alcohol, giving 6.8 g. (83% yield) of β-(*o*-benzyl-*p*-chlorophenoxy)-ethyltrimethylammonium iodide, m. p. 162.0–163.0°.

In Table I are contained data on other quaternary salts which were prepared similarly. Isopropyl alcohol was used as the reaction solvent in most preparations, although on the basis of a few experiments acetone is equally as satisfactory. Since the velocity of the reaction varied with the nature of the amine and halide, modifications of the above general procedures were often necessary. An exothermic reaction almost always followed the addition of the halide to the solution of the amine. If the quaternary crystallized on cooling the solution, it was immediately collected by filtration. If it oiled out, the mixture was placed in the cold-room overnight. This usually caused the oil to solidify. In a few experiments, the quaternary did not precipitate readily from the solution either as a solid or as an oil. A few hours of refluxing, followed by cooling, was usually sufficient to cause precipitation of the quaternary. If the quaternary still did not separate from the reaction mixture, the solvent was evaporated under reduced pressure and the residue recrystallized from a suitable solvent.

**β-(*p*-Benzylphenoxy)-ethyltrimethylammonium Iodide.**—This preparation was carried out as described above in method B, using 44 g. (0.10 mole) of N,N-dimethyl β-(*p*-benzylphenoxy)-ethylamine dihydrogen citrate and 17 g. (0.12 mole) of methyl iodide. There was obtained 22.0 g. (55% yield) of β-(*p*-benzylphenoxy)-ethyltrimethylammonium iodide, m. p. 149.5–151.5° (recrystallized from acetone).

*Anal.* Calcd. for $C_{18}H_{24}ONI$: C, 54.5; H, 6.1. Found: C, 54.6; H, 6.2.

**β-(*o*-2-Thenylphenoxy)-ethyltrimethylammonium Iodide.**—From 26.1 g. (0.100 mole) of N,N-dimethyl β-(*o*-2-thenylphenoxy)-ethylamine and 15.6 g. (0.110 mole) of methyl iodide there was obtained according to the procedure described in method A, 30.4 g. (75% yield) of β-(*o*-2-thenylphenoxy)-ethyltrimethylammonium iodide, m. p. 181.5–182.5° (recrystallized from methyl alcohol).

*Anal.* Calcd. for $C_{16}H_{22}ONIS$: C, 47.7; H, 5.5. Found: C, 47.8; H, 5.6.

The quaternary salts acquire a yellow color on exposure to light, especially when not completely dry. It was therefore found advantageous to dry the recrystallized quaternaries as quickly as possible in a covered vacuum desiccator and store them in brown bottles.

**Acknowledgment.**—The authors are indebted to Mrs. Neva Knight and Mr. Richard M. Downing, who performed the analyses reported herein.

## Summary

A series of benzylphenoxyalkyl trialkylammonium halides has been prepared by allowing the corresponding tertiary amine to react with an alkyl halide. Many of these quaternary salts are potent vasopressor agents.

SYRACUSE 1, N. Y. RECEIVED MAY 3, 1950

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

# A New Reaction of Nitriles. V. Preparation of N-(2-Halo-1-ethyl)-amides[1]

BY ROBERT M. LUSSKIN[2] WITH JOHN J. RITTER

The general reaction of nitriles with either alkenes or secondary or tertiary alcohols in strongly acidic media to form N substituted amides has been the subject of previous articles in this series.[3] The present paper describes an extension of this work: the reaction of nitriles with certain halo alkenes or halo hydrins. The products, N-(2-halo-1-ethyl)-amides (Table I) in which R is alkyl or aryl and R′ is hydrogen or methyl, were then dehydrohalogenated to 2-oxazolines.

The reaction of acetonitrile, benzonitrile, phenylacetonitrile, or ethyl cyanoacetate with methallyl chloride, styrene chloro- or bromohydrin, or alpha methylstyrene chlorohydrin afforded no difficulty and the amides listed in Table I were isolated. However, the reaction of allyl chloride, which yielded N-(1-chloro-2-propyl)-phenylacetamide with phenylacetonitrile, gave only benzamide itself with benzonitrile.

The N-(2-halo-1-ethyl)-amides were found to be unstable with respect to cyclic isomers, oxazoline salts, and converted to them, slowly at room temperature and more rapidly at 50°. For example, when N-(1-chloro-2-methyl-2-propyl)-phenylacetamide, m. p. 98°, remained four months at room temperature or two months at 50°, complete isomerization to 4,4-dimethyl-2-benzyl-2-oxazoline hydrochloride, m. p. 142°, occurred. A more satisfactory procedure for the preparation of the oxazolines (Table II) was treatment of the amides with one equivalent of alcoholic potassium hydroxide at 60° for 1.5 minutes.[4]

The halogen of the N-(2-halo-1-ethyl)-amides was replaced readily. Thus, N-(1-chloro-2-methyl-2-propyl)-benzamide and N-(2-chloro-1-phenylethyl)-acetamide were hydrolyzed by aqueous sodium carbonate to the hydroxy amides. Oxidation of N-(2-chloro-1-phenylethyl)-acetamide gave α-acetaminophenylacetic acid. Bringing an alcoholic silver nitrate solution of any of the halo amides to reflux led to immediate precipitation of silver chloride.

Because the N-(1-chloro-2-methyl-2-propyl)-amides (derived from methallyl chloride) are neopentyl chlorides in which one methyl has been replaced by an amide group, the halogen might have been expected to show the neopentyl lack

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[1] Abstracted from a portion of the thesis submitted by Robert M. Lusskin to the Graduate Faculty of New York University, February, 1949, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

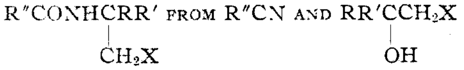
[2] Trubek Laboratories, East Rutherford, New Jersey.

[3] (a) Ritter and Minieri, THIS JOURNAL, **70**, 4045 (1948); (b) Ritter and Kalish, *ibid.*, **70**, 4048 (1948); (c) Benson with Ritter, *ibid.*, **71**, 4128 (1949); (d) Hartzel with Ritter, *ibid.*, **71**, 4130 (1949).

[4] (a) Gabriel and Heymann, *Ber.*, **23**, 2493 (1890); (b) Elfeldt, *ibid.*, **24**, 3223 (1891); (c) Adams and Leffler, THIS JOURNAL, **59**, 2252 (1937).

TABLE I

N-(2-HALO-1-ETHYL)-AMIDES



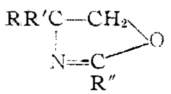
$R''CONH\underset{CH_2X}{C}RR'$ FROM $R''CN$ AND $RR'\underset{OH}{C}CH_2X$

| R | R′ | R″ | M. p., °C. | Yield, % | Formula | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|
| H– | $C_6H_5$– | $CH_3$– | 100[a] | 78 | $C_{10}H_{12}ONCl$ | 7.05 | 6.83 |
| $CH_3$– | $C_6H_5$– | $CH_3$– | 97.5[a] | 84 | $C_{11}H_{18}O_3NCl$[e] | 5.66 | 5.67 |
| H– | $C_6H_5$– | $CH_3$– | 84[a] | 92 | $C_{10}H_{12}ONBr$ | 5.79 | 5.74 |
| $CH_3$– | $CH_3$– | $CH_3$– | 200[b] | 55 | $C_6H_{12}ONCl$ | 9.37 | 9.57 |
| $CH_3$– | $CH_3$– | $C_6H_5$– | 130[c] | 40 | $C_{11}H_{14}ONCl$ | 6.63 | 6.64 |
| $CH_3$– | $CH_3$– | $C_2H_5OCOCH_2$– | 124[d] | 65 | $C_9H_{18}O_4NCl$[f] | 5.84 | 5.71 |
| H– | $CH_3$– | $C_6H_5CH_2$– | 99[b] | 40 | $C_{11}H_{14}ONCl$ | 6.63 | 6.65 |
| $CH_3$– | $CH_3$– | $C_6H_5CH_2$– | 98.5[a] | 74 | $C_{12}H_{16}ONCl$ | 6.20 | 6.02 |

[a] Cryst. from aq. acetone. [b] Cryst. from water. [c] Cryst. from hexane. [d] Cryst. from ethyl acetate. [e] Dihydrate. [f] Monohydrate. Calcd.: Cl, 14.82. Found: Cl, 14.67.

TABLE II

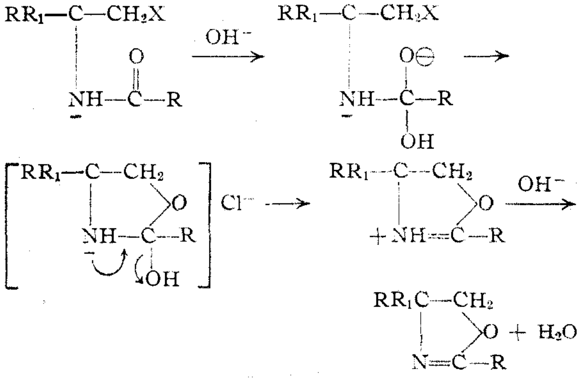
2-OXAZOLINES



| R | R′ | R″ | M. p., °C. | Formula | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|
| H– | $C_6H_5$– | $CH_3$– | 120 | $C_{10}H_{11}ON$ | 8.70 | 9.00 |
| $CH_3$– | $CH_3$– | $C_6H_5$– | 87.5[a] | $C_{11}H_{13}ON$ | 8.00 | 7.81 |
| $CH_3$– | $CH_3$– | $C_6H_5CH_2$– | 75 | $C_{12}H_{15}ON$ | 7.41 | 7.35 |
| $CH_3$– | $CH_3$– | $C_2H_5OCOCH_2$– | 101[b] | $C_9H_{15}O_3N$ | 7.57 | 7.42 |

[a] B. p. 105–110° (1 mm.). [b] B. p. 100–103° (5 mm.).

of reactivity. It had been demonstrated[5] that the stability of the chlorine in the neopentyl system was due to a steric effect. Amide is similar to methyl in size and it is suggested, therefore, that the reactivity of halide in the substituted amides must be due to an intramolecular, rather than intermolecular, displacement. The displacing agent would be keto oxygen, as



## Experimental

**N-(2-Halo-1-ethyl)-amides.**—To a solution of 0.3 mole of the nitrile in 70 g. of concd. sulfuric acid, 0.1 mole of the halohydrin or haloalkene was added in 30 min. at 35–40° with stirring. The viscous mixture was stirred for three hours at 35° and then poured into 300 g. of ice and water. After the addition of 20 g. of sodium carbonate (in portions) and ten minutes of additional stirring, the oily amide solidified and was collected by filtration. The product was washed with 10% sodium carbonate solution and purified by recrystallization.

**2-Oxazolines.**—One-tenth mole of the N-(2-halo-1-ethyl)-amide was mixed 90 sec. at 60–65° with 0.1 mole of potassium hydroxide in 200 cc. of ethanol. One gram of sodium bicarbonate was added and the solution filtered. After distilling the alcohol, the residual 2-oxazoline was crystallized from aqueous alcohol. The yields from the amides were 60–70%.

**Hydrolysis of the Chloro Amides.**—Five grams of the chloro amide and a solution of 3.5 g. of sodium carbonate in 75 cc. of water were allowed to stand twelve hours at room temperature and then refluxed one hour. The solution was extracted with three 25-cc. portions of ethyl acetate. After removal of the solvent the residue was distilled or recrystallized: N-(2-hydroxy-1-phenylethyl)-acetamide, m. p. 114–116° (from benzene–alcohol); yield, 90%; nitrogen, %, calcd., 7.82; found, 7.76; N-(1-hydroxy-2-methyl-2-propyl)-benzamide, b. p. 231–240°; yield, 55%; nitrogen, %, calcd., 7.26; found, 7.25.

**α-Acetaminophenylacetic Acid.**—Five-tenths of a gram of N-(2-hydroxy-1-phenylethyl)-acetamide was dissolved in 13 cc. of water containing 0.1 g. of sodium hydroxide. Over 15 min. 1.0 g. of potassium permanganate was added at 30–32°. After standing for 30 min. the solution was filtered and decolorized with 0.2 g. of sodium bisulfite. On acidification with hydrochloric acid and cooling in ice, 0.3 g. (55%) of α-acetaminophenylacetic acid separated. After recrystallization from water the melting point was 191.5–192.0° (reported,[6] 191°).

## Summary

N-(2-Halo-1-ethyl)-amides were prepared by the reaction of nitriles with halo alcohols or halo alkenes. Several of these amides were dehydrohalogenated to 2-oxazolines.

NEW YORK, N. Y. RECEIVED MARCH 22, 1950

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(5) (a) Bartlett and Cohen, THIS JOURNAL, **62**, 1183 (1940); (b) Bartlett and Rosen, *ibid.*, **64**, 543 (1942).

(6) Neubauer and Warburg, *Z. physiol. Chem.*, **70**, 5 (1911).