13}O_3N \cdot HCl$: CH_3CO, 16.1; Cl, 13.25. Found: CH_3CO, 16.8; Cl, 13.1.

A more direct preparation of β-hydroxyethyl 8-quinolyl ether was accomplished by alkylation of 8-hydroxyquinoline with ethylene chlorohydrin. The yield, however, was only 19% using this method.

α-Methyl-β-hydroxyethyl and γ-Hydroxy-*n*-propyl 8-Quinolyl Ethers.—The compounds were prepared by alkylation of 8-hydroxyquinoline with the appropriate benzyloxyalkyl *p*-toluenesulfonates and hydrolyzing the intermediate benzyloxyalkyl ethers to the desired hydroxyalkyl derivatives.

α-Methyl-β-hydroxyethyl 8-quinolyl ether was purified by crystallization of its hydrochloride from alcohol; yield 40%.

Anal. Calcd. for $C_{12}H_{13}O_2N \cdot HCl$: Cl, 14.8; N, 5.8. Found: Cl, 14.6; N, 6.3.

The base was liberated from the hydrochloride and crystallized from ether; m. p. 65°. With acetyl chloride it gave a solid acetyl derivative, which was crystallized from acetone; m. p. 99°.

Anal. Calcd. for $C_{14}H_{15}O_3N$: CH_3CO, 17.5. Found: CH_3CO, 17.0, 18.1.

γ-Hydroxy-*n*-propyl 8-quinolyl ether was similarly purified; yield 59%; m. p. 129°.

Anal. Hydrochloride. Calcd. for $C_{12}H_{13}O_2N \cdot HCl$: Cl, 14.8. Found: Cl, 14.5. Base. Calcd. for $C_{12}H_{13}O_2N$: N, 6.9. Found: N, 7.1.

γ-Acetoxy-*n*-propyl 8-quinolyl ether was obtained as a reddish oil on acetylation with acetic anhydride and sodium acetate.

Anal. Calcd. for $C_{14}H_{15}O_3N$: CH_3CO, 17.5. Found: CH_3CO, 17.5, 17.6.

8-Ethoxyquinoline.—8-Hydroxyquinoline was alkylated in the usual way with ethyl *p*-toluenesulfonate; b. p. 178° at 28 mm.[10] The base was converted to hydrochloride, which was crystallized from alcohol.

Anal. Calcd. for $C_{11}H_{11}ON \cdot HCl$: Cl, 16.9. Found: Cl, 16.9.

Summary

The preparation of several hydroxyalkyl ethers of basic phenols has been described. Some

(10) Fischer and Renouf, *Ber.*, **17**, 759 (1884).

physiological properties of hydroxyalkyl 8-quinolyl ethers having a bearing on the chemotherapy of pneumonia have been presented briefly.

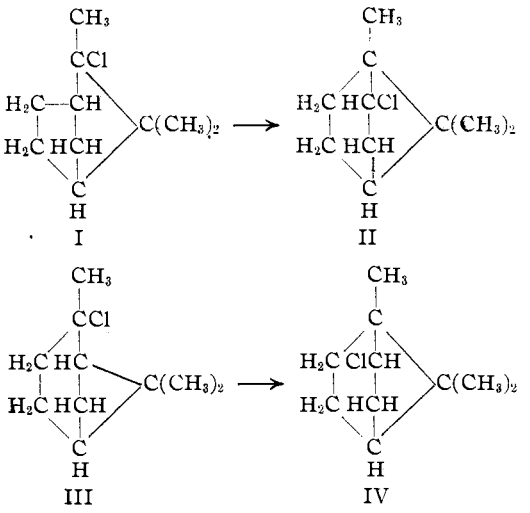
PITTSBURGH, PENNA. RECEIVED MAY 19, 1938

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Wagner–Meerwein Rearrangement. A Kinetic Reinvestigation of the Isomerization of Camphene Hydrochloride[1]

BY PAUL D. BARTLETT AND IRVING PÖCKEL

About a year ago we reviewed the evidence[2] that the rearrangement of camphene hydrochloride (I) into isobornyl chloride (II), and of pinene hydrochloride (III) into bornyl chloride (IV) involves complete Walden inversion at carbon atom no. 2 of the camphane ring system (the point of attachment of the chlorine in bornyl and isobornyl chlorides). Analogy with well-known cases of



I II

III IV

Walden inversion led us to propose that this rearrangement was a collision process, involving donors or acceptors of chloride ions, or both. Such a potential donor and acceptor is always present in solutions of camphene hydrochloride, since this compound dissociates rapidly and reversibly into camphene and hydrogen chloride, and this equilibrium is attained more rapidly than the rearrangement occurs.

If hydrogen chloride played an essential part in the rearrangement, the reaction could not be a spontaneous, monomolecular one as reported by Meerwein and van Emster.[3] Since these authors had not considered higher orders of reaction, we recalculated their data in terms of first, second and three-halves order equations and found that in six of the nine solvents studied the data were best fitted by the formulation of the second order with respect to camphene hydrochloride, while in the remaining three solvents the three-halves order formulation was best. This left it quite uncertain in what manner hydrogen chloride entered into the rearrangement process.

We have now carried out a number of kinetic experiments designed to provide clear evidence of the order of the reaction. Nitrobenzene was chosen as a solvent because it allows the rearrangement to proceed at the most convenient rate for measurement. The results show clearly that the rearrangement involves one molecule of camphene hydrochloride and one of hydrogen chloride, and they provide a complete explanation for the apparent variation of the order of the reaction with change of solvent under the conditions of measurement used by Meerwein and van Emster and, initially, by ourselves. The dissociation equilibrium

$$\text{Camphene hydrochloride} \rightleftharpoons \text{Camphene} + \text{HCl} \quad (1)$$

lies, in the case of most of our solutions, more than 94% to the left. With pure camphene hydrochloride, the hydrogen chloride concentration in the solution will be proportional to the square root of the camphene hydrochloride concentration, and hence the rate of reaction is proportional to the $^3/_2$ power of the camphene hydrochloride concentration. However, when a large excess of camphene is present, the amount of hydrogen chloride at equilibrium is diminished and its concentration becomes proportional to that of the camphene hydrochloride. The reaction under these conditions is slowed down and becomes apparently bimolecular with respect to camphene hydrochloride. The explanation of the fact that the rearrangement seems to be sometimes second and sometimes $^3/_2$ order is that it is almost im-

(1) Most of this material was included in a paper presented at the Organic Symposium at Richmond, Va., on December 30, 1937.

(2) Bartlett and Pöckel, THIS JOURNAL, **59**, 820 (1937).

(3) Meerwein and van Emster, *Ber.*, **55B**, 2500 (1922).