

*Anal.*<sup>23</sup> Calcd. for C<sub>4</sub>H<sub>4</sub>S<sub>2</sub>: C, 41.35; H, 3.47; S, 55.18. Found: C, 41.59, 41.63; H, 3.69, 3.71; S, 55.40.

2. **Dealkoxylation of VIb.**—VIb (17 g.), in absolute ethanol (17 ml.), was passed over alumina according to the procedure described for VIa above. There was obtained: (1) 3.76 g. (40%) of 1,4-dithiadene, b.p. 66° (10 mm.), *n*<sub>D</sub><sup>20</sup> 1.6285–1.6304; and (2) 3.58 g. (27.2%) of 2-ethoxy-1,4-dithiane-5, b.p. 68–72° (2 mm.), *n*<sub>D</sub><sup>25</sup> 1.5731. Fraction 1 had the pleasant odor of pure I.

*Anal.* of fraction 2. Calcd. for C<sub>6</sub>H<sub>10</sub>OS<sub>2</sub>: C, 44.41; H, 6.42. Found: C, 44.62; H, 6.21.

**Preparation of 1,4-Dithiadene Dioxide (X).**—A solution of 1.12 g. (9.65 mmoles) of I in 40 ml. of glacial acetic acid was cooled to 20° and 2.5 ml. of 30% hydrogen peroxide was added. The temperature was kept below 20° for 30 minutes. The solution was allowed to stand at room temperature for 20 hours, then concentrated to 5 ml. at reduced pressure. Water (50 ml.) was added and the solution was again concentrated to a small (2 ml.) volume. Benzene (50 ml.) was added and the last traces of water were removed by azeotropic distillation at atmospheric pressure. When about 25 ml. of benzene had been distilled, 10 ml. of petroleum ether (b.p. 60–68°) was added at the boiling point, and the solution was allowed to cool slowly. The solid, 615 mg. (m.p. 95–98°), was removed by filtration. The filtrate yielded an additional 240 mg. of crystalline material to bring the total yield to 60%. A sample of this product was sublimed at 0.6 mm. and 120° to give colorless stout rods, m.p. 99.0–100.0°.

*Anal.* Calcd. for C<sub>4</sub>H<sub>4</sub>S<sub>2</sub>O<sub>2</sub>: C, 32.42; H, 2.72. Found: C, 32.33; H, 2.93.

**Preparation of 1,4-Dithiadene Tetraoxide (XI).**—A 315-mg. sample of the dioxide (X), m.p. 95–98°, was refluxed for 1.5 hours in 15 ml. of glacial acetic acid containing 5 ml. of 30% hydrogen peroxide. The solution was allowed to stand overnight and 235 mg. (61%) of colorless crystalline disulfone (XI) was removed by filtration. A further 18 mg. (5%) of (XI) was obtained by concentration of the filtrate. The combined product was recrystallized from acetic acid (1 ml. for every 10 mg. of compound) to give colorless stout prisms, m.p. 241.5–242.5° (dec.) with darkening at 236° (capillary).

(23) The first analysis was performed by the Clark Laboratory, Urbana, Ill. All other analyses were performed by the Microanalytical Laboratory, University of Minnesota.

*Anal.* Calcd. for C<sub>4</sub>H<sub>4</sub>S<sub>2</sub>O<sub>4</sub>: C, 26.66; H, 2.44. Found: C, 26.77; H, 2.32.

A 44% yield of XI was obtained by allowing 1,4-dithiadene to stand for 1 hour at room temperature with 2 equivalents of hydrogen peroxide in acetic acid, followed by refluxing the solution for 1.5 hours with an additional 2.5 equivalents of hydrogen peroxide.

**Reduction of 1,4-Dithiadene Tetraoxide.** A.—A 95-mg. sample of XI was dissolved in 5 ml. of glacial acetic acid and 200 mg. of zinc dust was added carefully. The solution was refluxed for 1 hour and the solids were removed by filtration. These solids were washed with warm water to remove zinc salts and treated with 5 ml. of hot diluted (1:2) hydrochloric acid to remove excess zinc. The white solid remaining (57 mg., 59% yield) was recrystallized from 2 ml. of concentrated nitric acid to give 40 mg. of essentially pure 1,4-dithiane disulfone (XII). This material was obtained as a microcrystalline powder which did not melt below 370°, but decomposed slowly from 330 to 370°.

*Anal.* Calcd. for C<sub>4</sub>H<sub>8</sub>S<sub>2</sub>O<sub>4</sub>: C, 26.08; H, 4.38. Found: C, 26.11; H, 4.07.

B.—A mixture containing XI (108 mg.), glacial acetic acid (5 ml.), and prerduced platinum oxide (150 mg.) was stirred in an atmosphere of hydrogen for 20 hours at room temperature. A total of 32.5 ml. of hydrogen was absorbed (calculated for 2 equivalents 30.4 ml.). The mixture of catalyst and solid was removed by filtration and the catalyst was dissolved in hot nitric acid. The remaining solid was recrystallized from hot nitric acid to give 1,4-dithiane disulfone (dec. above 330°; identical X-ray powder diffraction pattern and infrared spectrum to authentic material).

Authentic 1,4-dithiane disulfone<sup>24</sup> was prepared by oxidation of 1,4-dithiane<sup>25</sup> with hydrogen peroxide. This product was purified by crystallization from concentrated nitric acid and showed the same melting characteristics as those reported for the reduction product of XI. The identity of this material to that obtained from 1,4-dithiadene was established by comparing the X-ray powder diffraction patterns<sup>14</sup> and the infrared spectra of the two samples.

(24) O. B. Helfrich and E. E. Reid, *THIS JOURNAL*, **42**, 1215 (1920).

(25) R. C. Fuson, R. D. Lipscomb, B. C. McKusick and I. J. Reed, *J. Org. Chem.*, **11**, 513 (1946).



MINNEAPOLIS, MINN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND LABORATORY FOR NUCLEAR SCIENCE AND ENGINEERING, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

## Rearrangements in the Reactions of 2-(4-Substituted)-phenylethylamines-1-C<sup>14</sup> with Nitrous Acid<sup>1,2</sup>

BY JOHN D. ROBERTS AND CLARE M. REGAN

RECEIVED SEPTEMBER 29, 1952

Treatment of a series of C<sup>14</sup>-labeled 2-(4-substituted)-phenylethylamines (X——CH<sub>2</sub>C<sup>14</sup>H<sub>2</sub>NH<sub>2</sub>) with nitrous acid in water and acetic acid has been found to yield more or less of the isotope-position rearrangement products (X——C<sup>14</sup>H<sub>2</sub>CH<sub>2</sub>Y; Y = —OH or —OAc) depending on the solvent and the nature of X. With X = —OCH<sub>3</sub>, —H and —NO<sub>2</sub>, the most rearrangement (45%) was observed in acetic acid with X = —OCH<sub>3</sub>, and the least (~5%) rearrangement when X = —NO<sub>2</sub> in water or acetic acid.

Considerable stereochemical<sup>3,4</sup> and kinetic<sup>4,5</sup> evidence has recently been accumulated for stabi-

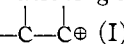
(1) Presented in part at the Symposium on Reaction Mechanisms at the 75th Anniversary Meeting of the American Chemical Society, September 7, 1951.

(2) Supported in part by the program of research of the U. S. Atomic Energy Commission.

(3) (a) D. J. Cram, *THIS JOURNAL*, **71**, 3863, 3883 (1949); (b) **74**, 2129 (1952).

(4) S. Winstein, M. Brown, K. C. Schreiber and A. H. Schlesinger, *ibid.*, **74**, 1140 (1952).

(5) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber and J. Corse, *ibid.*, **74**, 1113 (1952).

zation by the  $\pi$ -electron system of an aromatic ring of cationic intermediates of the type Ar— (I).

The stereochemical studies have led to the suggestion that symmetrical non-classical "phenonium" structures (II) are involved.<sup>3</sup> In the present research, the isotopic tracer technique<sup>6</sup> has been employed to detect rearrangements in the reactions

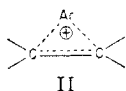
(6) (a) J. D. Roberts, R. E. McMahon, W. Bennett and E. W. Holroyd, Jr., *ibid.*, **74**, 4283 (1952); J. D. Roberts and J. A. Yancey, *ibid.*, **74**, 5943 (1952).

TABLE I  
 RADIOACTIVITY ANALYSES

Compound	Source	Measured activity, c./min. <sup>a</sup>	Corr. activity c./min./labeled C-atom <sup>b</sup>	Rearrangement, % <sup>c</sup>
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>3</sub> Cl	Redn. of C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> C <sup>14</sup> N	704 ± 4	1943 ± 12	0
C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> H	Oxdn. of C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>3</sub> Cl	1.3 ± 0.9	3.1 ± 2.2	
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> OCONHC <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>3</sub> Cl + HONO in H <sub>2</sub> O	377 ± 3	1951 ± 16 (1492 ± 15) <sup>d</sup>	
C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> H	Oxdn. of N-phenylcarbamate	224 ± 4	541 ± 7 (408 ± 4) <sup>d</sup>	(27 ± 1) <sup>i</sup>
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> OCONHC <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub> + HONO in CH <sub>3</sub> CO <sub>2</sub> H	363 ± 2	1881 ± 10 (1525 ± 31) <sup>d</sup>	24 ± 1
C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> H	Oxdn. of N-phenylcarbamate	188 ± 4	453 ± 10 (409 ± 3) <sup>d</sup>	(27 ± 1) <sup>i</sup>
4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>3</sub> Cl	Redn. of 4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> C <sup>14</sup> N	1806 ± 31	5612 ± 96	1.2 ± 0.2
4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	Oxdn. of 4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>3</sub> Cl	24 ± 1.4	65 ± 4	
4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH <sub>2</sub> OCONHC <sub>6</sub> H <sub>5</sub>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>3</sub> Cl + HONO in H <sub>2</sub> O	902 ± 8	4982 ± 42	33 ± 1
4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	Oxdn. of N-phenylcarbamate	589 ± 2	1627 ± 6	45 ± 2
4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH <sub>2</sub> OCONHC <sub>6</sub> H <sub>5</sub>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub> + HONO in CH <sub>3</sub> CO <sub>2</sub> H	822 ± 16	4541 ± 88	
4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H <sup>e</sup>	Oxdn. of N-phenylcarbamate	163 ± 4	2027 ± 46	
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>3</sub> Cl	Nitr. of C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> C <sup>14</sup> H <sub>2</sub> NH <sub>2</sub>	176 ± 3.5	486 ± 10	3.0 ± 0.8
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	Oxdn. of 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>3</sub> Cl	6 ± 1.6	15 ± 4	
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH <sub>2</sub> OCONHC <sub>6</sub> H <sub>5</sub> <sup>f</sup>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>3</sub> Cl + HONO in H <sub>2</sub> O	105 ± 2	559 ± 9	8 ± 1
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	Oxdn. of N-phenylcarbamate	18 ± 1	43 ± 3	(5 ± 2) <sup>g</sup>
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH <sub>2</sub> OCONHC <sub>6</sub> H <sub>5</sub>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub> + HONO in CH <sub>3</sub> CO <sub>2</sub> H	95 ± 2	492 ± 11	8 ± 2
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	Oxdn. of N-phenylcarbamate	17 ± 2	41 ± 5	(5 ± 3) <sup>g</sup>

<sup>a</sup> Measured activities of "infinitely thick" barium carbonate precipitates in counts/min. corrected for background with standard deviations. The samples were prepared as described by J. D. Roberts, W. Bennett, E. W. Holroyd, Jr., and C. H. Fugitt, *Anal. Chem.*, **20**, 904 (1948), and counted with a windowless methane-filled proportional counter ("Nucleometer"). <sup>b</sup> Calculated from the measured activities as described by J. D. Roberts, R. E. McMahon and J. S. Hine, *THIS JOURNAL*, **72**, 4237 (1950). <sup>c</sup> Percentage rearrangement obtained from activity of benzoic acid or derivative/activity of the corresponding phenylethyl compound. <sup>d</sup> Values in parentheses correspond to duplicate determination. <sup>e</sup> Counted as the anilide. <sup>f</sup> M.p. 129.8–130.2°. *Anal.* Calcd. for C<sub>16</sub>H<sub>17</sub>O<sub>3</sub>N: C, 70.83; H, 6.32. Found: C, 71.08; H, 6.44. <sup>g</sup> Values in parentheses corrected for apparent 3% rearrangement noted in the oxidation of the 4-nitrophenylethylamine-1-C<sup>14</sup>.

of some 2-(4-substituted)-phenylethylamines with nitrous acid. It was hoped to throw light on the



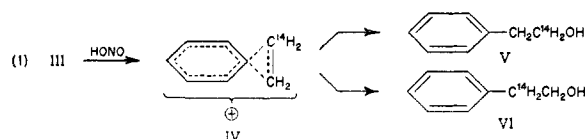
nature of the intermediates using reactants and reactions which are not very amenable to study by either stereochemical or kinetic approaches.

The procedure may be illustrated by a specific example. 2-Phenylethylamine-1-C<sup>14</sup> (III) was prepared by sodium in ethanol reduction of phenylacetonitrile-1-C<sup>14</sup> which was obtained from the reaction of benzyl chloride with sodium cyanide-C<sup>14</sup>.<sup>7</sup> Treatment of III with nitrous acid in water gave 2-phenylethanol which was converted to and purified as the N-phenylcarbamate. No appreciable amounts of 1-phenylethanol appeared to be present among the reaction products.<sup>8</sup> The C<sup>14</sup>-distribution in the ethyl group was determined by oxidation of the N-phenylcarbamate and comparison of the C<sup>14</sup>-contents of the N-phenylcarbamate and the resulting benzoic acid. The C<sup>14</sup>-

(7) Sodium cyanide-C<sup>14</sup> was obtained from Tracerlab, Inc., on allocation from the U. S. Atomic Energy Commission.

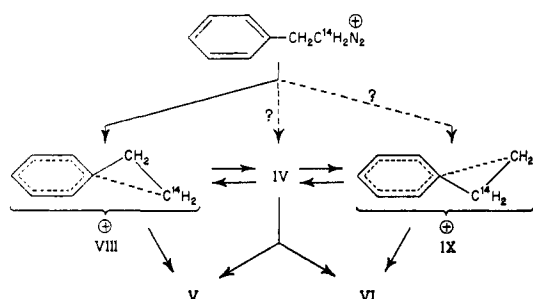
(8) Similar observations have been made by D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 838 (1934). It is interesting that 2-cyclohexylethylamine with nitrous acid gives considerable amounts of 1-cyclohexylethanol, O. Wallach, *Ann.*, **359**, 312 (1908).

analyses (Table I) indicate 73 and 27% of the original radioactivity to be at the 1- and 2-positions of the 2-phenylethanol, respectively. If all of the reaction proceeded by way of an intermediate such as IV, water would have equal probability of attacking C-1 and C-2 (neglecting the isotope effect) and the C<sup>14</sup> in the product would be equally distributed between C-1 and C-2. Since only 54% (27/50, × 100) of the possible rearrangement expected from IV was actually observed, it is clear that at least some 2-phenylethanol was formed by way of intermediates other than IV.



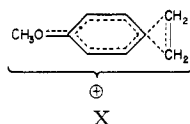
One possible interpretation of the results is that 54% of the reaction proceeded through IV and the balance involved a direct nucleophilic attack of water on the diazonium ion to yield unrearranged 2-phenylethanol. Alternatively, the diazonium ion VII could lose nitrogen to give more or less directly an unsymmetrical phenonium ion VIII<sup>4,5</sup> which would not have the plane of symmetry of IV and unless converted to IV or IX would be expected

to give only 2-phenylethyl-1-C<sup>14</sup> derivatives on reaction with solvent.



The observed rearrangement would result from more or less of VIII being converted to IV or IX depending on reaction conditions and substituent groups. It is possible that IV need not be an actual stable intermediate but simply a transition state through which VIII and IX are slowly interconverted. At present, no experimental evidence may be cited to show the true role of IV in these reactions.<sup>4,9</sup>

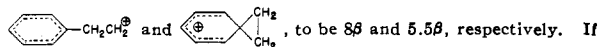
The results (Table I) with other substituent groups agree satisfactorily with the above formulations. With 4-methoxyl, IV should be stabilized by delocalization of the unshared electron pairs on oxygen (*cf.* X) and conversion of VII (or VIII) to IV (or IX) would be expected to take place more readily. In acetic acid, the lifetimes of the ions would be longer and the chances for interconversion



considerably improved, thus leading to greater percentage of rearrangement in this solvent. With the (4-nitrophenyl)-ethylamine, IV is expected to be unfavorable because of electron withdrawal by the nitro group and the amount of rearrangement is expected to be small irrespective of solvent.

It is notable that very little, if any, hydrogen migration to give 1-phenylethanol is observed in these reactions.<sup>8</sup> The fact seems significant in view of extensive hydrogen migration in the reactions of *n*-propyl-, *n*-butyl- and isobutylamines with nitrous acid<sup>10</sup> and because such migrations with a classical 2-phenylethyl cation analogous to I would yield a particularly stable benzyl-type cation as a reaction intermediate. The lack of hydrogen migration may indicate essentially direct

(9) In this connection, it is of interest that simple molecular orbital calculations indicate the  $\pi$ -electron energies of the extreme ions,

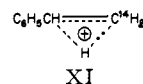


one counts C-C single-bond energies as 3 $\beta$  each and employs 1.5 $\beta$  for the strain energy of the three-membered ring, the total carbon-carbon binding energies for the two ions are 32 $\beta$  and 31 $\beta$ , respectively. These calculations thus favor the classical structure over the bridged structure since  $\beta$  is about -17 kcal. Extra electron delocalization

as symbolized in would be expected to stabilize each ion to an unknown further degree.

(10) A. Siersch, *Ann.*, **144**, 137 (1867); F. C. Whitmore and D. P. Langlois, *This Journal*, **54**, 3441 (1932); E. Linnemann, *Ann.*, **162**, 12 (1872).

formation of IV or VIII<sup>11</sup> by loss of nitrogen from the diazonium ion VII or else the cation XI resulting from hydrogen participation is converted almost exclusively to styrene rather than 1-phenylethanol-2-C<sup>14</sup>,



## Experimental

**2-Phenylethylamine-1-C<sup>14</sup>.**—Phenylacetonitrile-1-C<sup>14</sup> was prepared in 72% yield (based on sodium cyanide) from benzyl chloride and sodium cyanide-C<sup>14</sup>;<sup>7,12</sup> b.p. 100–101° (8.5 mm.).

The labeled phenylacetonitrile (12.1 g.) was dissolved in 100 ml. of absolute ethanol and 11 g. of sodium added rapidly. The solution was heated under reflux until the sodium completely dissolved (1.5 hours). Water (50 ml.) was added and the ethanol distilled. The basic residue was extracted thoroughly with ether, the extract was dried and on distillation there was obtained 4.1 g. (33%) of 2-phenylethylamine-1-C<sup>14</sup>, b.p. 72–75° (8 mm.). The hydrochloride had m.p. 219–219.6° after crystallization from an ether-absolute ethanol mixture.

**2-(4-Nitrophenyl)-ethylamine-1-C<sup>14</sup>.**—Nitration<sup>13</sup> of 2-phenylethylamine-1-C<sup>14</sup> gave a 39% yield of 2-(4-nitrophenyl)-ethylamine-1-C<sup>14</sup> which was isolated as the hydrochloride, m.p. 212–214°, after crystallization from an ether-absolute ethanol mixture.

**2-(4-Methoxyphenyl)-ethylamine-1-C<sup>14</sup>.**—A solution of 20 g. of freshly-prepared *p*-methoxybenzyl chloride in 100 ml. of acetone was mixed with 7 g. of sodium cyanide-C<sup>14</sup> dissolved in 10 ml. of water. The mixture was stirred and heated under reflux on a steam-cone for 9 hours and allowed to stand for 3 days. Water (300 ml.) was added and the whole was extracted with three 150-ml. portions of ether. The extract was washed with water to remove acetone, dried and distilled. The yield of (4-methoxyphenyl)-acetonitrile-1-C<sup>14</sup> was 13.9 g. (67% based on cyanide), b.p. 95.5–97.0° (0.7 mm.).

The nitrile (14 g.) was reduced with 9 g. of lithium aluminum hydride<sup>14</sup> and yielded 5 g. (35%) of 2-(4-methoxyphenyl)-ethylamine-1-C<sup>14</sup>, b.p. 78–82° (0.7 mm.). An additional 1.5 g. (8.5%) of the amine was isolated as crude hydrochloride from the distillation residue. The pure hydrochloride had m.p. 213.5–214.5° after crystallization from an ether-absolute ethanol mixture.

**Reactions of Amines with Nitrous Acid. A. In Water Solution.**—The amine hydrochloride (about 3.6 g.) was dissolved in water, the solution cooled to 0° and an excess (40%) of either sodium or silver nitrite added. When silver nitrite was employed, the silver chloride was removed by filtration before proceeding further. The reaction mixture was allowed to stand at room temperature for an hour and then heated under reflux for 2 hours. The mixture was cooled, acidified and extracted with ether. The extract was dried and the ether distilled. The residue was heated with an equal volume of phenyl isocyanate and the resulting *N*-phenylcarbamate recrystallized from chloroform-ligroin. The over-all yields ranged from 20–50%.

**B. In Acetic Acid Solution.**—About 4 g. of amine was dissolved in 25 ml. of glacial acetic acid and excess sodium nitrite added slowly. The mixture was allowed to stand at room temperature for 2 hours and if sodium acetate precipitated a few drops of water were added to keep the mixture homogeneous. The solution was poured into excess aqueous sodium hydroxide and extracted with ether. The ether was removed and the residual crude acetate hydrolyzed with hot sodium hydroxide solution. The acetate obtained from 2-(4-nitrophenyl)-ethylamine-1-C<sup>14</sup> was converted to the corresponding alcohol by ester interchange with methanol containing hydrogen chloride. The crude alcohols were

(11) Either IV or VIII should be sterically unfavorable for hydrogen migration since all of the hydrogens of the ethyl groups would tend to assume eclipsed configurations.

(12) "Organic Syntheses," John Wiley and Sons, Inc., Coll. Vol. I, New York, N. Y., 1948, p. 107.

(13) F. Ehrlich and P. Pitschmuka, *Ber.*, **45**, 2431 (1912).

(14) L. H. Amundsen and L. S. Nelson, *This Journal*, **73**, 242 (1951).

converted to the N-phenylcarbamates as described above.

**Degradation Procedures.**—The amines and N-phenylcarbamates were oxidized to the corresponding benzoic acids by conventional procedures.<sup>15</sup> Alkaline permanganate

(15) R. L. Shriner and R. C. Fuson, "Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 198.

was employed for the unsubstituted and 4-methoxy compounds while chromic acid oxidation was necessary for the 4-nitro derivatives. In some experiments, the 4-methoxybenzoic acid appeared to be contaminated with 4-hydroxybenzoic acid and the material was converted to and purified as the anilide.

CAMBRIDGE 39, MASSACHUSETTS

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY OF MICHIGAN STATE COLLEGE]

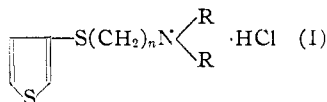
## The Preparation and Properties of Some $\omega$ -(N,N-Dialkylamino) Alkyl-3-thienyl Sulfide Hydrochlorides<sup>1</sup>

BY WM. H. HOUFF<sup>2</sup> AND ROBERT D. SCHUETZ

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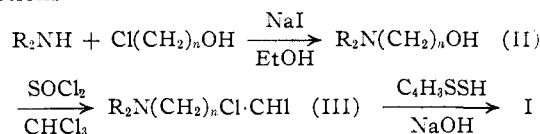
The synthesis and properties of a series of  $\omega$ -(N,N-dialkylamino) alkyl-3-thienyl sulfide hydrochlorides, and the intermediates involved, are described.

Several  $\omega$ -(N,N-dialkylamino) alkyl-3-thienyl sulfide hydrochlorides were prepared as a consequence



of the observation<sup>3</sup> that some analogous phenyl compounds showed local anesthetic activity comparable with that of procaine.

The aminoalkyl-3-thienyl sulfides of the present investigation were prepared by the sequence of reactions



The N-( $\omega$ -hydroxyalkyl) amines II, where the amine was piperidine or morpholine and the alkyl chain contained two to five carbon atoms, including a branched alkyl chain of three carbon atoms, were prepared by the reaction of a two-molar excess of the secondary amine with the corresponding chlorohydrin in dry ethanol, following the procedure employed by Clinton, *et al.*<sup>4</sup>

The N-( $\omega$ -chloroalkyl)-amine hydrochlorides (III) were obtained from the corresponding N-( $\omega$ -hydroxyalkyl)-amines by an adaptation of the method, described by Mason and Block,<sup>6</sup> employing thionyl chloride and dry chloroform as a solvent.

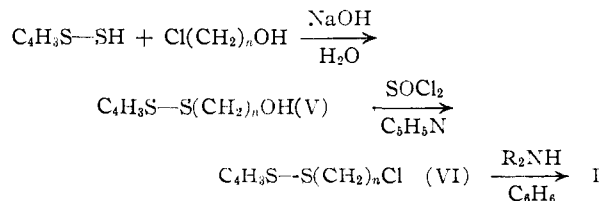
One of the N-( $\omega$ -chloroalkyl)-amines, namely,  $\gamma$ -morpholine-*n*-propyl chloride, was prepared in a single step reaction by the method of Adams and Whitmore,<sup>6</sup> which involved the reaction of a two-mole excess of morpholine with trimethylene chlorobromide in dry benzene. An attempt was made to

adapt this shorter procedure for preparing N-( $\omega$ -chloroalkyl)-amines to the use of ethylene and propylene chlorobromide, but was unsuccessful due to the formation of a quaternary ammonium salt which may have been an ethylimmonium halide.

The properties of five N-( $\omega$ -chloroalkyl)-amine hydrochlorides which have not previously been reported are listed in Table I.

The  $\omega$ -(N,N-dialkylamino) alkyl-3-thienyl sulfides were obtained, in yields of 77 to 93%, from the N-( $\omega$ -chloroalkyl)-amine hydrochlorides by interaction with a slight excess of 3-thiophenethiol dissolved in aqueous sodium hydroxide. The tertiary amines were converted to their hydrochloride salts and isolated and characterized as such. Altogether, ten new  $\omega$ -(N,N-dialkylamino) alkyl-3-thienyl sulfide hydrochlorides, were prepared and some of their properties are summarized in Table II.

A second general method of synthesis for the preparation of the  $\omega$ -(N,N-dialkylamino) alkyl-3-thienyl sulfide hydrochlorides was studied with the aim of obtaining better yields and permitting the preparation of more than one type of final compound from the intermediates. This method may be represented by the series of reactions



Three new  $\omega$ -hydroxyalkyl-3-thienyl sulfides (V) were readily prepared by the interaction of the corresponding chlorohydrin and 3-thiophenethiol dissolved in aqueous sodium hydroxide. Brooks in some unpublished work<sup>7</sup> reported, without experimental details, the preparation of  $\beta$ -hydroxyethyl-3-thienyl sulfide from ethylene chlorohydrin and 3-thiophenethiol, giving only the boiling point of the material. A few of the properties of these compounds are summarized in Table III.

(7) H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p. 429.

(1) Presented before the Division of Medicinal Chemistry of The American Chemical Society at Atlantic City, N. J., on September 15, 1952.

(2) Abstracted in part from the M.S. Thesis, Michigan State College, of Wm. H. Houff, 1952.

(3) M. H. Kim and R. D. Schuetz, THIS JOURNAL, **74**, 5102 (1952).

(4) R. O. Clinton, U. S. Salvador and S. C. Laskowski, *ibid.*, **71**, 3366 (1949).

(5) J. P. Mason and H. W. Block, *ibid.*, **66**, 1443 (1940).

(6) R. R. Adams and F. C. Whitmore, *ibid.*, **67**, 735 (1945).