Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.98; H, 7.50.

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AUSTIN, TEXAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

The Formation of 4-Chlorodibutylamine from N-Chlorodibutylamine[1]

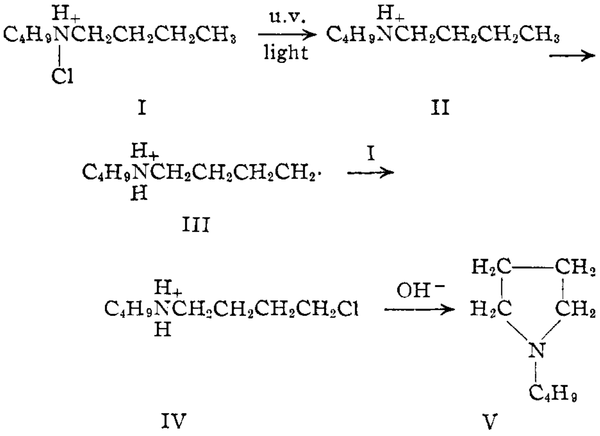
BY S. WAWZONEK AND T. P. CULBERTSON[2]

RECEIVED DECEMBER 8, 1958

4-Chlorodibutylamine has been isolated as the hydrochloride from the irradiation of N-chlorodibutylamine in sulfuric acid. The structure was demonstrated by synthesis from 4-phenoxybutyronitrile and by the conversion of the salt to N-butylpyrrolidine with alkali and to N-nitroso-4-chlorodibutylamine with sodium nitrite. Lithium aluminum hydride reduction of the nitroso compound gave mainly 1,1-dibutylhydrazine and N-nitrosodibutylamine. Trifluoroacetic acid can be substituted for the sulfuric acid as a solvent in this reaction but gives poorer yields.

Secondary aliphatic amines can be converted into nitrogen-containing heterocyclic compounds by heating[3] or irradiating[4] the N-bromo or N-chloro derivatives in sulfuric acid and treating the resulting solutions with alkali.

The mechanism proposed from observations made on the irradiation of N-bromo-4-ethylpiperidine,[4b] if applied to the irradiation of N-chlorodibutylamine, would postulate the formation of a 4-chlorodibutylamine (IV) salt as an intermediate; cyclization to N-butylpyrrolidine (V) would occur after treatment with alkali. This intermediate has now been isolated as the hydrochloride IV after partial neutralization of the sulfuric acid with sodium bicarbonate and removal of the sulfate with barium chloride.[5] Its structure was demonstrated by synthesis and its reactions.



I II III IV V

The hydrochloride IV was prepared from 4-phenoxybutyronitrile in the manner shown

$$C_6H_5O(CH_2)_3CN \xrightarrow[C_2H_5OH]{Na} C_6H_5O(CH_2)_4NH_2 \xrightarrow{CH_3(CH_2)_2COCl}$$

$$C_6H_5O(CH_2)_4NHCOCH_2CH_2CH_3 \xrightarrow{LiAlH_4}$$

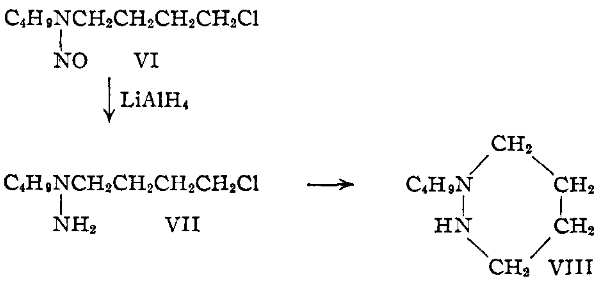
$$C_6H_5O(CH_2)_3NH(CH_2)_3CH_3 \xrightarrow[180°]{HCl}$$

$$ClCH_2CH_2CH_2CH_2\overset{+}{N}H_2C_4H_9\ Cl^-$$

The two samples had the same melting point and identical infrared spectra.

The 4-chlorodibutylamine hydrochloride (IV) in its reactions behaved as expected. It was converted by cold alkali into N-butylpyrrolidine (V) in a 64% yield. The yield of pyrrolidine obtained by irradiation without isolation of the intermediate ran as high as 78%. It also could be nitrosated to N-nitroso-4-chlorodibutylamine. This compound, which could also be obtained from the sulfuric acid solution after partial neutralization with potassium carbonate and treatment with sodium nitrite, distilled with some decomposition and could not be obtained pure. The corresponding N-nitroso-N-methyl-4-chlorobutylamine, which was prepared from the irradiated solution of the corresponding N-chloroamine, boiled at a lower temperature and gave a correct analysis.

In order to obtain a more stable derivative, the reduction of N-nitroso-4-chlorodibutylamine (VI) with lithium aluminum hydride to the corresponding hydrazine VII was investigated. This hydrazine VII under the conditions of the reduction would be expected to cyclize to N-butylpiperidazine (VIII). The reaction when carried out gave 1,1-dibutylhydrazine, N-nitrosodibutylamine and a small fraction which formed an oxalate that was



VI VII VIII

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[1] Abstracted in part from the Ph.D. Thesis of T. P. Culbertson, February, 1959.

[2] Ethyl Corporation Fellow, 1957–1958.

[3] (a) G. H. Coleman and G. E. Goheen, THIS JOURNAL, **60**, 730 (1938); (b) G. H. Coleman, G. Nichols and T. F. Martens, *Org. Syntheses*, **25**, 14 (1945).

[4] (a) S. Wawzonek and P. J. Thelen, THIS JOURNAL, **72**, 2118 (1950); (b) S. Wawzonek, M. F. Nelson, Jr., and P. J. Thelen, *ibid.*, **73**, 2806 (1951).

[5] A similar intermediate has been isolated in the irradiation of 20-N-chloro-3-β-dimethylamino-20-α-methylaminoallopregnane; E. J. Corey and W. R. Hertler, *ibid.*, **80**, 2903 (1958).

different from 1,1-dibutylhydrazine hydrogen oxalate. The elementary analysis pointed to N-butylpiperidazine hydrogen oxalate. The amount obtained was too small to investigate further. The results obtained indicate that the reduction of an alkyl chloride proceeds more readily than that of the N-nitrosoamino group.

Studies were also made on facilitating the isolation of the chloroalkylamine and found that the use of 1.5 molal solutions of the N-chloramine gave better yields of the pyrrolidine than the 0.3 molal solutions cutomarily used and reduced the amount of sulfuric acid that had to be removed.

Substitution of the more volatile trifluoroacetic acid as a solvent in place of the sulfuric acid gave a 42.6% yield of N-butylpyrrolidine and 31% of dibutylamine after treatment with alkali. Evaporation of the trifluoroacetic acid followed by distillation gave N,N-dibutyltrifluoroacetamide and tars as products.

Experimental[6]

N-Butylpyrrolidine. a. 85% Sulfuric Acid.—Dibutylamine (16.1 g.) was converted into the N-chloro derivative by the method of Coleman.[3b] Extraction from the petroleum ether solution with 85% sulfuric acid (50 ml.) was followed by irradiation in a quartz flask with an ultraviolet lamp at 20° for 48 hours. The irradiated sulfuric acid solution was poured onto an equal weight of crushed ice. Concentrated sodium hydroxide solution was added with vigorous stirring until the solution was strongly alkaline while keeping the temperature at 20°. The amines were steam distilled into excess hydrochloric acid and the resulting distillate, after concentration to 100 ml., was made alkaline. A Hinsberg separation gave N,N-dibutylbenzenesulfonamide (1.44 g., 4%) and N-butylpyrrolidine which was isolated as the picrate (17.2 g., 78.5%). The irradiation of the N-chloro derivative from 6.2 g. of amine in 100 ml. of 85% sulfuric acid for 24 hours gave a 59% yield of N-butylpyrrolidine and 11.7% yield of dibutylamine.

b. F_3CCOOH.—Dibutylamine (6.3 g.) was converted into the N-bromo derivative by the method used previously[4b] using pentane as a solvent. Removal of the pentane was followed by addition of the bromoamine dropwise to trifluoroacetic acid (40 ml.) at 0–5°. The resulting red solution was irradiated for 24 hours at 25°, poured onto ice, and treated in a similar manner to that used for the sulfuric acid solution. In this manner 4.1 g. of N,N-dibutylbenzenesulfonamide and 7.5 g. of N-butylpyrrolidine picrate were obtained.

N,N-Dibutyltrifluoroacetamide.—A solution of the N-bromoamine from 5.2 g. of dibutylamine in a mixture of trifluoroacetic acid (26.8 g.) and water (1.5 g.) was irradiated for 20 hours at 25°. The resulting solution was evaporated under reduced pressure at 100° and gave an oil which was poured into water. Extraction with ether gave an oil (7.5 g.) which distilled at 180° (2 mm.) and solidified. Considerable tar remained in the flask. Recrystallization several times from heptane gave a white solid melting at 137–138°. This compound could also be obtained by heating equal amounts of trifluoroacetic anhydride and dibutylamine.

Anal. Calcd. for $C_{10}H_{18}ONF_3 \cdot H_2O$: C, 49.38; H, 8.29. Found: C, 48.88; H, 8.15.

4-Chlorodibutylamine Hydrochloride.—N-Chlorodibutylamine was prepared in the usual manner from dibutylamine (64.5 g.) and extracted into pentane. The pentane solution was shaken with cold 85% sulfuric acid (200 ml.) and the pentane removed under reduced pressure. The sulfuric acid was irradiated for 48 hours at 25° and then diluted to 500 ml. with ice and water. After removal of unreacted chloramine with hexane a 150-ml. portion was treated slowly with dry sodium bicarbonate (110 g.). The resulting solution was filtered from the sodium sulfate which crystallized and then was treated with an aqueous solution containing barium chloride (37 g.). The barium sulfate was removed by filtration and the resultant solution was evaporated to dryness at 100° under reduced pressure using a water aspirator. The last traces of water were removed by azeotroping with benzene. The resulting hydrochloride was recrystallized from acetone three times and gave waxy plates melting at 211–212° with slight decomposition; yield 11.22 g. (37.4%).

Anal. Calcd. for $C_8H_{19}NCl_2$: C, 48.00; H, 9.57. Found: C, 48.59; H, 9.22.

Synthesis of 4-Chlorodibutylamine Hydrochloride. a. 4-Phenoxybutylamine was prepared from 4-phenoxybutyronitrile by the directions of Gabriel[7] and is a colorless liquid boiling at 80–81° (1 mm.), n^{23}D 1.5244, d^{20}_4 1.006. The picrate was recrystallized from ethanol and melted at 163–164°. The literature reports a value of 159.5°.[8] No analysis, however, was reported.

Anal. Calcd. for $C_{16}H_{18}O_8N_4$: C, 48.73; H, 4.60. Found: C, 48.58; H, 5.10.

b. N-(4-Phenoxybutyl)-butyramide.—A solution of 4-phenoxybutylamine (10 g.) and triethylamine (6.1 g.) in absolute ether (50 ml.) was treated dropwise at 0° with butyryl chloride (7.00 g.) in absolute ether (25 ml.). The addition required 30 minutes. The resulting mixture was allowed to come to room temperature and to stand overnight. The triethylamine hydrochloride was filtered and the filtrate concentrated until the N-(4-phenoxybutyl)-butyramide crystallized; yield 12.0 g. Recrystallization from a mixture of petroleum ether (60–70°) and either benzene or ether gave colorless flakes, m.p. 52–53°.

Anal. Calcd. for $C_{14}H_{21}O_2N$: C, 71.45; H, 9.02. Found: C, 71.02; H, 8.99.

c. 4-Phenoxydibutylamine.—A solution of N-(4-phenoxybutyl)-butyramide (10 g.) in absolute ether was added dropwise to a well stirred slurry of lithium aluminum hydride (1.62 g.) in absolute ether (75 ml.) and the mixture was refluxed for 16 hours. Decomposition with water was followed by extraction of the ether solution with four 50-ml. portions of 1.2 *N* hydrochloric acid. The acid solution upon neutralization with base gave 4-phenoxydibutylamine which was purified by distillation at 115–118° (1.5 mm.), yield 5.00 g., n^{20}D 1.5018, d^{20}_4 0.950. N-(4-Phenoxybutyl)-butyramide was recovered to the extent of 1.6 g.

Anal. Calcd. for $C_{14}H_{23}ON$: C, 75.97; H, 10.50. Found: C, 75.68; H, 10.48.

d. 4-Chlorodibutylamine Hydrochloride.—4-Phenoxydibutylamine (4.5 g.) was heated with concentrated hydrochloric acid (30 ml.) in a sealed tube at 160–210° for 7 hours. The phenol formed was removed with ether and the aqueous solution was evaporated to dryness under reduced pressure. The solid obtained was recrystallized from acetone and gave white plates melting at 211–213°, yield 1.0 g. A mixture with the sample obtained by the irradiation of the N-chloroamine melted at 211–213°. The literature reports a melting point of 226–229° for this compound.[9] The infrared spectra for the two compounds were identical.

Reactions of 4-Chlorodibutylamine Hydrochloride. a. Formation of N-Butylpyrrolidine.—4-Chlorodibutylamine hydrochloride (3.0 g.) in water (10 ml.) was made alkaline with sodium hydroxide. Extraction with two 25-ml. portions of ether was followed by the addition of a saturated solution of picric acid in absolute ethanol until acid to litmus. The N-butylpyrrolidine picrate (3.7 g.) obtained melted at 125–126°.

b. Formation of N-Nitroso-4-chlorodibutylamine.—A concentrated solution of sodium nitrite (3.75 g.) was added slowly with stirring to 4-chlorodibutylamine hydrochloride (9.65 g.) in water (50 ml.). The mixture was stirred at 100° for 30 minutes and at room temperature for an additional 30 minutes. The solution was saturated with potassium carbonate and extracted with ether. Distillation gave 5.5 g. of a yellow liquid boiling at 94° (0.04 mm.). Considerable tarring occurred during the distillation. A center cut had n^{20}D 1.4734, d^{20}_4 1.042. The compound apparently contained dissolved hydrogen chloride since an aqueous solution was acidic. The analysis was not satisfactory.

Anal. Calcd. for $C_8H_{17}N_2OCl$: C, 49.86; H, 8.89; Cl, 18.44. Found: C, 46.31; H, 8.18; Cl, 19.00.

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(6) Melting points are corrected; boiling points are not corrected.

(7) A. Gabriel, *Ber.*, **24**, 3231 (1891).

(8) H. W. Dudley and W. B. Thorpe, *Biochem. J.*, **19**, 846 (1925).

(9) E. Wilson and M. Tishler, This Journal, **73**, 3635 (1951).

N-Nitroso-4-chlorodibutylamine.—N-Chlorodibutylamine prepared from dibutylamine (64.5 g.) by the usual procedure was irradiated in 85% sulfuric acid (200 ml.) for 36 hours at 25°. The resulting brown solution was diluted to 500 ml. with ice and water and extracted with ether to remove the color. A concentrated solution of potassium bicarbonate (500 g.) was added slowly followed by a concentrated solution of sodium nitrite (70 g.). The resulting mixture was heated at 100° for 30 minutes, cooled, and extracted with ether. The yellow oil (60.0 g.) obtained distilled at 88° (0.017 mm.) with some decomposition; n^{20}_D 1.4733, d^{20}_4 1.042.

N-Nitroso-N-methyl-4-chlorobutylamine.—N-Chloro-N-methylbutylamine was prepared in the usual way from methylbutylamine (43.6 g.) and irradiated in 85% sulfuric acid (150 ml.) at 10° for 42 hours. The solution when treated as above for the N-nitroso-4-chlorodibutylamine gave 7.52 g. of a yellow liquid boiling at 78° (1.5 mm.). Considerable tar was formed during the distillation.

Anal. Calcd. for $C_5H_{11}ON_2Cl$: C, 39.87; H, 7.36. Found: C, 39.65; H, 6.91.

Lithium Aluminum Hydride Reduction of N-Nitroso-4-chlorodibutylamine.—A solution of freshly distilled N-nitroso-4-chlorodibutylamine (58 g.) in absolute ether (100 ml.) was treated slowly with a slurry of lithium aluminum hydride (12.5 g.) in absolute ether (200 ml.) over a period of 2.5 hours. The resulting mixture was allowed to stand overnight and decomposed with water. Removal of the ether gave an oil which on distillation gave three fractions.

The first fraction (5.1 g.) distilled at 68–94° (29 mm.) and on refractionation gave a product (3.00 g.) boiling at 68–76° (29 mm.). This product, N-butylpiperidazine, gave a positive Fehling test, contained no chlorine and gave an acid oxalate, when mixed with an equimolar amount of oxalic acid dihydrate in absolute ethanol, which melted at 220–220.5°.

Anal. Calcd. for $C_{10}H_{20}O_4N_2$: C, 51.71; H, 8.68. Found: C, 50.63; H, 8.68.

The second fraction distilled at 94–106° (29 mm.). Redistillation gave a liquid (5 g.) boiling at 62–65° (10 mm.), d^{20}_4 0.808. 1,1-Dibutylhydrazine is reported to boil at 60–62° (11 mm.), d^{20}_4 0.8029.[10] The oxalate had a melting point of 166–168° after several recrystallizations from ethanol. This compound did not depress the melting point (168–169°) of an authentic sample of 1,1-dibutylhydrazine hydrogen oxalate.[11]

The third fraction, b.p. 110–142° (29 mm.), gave on redistillation a liquid (17.46 g.) boiling at 124–126° (21 mm.), n^{20}_D 1.4485, d^{20}_4 0.900. Similar properties are reported for N-nitrosodibutylamine.[12]

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[10] A. I. Vogel, W. T. Cressell, G. H. Jeffrey and J. Leichester, *J. Chem. Soc.*, 514 (1952).

[11] R. A. Rowe and L. F. Audrieth, THIS JOURNAL, **78**, 563 (1956).

[12] A. I. Vogel, *J. Chem. Soc.*, 1849 (1948).

IOWA CITY, IOWA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, TULANE UNIVERSITY]

Acid-catalyzed Reactions between Carbonyl Compounds and Organic Azides. III. Aromatic Ketones[1]

BY J. H. BOYER AND L. R. MORGAN, JR.

RECEIVED DECEMBER 19, 1958

Aromatic ketones of the type $C_6H_5COCH_2R$ in an inert solvent containing concentrated sulfuric acid are transformed by certain alkyl azides into benzaldehyde and an aldehyde corresponding to the alkyl group (RCH_2). The best yields (70–85%) of benzaldehyde are obtained from acetophenone. Alkyl azides are reduced to corresponding primary amines in 50–65% yields. A probable explanation requires (1) a Lewis acid–base reaction between the ketone conjugate acid and an alkyl azide, (2) dehydration and elimination of nitrogen and (3) recombination with water followed by proton elimination and breakdown of a proposed intermediate adduct of an α-ketoalcohol and a primary amine. The last step (3) apparently occurs only after dilution with water and is supported by the acid-catalyzed breakdown of phenacyl alcohol into benzaldehyde and formaldehyde.

The first acid-catalyzed reaction between organic azides and the carbonyl function was realized in the transformation of aromatic aldehydes into amides or their derivatives.[2–4] In a recent communication a one-step transformation of acetophenone into benzaldehyde using alkyl azides in the presence of sulfuric acid was announced.[5] A study of this new transformation as well as similar investigations on propiophenone, isobutyrophenone, benzophenone, desoxybenzoin *p*-nitrobenzyl phenyl ketone, *m*-nitroacetophenone, *p*-hydroxyacetophenone and *o*-acetylbenzoic acid is described here.

Benzaldehyde, in 70–85% yield, is obtained from acetophenone in combination with each of four alkyl azides but not with phenyl, benzyl, β-phenylethyl or γ-phenylpropyl azides. With the latter four, other acid-catalyzed transformations occur. The reaction may be carried out using sulfuric acid as a catalyst in either benzene or nitrobenzene at 70–75°. The methyl group of acetophenone is transformed into formaldehyde, isolated in 80–86% yield as its bis-methone condensation, and the alkyl azide is reduced to the corresponding primary amine in 50–65% yield. These data describe an acid-catalyzed oxidation–reduction reaction with no over-all molecular rearrangement.

In a similar manner propiophenone is transformed into benzaldehyde (62%) and acetaldehyde (50%). The higher and very critical temperature of 90–91° is required. Below and above this temperature propiophenone has been quantitatively recovered. Tar formation increases with temperature and apparently results from azide decomposition. Isobutyrophenone is not transformed into benzaldehyde using *n*-butyl azide and sulfuric acid in either benzene or nitrobenzene at temperatures ranging from 75 to 115°. In all cases isobutyrophenone may be recovered, and at the higher temperatures there is considerable tar formation. Similar results are obtained from the combination

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[1] Financial assistance under a National Institutes of Health Grant No. H-2295 and contracts Nos. DA-01-009-ORD-428 and DA-01-009-ORD-699 with Office of Ordnance Research is gratefully acknowledged.

[2] J. H. Boyer and J. Hamer, THIS JOURNAL, **77**, 951 (1955), Part I.

[3] J. H. Boyer and L. R. Morgan, Jr., *J. Org. Chem.*, **24**, in press (1959), Part II.

[4] Earlier attempts to realize a similar reaction between methyl azide and either benzoic acid (L. H. Briggs, G. G. De Ath and S. R. Ellis, *J. Chem. Soc.*, **61**, (1942)) or acetophenone (P. A. S. Smith, THIS JOURNAL, **70**, 320 (1948)) were unsuccessful.

[5] J. H. Boyer and L. R. Morgan, Jr., *ibid.*, **80**, 2020 (1958).