When the decomposition was carried out at 50° none of the peroxides formed at room temperature were present in the residue. However, a paper chromatogram of the residue showed the presence of acetic and propionic acids as compared with control chromatograms of these acids.

1,1,4,4,7,7-Hexaethyl-1,4,7-cyclononatriperoxane (I).—The solvent from the mother liquors, after most of peroxides IV and VI had been separated, was removed in vacuum and the viscous residue dissolved in methyl alcohol and cooled to −70°. A white solid separated out which was recrystallized several times from methyl alcohol; m.p. 58–59°. This peroxide fails to react with potassium iodide in glacial acetic acid. However, it gives normal active oxygen values with hydrogen iodide in glacial acetic acid. A paper chromatogram using hydrogen iodide–glacial acetic acid as the spraying agent gave a single spot with an R_f of 0.91.

Anal. Calcd. for $C_{15}H_{30}O_6$: C, 58.78; H, 9.87; (O), 15.67; mol. wt., 306. Found: C, 58.52; H, 9.87; (O), 15.20; mol. wt., 302 (in exaltone).

The infrared spectrum 10% in chloroform showed the following bands in cm.$^{-1}$: 3000(7.5); 2920(4.5); 1460(7.5); 1445(6); 1375(3); 1345(4.5); 1335(4.5); 1280(5); 1210–1250(5); 1165(8); 1140(8); 1070(3.5); 1050(3.5); 1020 (3.5); 980(8.5); 960(6.5); 930(7.5).

1,1,4,4,7,7,10,10-Octaethyl-1,4,7-triperoxy-1,10-dihydroperoxide (II).—After most of peroxides I, IV and VI had been removed from the original mixture by standard procedures, it was not found possible to separate any other peroxides in the pure form, yet the final mother liquors, after most of peroxide I had been removed, still contained, according to our paper chromatographic analysis, all of the original six peroxides but I, IV and VI to a much lesser degree.

After much experimentation with cellulose powder chromatographic columns, we have found the following procedure satisfactory for the separation of all peroxides present in the final mother liquors. The solvent from these liquors was removed in vacuum and the residue dissolved in pentane (1:1). A column was prepared as follows: Cellulose powder (300 g., Whatman standard grade) was impregnated with 100 g. of dimethyl formamide in 600 cc. of ethyl ether. The ether was then evaporated at 50° and the impregnated cellulose washed once with pentane saturated with dimethylformamide. The cellulose was then pressed into a column (1.6 × 40 cm.) by pounding with a thick glass rod flattened and flanged at the bottom. The cellulose was held down by a heavy weight of mercury or lead sealed into a glass tube. Before fixing the peroxides on the column the cellulose was washed once again with pentane saturated with dimethylformamide. The peroxide mixture in pentane was then dropped on the top of the column and pentane saturated with dimethylformamide passed through the column at the rate of 3.2–3.3 cc. per min. Ten-cc. fractions were collected and examined by paper chromatography. The first few fractions contained peroxide I. After this, peroxide II began to come out. Thirty-two 10-cc. fractions which contained this peroxide were combined and concentrated in vacuum to about 30 cc. which was washed several times with water to remove the dimethylformamide, dried and the solvent removed in vacuum. A semi-solid separated out which was recrystallized at low temperatures and the crystals subjected to a vacuum over phosphorus pentoxide; m.p. 69–70°. This peroxide gave a single spot on the paper with an R_f of 0.86.

Anal. Calcd. for $C_{20}H_{42}O_{10}$: C, 54.29; H, 9.59; (O), 18.10; mol. wt., 442.5. Found: C, 54.45; H, 9.65; (O), 18.44; mol. wt., 461 (in exaltone).

The infrared spectrum 10% in chloroform showed the following bands in cm.$^{-1}$: 3480(6.5); 3000(7.5); 2920(4.5); 1465(7); 1450(6.5); 1380(5.5); 1350(5.5); 1275(4.5); 1210–1235(5); 1155(6.5); 1130(7); 1070(3.5); 1045(4); 1015(3); 960–975(6.5); 905–920(8); 865(4).

1,1,4,4,7,7-Hexaethyl-1,4-diperoxy-1,7-dihydroperoxide (III).—From several chromatographic separations, fractions which were collected immediately after those containing peroxide II and which showed a single spot on the paper chromatogram with an R_f 0.70 were combined, the dimethylformamide washed away as before and the pentane solution dried and the solvent removed in vacuum. A small amount of peroxide was obtained which could not be crystallized.

Anal. Calcd. for $C_{15}H_{32}O_8$: (O), 18.82. Found: (O), 19.00.

Following the removal of peroxide III from the column, fractions containing only peroxide IV were collected as shown by paper chromatograms containing single spots corresponding to R_f 0.53. Since this peroxide was obtained by other methods no attempt was made to isolate it from these fractions.

The quantities of peroxide V were so small that it was not possible to isolate it by this procedure. Peroxide VI was the last to come out from the chromatographic column and since this too was obtained by other means no attempt was made to isolate it from the column.

Acknowledgment.—The authors are indebted to Dr. Belič for the paper chromatographic analyses and for valuable discussion, to Dr. Nagy for all the combustion analyses, to Dr. Nelson and associates for the infrared spectra and to Lucidol Division of Wallace and Tiernan, Inc., for the financial support of this investigation.

Cambridge 39, Mass.

[Contribution from the Department of Chemistry, The University of Texas]

Reaction of Phenolic Mannich Base Methiodides and Oxides with Various Nucleophiles

By Pete D. Gardner, Hossein Sarrafizadeh Rafsanjani and Leon Rand

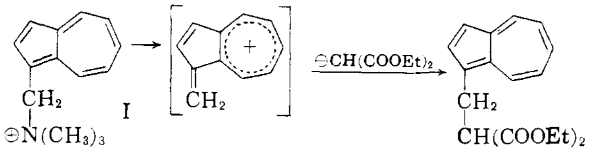
Received November 26, 1958

Several Mannich base methiodides and oxides derived from phenols have been shown to undergo reaction with OCH_3^-, CN^-, $(EtOOC)_2CH^-$ and H^- in basic media to give products derived from displacement of the nitrogen atom by the nucleophile. The ease with which reaction occurs is rationalized on the basis of electron release by the oxygen atom of the initially formed substituted phenoxide ion.

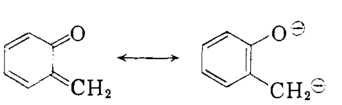
The displacement of tertiary and quaternary nitrogen atoms by nucleophilic reagents is a rather well known reaction.[1] Many substituted benzylamine derivatives, for example, have been induced to undergo reaction either as the amine or as the quaternary salt with such nucleophiles as cyanide ion, alkoxide and phenoxide ions, acetate ion and malonate ion. An inspection of reported yields and reaction conditions used reveals that, although the reaction is very general and useful synthetically, it proceeds with ease in relatively few systems. These examples are conspicuous in the ability of the alkylating moiety to sustain positive charge thus indicating that the reaction is facilitated by electron release to the carbon atom

[1] For a good review of this type of reaction, see J. H. Brewster and E. L. Eliel in R. Adams, "Organic Reactions," Vol. VII, John Wiley and Sons. Inc., New York, N. Y., 1953, pp. 99–197.

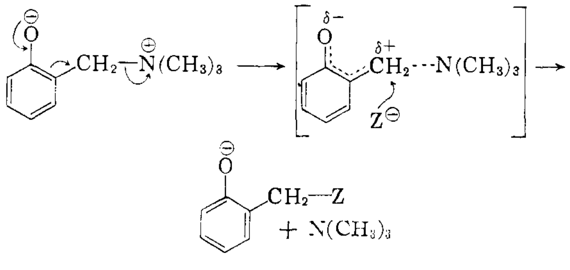
at which displacement occurs. This is illustrated by the reaction of derivatives of gramine[2] (electron release by the ring-nitrogen), ferrocene[3] (electron release due to small resident charge on cyclopentadienyl rings) and is pictured below for the case of the azulene derivative I.[4] It is not implied that the bracketed intermediate necessarily has finite existence; it may be formed but it is also possible that the transition state is bimolecular with some of the character of this intermediate.[5]

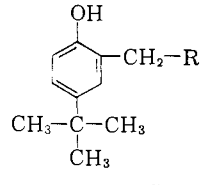


These considerations prompted the study of this reaction with phenol derivatives as a route to intermediates which could prove useful in the synthesis of quinone methide (II) and derivatives. It would be expected that electron release by the anionic oxygen atom of a quaternarized Mannich base should facilitate displacement of the amine moiety by a nucleophile, *i.e.*[7] This was shown to be true in early work during which it was observed that the methiodide of 2-cyclohexylaminomethyl-5-*t*-butylphenol (III) reacted readily with alkoxide ion to yield the corresponding ether IV.[8] As suggested above, the novelty of this reaction is mostly in the ease with which it occurs. For example, the displacement of trimethylamine from 2,4,6-trimethylbenzyltrimethylammonium chloride by alkoxide ion has been previously reported[9] but it appears that the conditions required are considerably more drastic. By contrast, in the course of an extension of the study here described, it was noted that the reaction of a typical phenolic Mannich base methiodide with sodium hydroxide in methanol was complete in less than five minutes with resulting formation of a high yield of the corresponding ether.

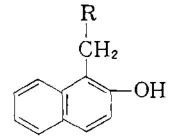


II

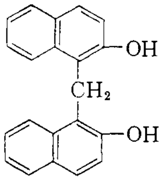




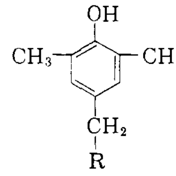
III, R = $NH-C_6H_{11}$
IV, R = alkoxyl
V, R = $N(CH_3)_2$
VI, R = $N(CH_3)_3I$
VII, R = H



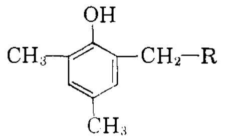
VIII, R = $N(CH_3)_2$
IX, R = $N(CH_3)_3I$
X, R = $N(O)(CH_3)_2$
XI, R = OCH_3
XII, R = H



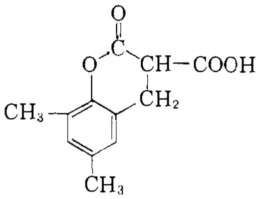
XIII



XIV, R = $N(CH_3)_2$
XV, R = $N(CH_3)_3I$
XVI, R = COOH



XVII, R = $N(CH_3)_2$
XVIII, R = $N(CH_3)_3I$
XIX, R = $N(O)(CH_3)_2$
XX, R = COOH



XXI

Mannich bases were prepared in the traditional manner from the phenol, amine and formaldehyde. These were converted to the methiodides or, in two cases, the oxides and submitted to reaction with one or more of the nucleophiles; OCH_3^-, CN^-, $(EtOOC)_2CH^-$ and H^-. The product of each was that resulting from straightforward displacement of trimethylamine by the nucleophile. Nitriles were not characterized but were hydrolyzed directly to the acids. The single example of the displacement by diethyl malonate anion (XVIII) resulted in formation of the lactone acid XXI.

The use of nucleophiles chosen ensures that reaction media were sufficiently basic in all cases to induce preliminary salt formation. Since the reaction is probably bimolecular with bond breaking occurring somewhat faster than bond formation, the transition state must resemble quite closely

---

(2) H. R. Snyder and E. L. Eliel, THIS JOURNAL, **71**, 663 (1949).

(3) C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **22**, 1246 (1957).

(4) K. Hafner, *Angew. Chem.*, **70**, 419 (1958).

(5) The mechanism of this type of reaction has not been illucidated. An S_N2 displacement has been observed in the case of a simple optically active benzylamine derivative,[6] but reaction appears to proceed very slowly. Those examples cited above would seem capable of reacting by an S_N1 mechanism thereby yielding intermediates of the type shown for the azulene derivative. It is clear that such structures would be stabilized by electron-releasing substituents. On the other hand, it should be pointed out that the formation of an S_N2 transition state possessing some of the character of this intermediate is entirely reasonable. Thus, on the basis of existing data it is not possible to choose, but until a clean-cut S_N1 reaction is demonstrated for some system other than β-amino ketone derivatives an S_N2 mechanism with considerable S_N1 character would seem most plausible for systems of the type considered here.

(6) H. R. Snyder and J. H. Brewster, THIS JOURNAL, **71**, 291 (1949).

(7) If the reaction is S_N1, quinone methode (II) itself is intermediate to formation of the product.

(8) W. J. Burke and P. D. Gardner, unpublished data, 1953.

(9) C. R. Hauser and D. N. Van Eenam, THIS JOURNAL, **79**, 6277 (1957).

TABLE I

Compound	Reaction time, hr.	Reaction temp., °C.	Yield, %	M.p., °C.	Formula	Analyses, %			
						Calculated		Found	
						C	H	C	H
V	12	35	44	79	[a]				
VI	3	35	50	195–201	$C_{14}H_{24}NOI$	48.14	6.93	48.22	6.75
VII	15	65	85		[a]				
IX	12	40	75	240 d.	[b]				
X	12	20	53	173–175 d.	[b]				
XI	10	80	67[c]	195–196	$C_{12}H_{12}O_2$[d]	76.66	6.38	76.22	6.40
XII	12	65	29[c]	111[e]					
XIV	10	40	75	120–122	$C_{11}H_{17}NO$	73.74	9.49	74.08	9.60
XV	8	0	80	192–193	$C_{12}H_{20}ONI$	44.85	6.23	44.96	6.66
XVI	15	80	80	142–143	$C_{10}H_{12}O_3$	66.66	6.66	66.30	6.74
XVII	10	80	85	[h]	$C_{11}H_{17}NO$	73.74	9.49	74.35	9.60
XVIII	12	35	75	182	$C_{12}H_{20}ONI$	44.85	6.23	44.66	6.19
XIX	3	35	77	115	$C_{11}H_{17}NO_2$	67.69	8.71	67.66	8.78
XX	12	80	50	200–201	$C_{10}H_{12}O_3$	66.66	6.66	66.72	6.81
XXI	12	80	56[f]	145 d.	$C_{12}H_{12}O_4$[g]	65.44	5.50	65.36	5.67

[a] See Experimental section. [b] Sufficient decomposition occurred during purification attempts to thwart attempts to obtain satisfactory analytical data. [c] Essentially identical results were obtained using the methiodide or the oxide. [d] Acetate, m.p. 215°. Calcd. for $C_{14}H_{14}O_3$: C, 73.51; H, 6.16. Found: C, 72.82; H, 6.26. [e] K. Fries and E. Hübner, *Ber.*, **39**, 435 (1906), report m.p. 110°. [f] Obtained from the oxide. [g] Calculated neut. equiv. 220, found 217. [h] B.p. 90° (0.9 mm.).

the quinone methide structure in its charge-separated state (II).[10]

Experimental[11]

Preparation of Mannich Bases.—The procedure employed is a more or less standard one and is described for the case of 2,4-dimethyl-6-dimethylaminomethylphenol (XVII).

A solution comprised of 20.7 g. of 2,4-dimethylphenol, 30 ml. of 25% aqueous dimethylamine solution, 13 ml. of 38% aqueous formaldehyde solution and 100 ml. of ethanol was heated under reflux for 10 hr. The cool solution was made acidic by the addition of 200 ml. of *N* hydrochloric acid and extracted with ether. Careful neutralization of the aqueous phase to *ca.* *p*H 8 by the addition of dilute aqueous sodium hydroxide afforded the amine which was then isolated by ether extraction and purified by distillation. There was obtained 25.6 g. (85%) of XVII as a colorless liquid, b.p. 90° (0.9 mm.). Analytical data are recorded in Table I.

Those bases which crystallized were purified by recrystallization from ethyl acetate–petroleum ether (30–68°).

In one case, 2-dimethylaminomethyl-4-*t*-butylphenol, reaction was never complete and the product was most easily isolated as a 1:1 molecular compound with 4-*t*-butylphenol, m.p. 79.0°, yield 44%.

Anal. Calcd. for $C_{23}H_{35}NO_2$: C, 77.26; H, 9.87; N, 3.92. Found: C, 76.81; H, 10.14; N, 3.81.

At least one other example of molecular-compound formation by Mannich bases has been reported.[12]

The synthesis of 1-dimethylaminomethyl-2-naphthol (VIII) proceeded as reported.[13] When more severe conditions were used (10 hr. at reflux) up to 30% yields of 2,2′-dihydroxy-1,1′-dinaphthylmethane (XIII) were obtained, m.p. after recrystallization from ethyl acetate–petroleum ether 205–207° dec. (lit.[14] 188–189°).

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 83.97; H, 5.37. Found: C, 83.91; H, 5.59.

The diacetate, prepared in acetic anhydride and pyridine and recrystallized from acetic acid, had m.p. 217–218°.

Anal. Calcd. for $C_{25}H_{20}O_4$: C, 78.12; H, 5.24. Found: C, 77.75; H, 5.50.

Mannich base methiodides were prepared by stirring Mannich bases with excess methyl iodide in dry ether at room temperature.

Mannich Base Oxides.—This general procedure is illustrated with the preparation of the N-oxide of 1-dimethylaminomethyl-2-naphthol. To a suspension of 16.0 g. of VIII in 80 ml. of methanol was added 24 ml. of 30% hydrogen peroxide solution. This mixture was stirred at room temperature for 15 hr. and the product (X) collected by filtration, 9.2 g. (53%), m.p. 173–175° dec. This substance underwent slight decomposition during purification attempts such that a satisfactory analysis could not be obtained. It was necessary to moderate the temperature rise in large scale runs such that it did not exceed 40°.

Displacement Reactions.—Mannich base methiodides and N-oxides were allowed to react with sodium methoxide in methanol solution, sodium cyanide in ethanol or aqueous ethanol solution, sodiomalonic ester in benzene or lithium aluminum hydride in tetrahydrofuran. Conditions of time and temperature are indicated in Table I. Isolation of the product was, in all cases, effected by acidification of the reaction mixture followed by ether extraction. This general type of reaction is described below with two examples.

A. **2,4-Dimethylphenol-6-acetic Acid (XX).**—To a suspension of 6.0 g. of sodium cyanide and 200 ml. of ethanol was added 20.0 g. of the methiodide of 2,4-dimethyl-6-dimethylaminomethylphenol (XVIII). The mixture was heated under reflux for 12 hr. and then concentrated to a very small volume. Water (100 ml.) was added followed by concd. hydrochloric acid until the solution was strongly acidic. Isolation in the usual manner by ether extraction gave the nitrile as a viscous liquid. Characterization was made by hydrolyzing to the acid. The entire product was dissolved in a solution composed of 40 g. of potassium hydroxide, 30 ml. of water and 200 ml. of ethylene glycol. Following an 18-hr. period of reflux, the solution was concentrated to a small volume under reduced pressure and extracted with ether. A normal isolation procedure afforded, after recrystallization from ethyl acetate–petroleum ether, 5.9 g. (50%) of XX having properties described in Table I.

B. **2-Methyl-4-*t*-butylphenol (VII).**—Two grams of the methiodide of 2-dimethylaminomethyl-4-*t*-butylphenol (VI) was added to a suspension of 0.50 g. of lithium aluminum hydride in 50 ml. of purified tetrahydrofuran. Following a 15-hr. period of reflux, the mixture was treated cautiously with water and then with dilute hydrochloric acid. Chloroform extraction and isolation in the usual manner gave the crude product as a liquid. It was characterized by conversion to the benzoate (1.3 g., 85%) which, after recrystallization from ethyl acetate–petroleum ether, had m.p. 70–71°.

---

(10) For the probable importance of quinone methide as an intermediate in other chemical processes see K. Hultzsch, "Chemie der Phenolharze," Springer-Verlag, Berlin, 1950; K. Hultzsch, *Angew. Chem.*, **60**, 179 (1948) and **61**, 93 (1949), and N. J. L. Megson, "Phenolic Resin Chemistry," Academic Press, Inc., New York, N. Y., 1958.

(11) Melting points are corrected. Reaction times and temperatures recorded are not optimum—it is felt that much shorter reaction times would suffice for most of the displacement reactions reported.

(12) W. J. Burke and R. J. Reynolds, THIS JOURNAL, **76**, 1291 (1954).

(13) H. R. Snyder and J. H. Brewster, *ibid.*, **70**, 4230 (1948).

(14) J. Abel, *Ber.*, **25**, 3478 (1892).

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.98; H, 7.50.

Acknowledgment.—The authors are indebted to the Robert A. Welch Foundation for the financial support of this study.

AUSTIN, TEXAS

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

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

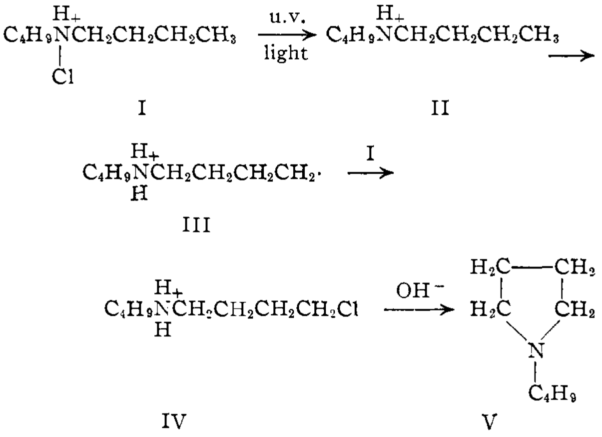
BY S. WAWZONEK AND T. P. CULBERTSON[2]

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.



$$\underset{\substack{|\\ Cl}}{C_4H_9\overset{H_+}{N}CH_2CH_2CH_2CH_3}\ \xrightarrow[light]{u.v.}\ C_4H_9\overset{H_+}{N}CH_2CH_2CH_2CH_3 \longrightarrow$$

I II

$$C_4H_9\underset{H}{\overset{H_+}{N}}CH_2CH_2CH_2CH_2\cdot \xrightarrow{I}$$

III

$$C_4H_9\underset{H}{\overset{H_+}{N}}CH_2CH_2CH_2CH_2Cl \xrightarrow{OH^-}$$

IV V

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

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

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

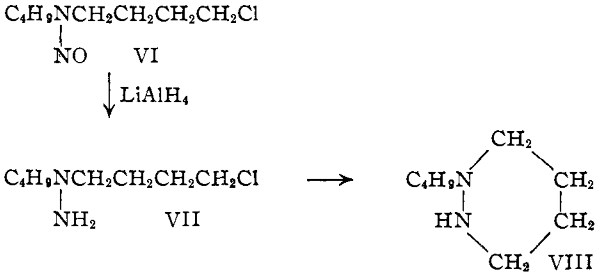
$$C_6H_5O(CH_2)_3NH(CH_2)_3CH_3 \xrightarrow[180°]{HCl}$$

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

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



$$C_4H_9\underset{\substack{|\\ NO}}{N}CH_2CH_2CH_2CH_2Cl$$

VI

$$C_4H_9\underset{\substack{|\\ NH_2}}{N}CH_2CH_2CH_2CH_2Cl \longrightarrow$$

VII VIII

---

[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).