The Mechanism of the Base-Promoted Rearrangement of *N, N*-Dichlorodiphenylethylamine to Desylamine

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Some years ago, Baugarten and his coworkers showed that the treatment of *N, N*-dichlorodiphenylethylamine with sodium methoxide, followed by that with aqueous hydrochloric acid, gave desylamine hydrochloride in a substantial yield.[1] They then successfully extended this remarkable reaction to various *N, N*-dichloro-*s*-alkylamines.[2] A similar rearrangement of *N, N*-dichlorocyclohexylamine to 2-aminocyclohexanone hydrochloride has also recently been reported.[3]

The following mechanism has been suggested for this reaction (Fig. 1):

Although this mechanism appears to be valid and although it is essentially the same as that of Neber Rearrangement of the corresponding oxime tosylate which was proposed earlier by Cram and Hatch,[4,5] there is no unequivocal evidence to support it. Meanwhile, since *N*-chloro compounds are known to halogenate the benzylic methylene group very readily,[6] and since the resulting halogenated benzylic compound would undergo a facile hydrolysis,[7] one can postulate another possible mechanism, namely, one involving the initial *gem*-dichlorination of 2-methylene and the subsequent hydrolysis, thus giving product as is shown below (Fig. 2).

One noticeable difference between these two mechanisms is that the former involves the 1, 2-migration of the amino group, while in the later the amino group remains in the original position.

Recently, an *N*-chloroimine intermediate similar to II was actually isolated in the case of *N, N*-dichlorocyclohexylamine;[3] also, the formation of the azirine ring III was strongly supported by the successful isolation of *cis*-2, 3-diphenylethyleneimine in the reduction of the reaction mixture of *N, N*-dichloro-1, 2-diphenylethylamine with lithium aluminum hydride.[2]

These two pieces of evidence seem to support very strongly the former mechanism, involving the 1, 2-migration of the amino group via the formation of the azirine ring. However, in strong alkaline conditions such as sodium methoxide in the methanol used in this

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[1] H. E. Baumgarten and F. A. Bowel, *J. Am. Chem. Soc.*, **76**, 4561 (1954).

[2] H. E. Baumgarten and J. H. Petersen, ibid., **82**, 459 (1960).

[3] G. H. Alt and W. S. Knowels, *J. Org. Chem.*, **25**, 2047 (1960).

[4] D. J. Cram and M. S. Hatch, *J. Am. Chem. Soc.*, **75**, 33 (1953).

[5] M. S. Hatch and D. J. Cram, ibid., **75**, 38 (1953).

[6] For example see T. Takizawa and K. Hoshiai, *Mem. Inst. Sci. Ind. Research, Osaka Univ.*, **2**, 92 (1948); *Chem. Abstr.*, **45**, 11211 (1951).

[7] A. Streitwieser, Jr., *Chem. Revs.*, **56**, 571—572 (1956).

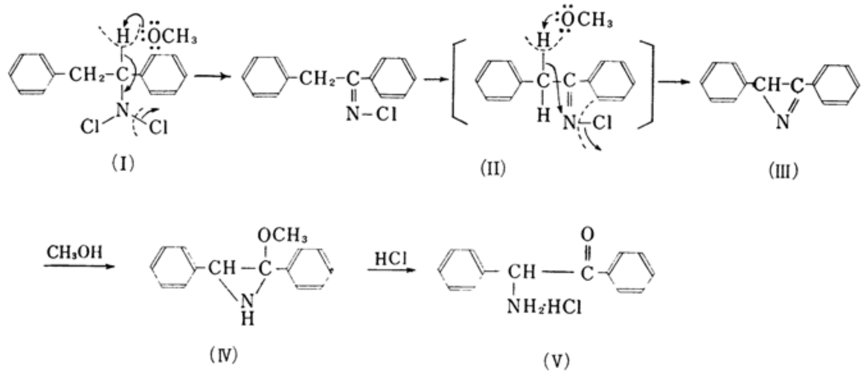

Fig. 1

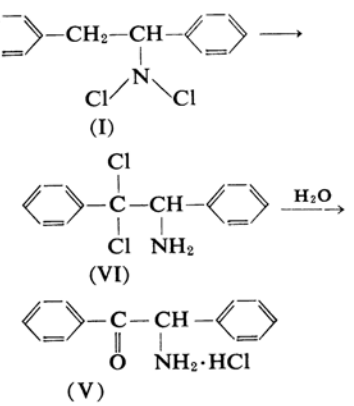

Fig. 2

reaction, one must also take into account the possibility of facile prototropy,8) as is shown below (Fig. 3).

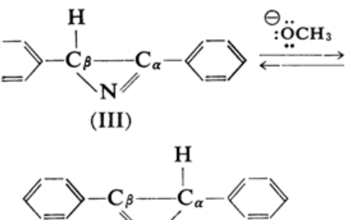

Fig. 3

If there were facile prototropy in III before the nucleophilic cleavage, the nucleophilic attack of the methoxy group could take place at both carbon atoms, C_α and C_β, with equal probability, yielding a fifty-fifty mixture of both 1, 2-shifted and unshifted aminoketones.

All these unresolved problems can be readily answered by tracing the fate of a labeled carbon atom placed either at the α or the β-position of the original *N, N*-dichloro-1, 2-diphenylethyl amine in the rearrangement.

Thus, *N, N*-dichloro-1, 2-diphenylethylamine-1-^{14}C has been synthesized, and a series of succesive degradations has been carried out. This paper will present detailed accounts of the results and implications of these experiments.

The synthetic and degradative methods of ^{14}C labeled desylamine may be shown as follows (Fig. 4).

Experimental

The Preparation of the *N, N*-Dichloro-1, 2-diphenylethylamine-1-^{14}C. — Phenylacetic acid-1-^{14}C9) (VIII) was obtained by the carbonation of benzylmagnesium bromide which had been prepared from 1.3 g. of magnesium and 6.3 g. of benzylchloride with $^{14}CO_2$ which had been generated from 7.0 g. (1.0 mc.) of barium carbonate. The yield was 4.3 g. in 63%; m. p. 76°C.

Phenylacetic acid-1-^{14}C (4.3 g.) was converted to phenylacetyl chloride (IX) by treating it with 3 g. of phosphoroustrichloride; the phenylacetyl chloride thus prepared was then treated with 3.8 g. of aluminum chloride in a benzene solution. From the reaction mixture deoxybenzoin-1-^{14}C10) (X) (4.3 g.) was obtained in a 75% yield; m. p. 56°C.

When deoxybenzoin-1-^{14}C (4.3 g.) was then allowed to react with a mixture of 6 g. of ammonium formate and 1 ml. of formic acid, 1,2-diphenylethylamine-^{14}C11) (3.7 g.) was obtained in a 85% yield; b. p. 143°C/2.4 mmHg.

1, 2-Diphenylethylamine-1-^{14}C (3.7 g.) was chlorinated with 5.5 g. of *t*-butylhypochlorite in dry benzene. The *N, N*-dichloro-1, 2-diphenylethylamine-1-^{14}C2) thus obtained was not isolated; the solution was used directly for the preparation of desylamine hydrochloride-*x*-^{14}C, as in the experiments of previous workers.2)

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8) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, New York (1953), pp. 530—575.

9) M. Calvin et al., "Isotopic Carbon," John Wiley and Sons, New York (1949), p. 180.

10) C. F. H. Allen and W. E. Barker, "Organic Syntheses," Coll. Vol. II, 156 (1943).

11) R. Adams, ed., "Organic Reactions," Vol. 5, John Wiley and Sons, New York (1949), p. 301.

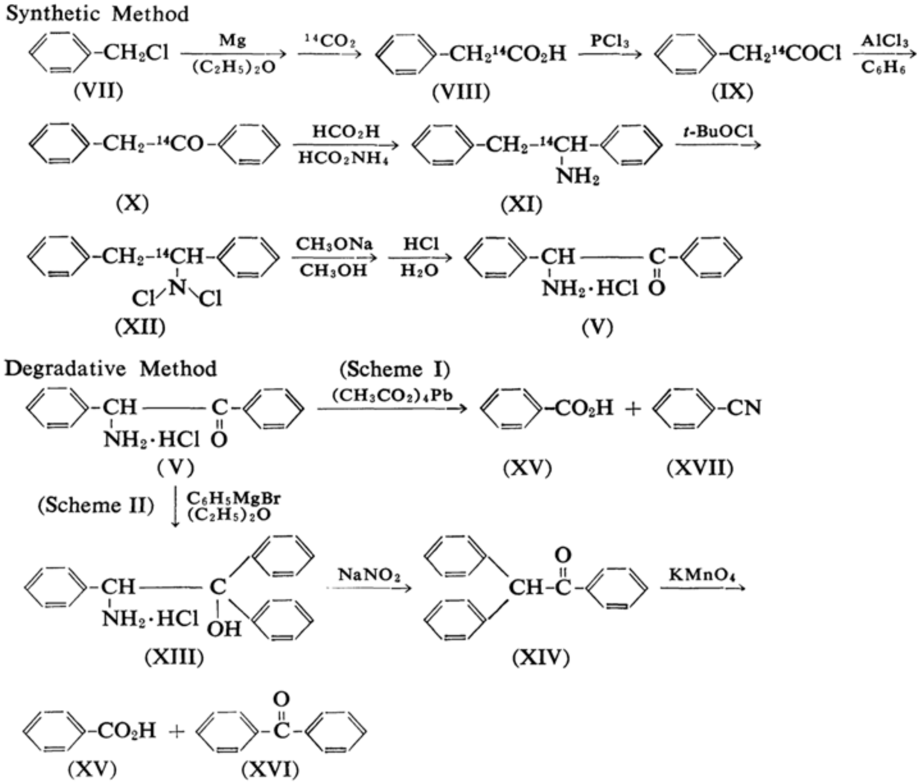

Fig. 4

The Rearrangement of *N,N*-Dichloro-1,2-diphenylethylamine-1-^{14}C. — The rearrangement of *N,N*-dichloro-1,2-diphenylethylamine-1-^{14}C was carried out following the procedure used previously.[2] Namely, the benzene solution of *N,N*-dichloro-1,2-diphenylethylamine-1-^{14}C prepared from 3.7 g. of 1,2-diphenylethylamine was treated in situ with 25 ml. of a methanol solution in which 2.5 g. of sodium had been dissolved. The yield was 1.7 g. (36%); m. p. 234°C.

The Degradation of Desylamine-*x*-^{14}C. — *Degradation Scheme I.* — In a 100 ml. three-necked flask equipped with a mechanical stirrer and a reflux condenser, 3.0 g. of desylamine hydrochloride-*x*-^{14}C was suspended in 50 ml. of dried benzene. To this mixture 10 g. of freshly prepared lead tetraacetate was added portion by portion, and then the mixture was heated for 2 hr. on a steam bath. After the mixture had cooled, the precipitated lead acetate was filtered off and washed with small portions of benzene. The combined benzene solution was extracted twice with 20 ml. of a 10% sodium carbonate solution. The aqueous extracts was acidified with concentrated hydrochloric acid. A white crystalline precipitate was thus obtained. Recrystallization from hot water gave hair-like crystals. These were identified as benzoic acid XV by a mixed melting point determination with authentic benzoic acid and by a study of the infrared spectrum. The yield was 1.0 g. (67.5%). The benzene solution was then evaporated and the residual oily substance (1.5 g.) distilled under reduced pressure to give benzonitrile XVI, which was identified by comparing its infrared spectrum with that of authentic benzonitrile. The yield was 0.3 g. (24%).

Degradation Scheme II.[12] — To a Grignard reagent prepared from 16 g. of bromobenzene and 2.4 g. of magnesium, 4.0 g. of powdered desylamine hydrochloride-*x*-^{14}C was added; 1,1,2-triphenyl-1-hydroxyethylamine hydrochloride-*x*-^{14}C was thus obtained in a 85% yield (4.5 g.).

1,1,2-Triphenyl-1-hydroxy-ethylamine hydrochloride-*x*-^{14}C (XIII) (4.5 g.) was deaminated by diazotization with 2.0 g. of sodium nitrite, followed by the migration of the phenyl group. Phenyldeoxybenzoin-*x*-^{14}C (XIV) was thus obtained (1.1 g.) in a 26% yield; m. p. 130—131°C.

The deoxybenzoin-*x*-^{14}C (0.25 g.) thus obtained was oxidized with 1.0 g. of potassium permanganate at room temperature; thus 50 mg. of benzoic acid (45%) and 0.17 g. of benzophenone (51%) were obtained. The benzoic acid XV was identified by mixed melting point determination. The benzophenone XVI thus obtained was derived to its 2,4-dinitrophenylhydrazone (m. p. 239°C).

The Measurement of the Activities.—*Scheme I.*— The activities of the ^{14}C which were distributed in the compounds were measured by using a Packard-liquid scintilation spectrometer model 500B, Tri-carb. The purified 1,2-diphenylethylamine-1-^{14}C

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[12] J. G. Burr, *J. Am. Chem. Soc.*, **75**, 1990 (1953); W. A. Bonner and C. J. Collins, ibid., **75**, 5372 (1953).

Table I. The ^{14}C counting obtained in Scheme I

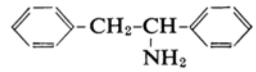
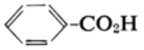
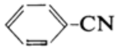
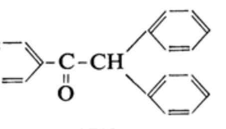
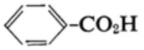
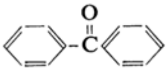
			
c. p. m./mmol.	4.00×10^5	2.75×10^5	3.52×10^3
%	(100%)	(68.8%)	(0.37%)

Table II. The ^{14}C counting obtained in Scheme II

			
c. p. m.	1712	1663	19
%	(100%)	(97.8%)	(1.1%)
c. p. m.	1692	1656	15
%	(100%)	(97.9%)	(0.90%)

was chosen as a standard for the original total activity. The counting methods were as follows. Three samples, namely, 4.985 mg. of 1,2-diphenylethylamine-1-^{14}C, 3.176 mg. of benzoic acid, and 9.958 mg. of benzonitrile, were dissolved separately in 20 ml. each of toluene containing POP and POPOP as scintilators; then they were subjected to a Packard Tri-carb. The data obtained are shown in Table I.

Scheme II. — The measurements of the activities of the samples were carried out in this case by a JRC Aloka 2π-gas flow proportional counter using Q-gas. Phenyl deoxybenzoin-*x*-^{14}C was used as the standard sample of the total activity. A known amount of a sample was thoroughly oxidized by the Van-Slyke method, and all the carbon dioxide formed was converted to a barium carbonate pellet which was then subjected to ^{14}C counting. The respective pellets of barium carbonate obtained were, i. e., 158.1 mg. (98%) from phenyldeoxybenzoin (11.4 mg.), 120.5 mg. (96%) from benzoic acid (11.0 mg.), and 110 mg. (94%) from benzophenone-2,4-dinitrophenylhydrazone (11.4 mg). The counting data obtained are shown in Table II.

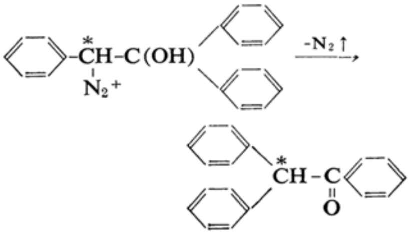
Results and Discussion

The results of the degradations of the desylamine-*x*-^{14}C obtained are shown in Tables I and II.

The first scheme of degradation involves the direct oxidation of desylamine hydrochloride with lead tetraacetate to yield benzoic acid and benzonitrile. The latter compound was obtained in rather a poor yield; however, it undoubtedly originated from the α-amino benzylic portion of desylamine. It carries only a very small portion of the ^{14}C activity (0.87%) of the original activity of desylamine employed.

On the other hand benzoic acid was obtained in a substantial yield; it is the only compound isolated that carries a substantial amount of ^{14}C activity. However, its activity was somewhat reduced; e. g., in one experiment, it was 68.8% of that of the desylamine employed. This apparently diminished activity of the benzoic acid is assumed to be caused by the dilution of the ^{14}C-active benzoic acid formed from the oxidation of the benzyl portion of desylamine with the non-active benzoic acid formed from the hydrolysis of benzonitrile during the treatment. Incidentally, this assumption seems to be quite valid in view of the results of the degradation by the second procedure. The very small amount of ^{14}C activity formed in the benzonitrile is quite significant, because it excludes both the ^{14}C scrambling that could be expected from the prototropy of the azirine ring III, and the *gem*-dichlorination hydrolysis mechanism. If the reaction were assumed to proceed according to the latter mechanism, all the ^{14}C activity would remain in the α-amino benzylic carbon and, hence, the benzonitrile would carry the same amount of specific activity as the original amine. This was found not to be the case. Therefore, since it is considered that a portion of the benzoic acid originates in the hydrolysis of benzonitrile, the results of this degradation can serve as strong evidence in support of the mechanism proposed by Baumgarten.

The second degradation scheme is a beautiful product of Collins et al., who have demonstrated unequivocally through a ^{14}C tracer experiment that the deamination of 1,1,2-triphenyl-1-hydroxy-ethylamine by diazotization undergoes the following rearrangement:



Therefore, the only uncertainty, if any, is in the step of the reaction between desylamine and phenylmagnesium bromide to give 1, 1, 2-triphenyl-1-hydroxy-ethylaminehydrochloride, however, this step is a straightforward reaction involving the nucleophilic attack of the phenyl Grignard reagent on the carbonyl carbon. Thus, according to this degradative scheme, benzoic acid may be considered to originate from the benzoyl group and benzophenone, from the benzhydryl group. Here again the data indicates that the benzoic acid carries practically all the activity, while benzophenone is incorporated with almost no ^{14}C activity.

These data on ^{14}C distribution obtained by the second scheme are in accord with those obtained by the first scheme; they clearly exclude any mechanisms involving an initial *gem*-dihalogenation and subsequent hydrolysis, and also that one involving a rapid prototropic equilibrium of the azirine ring.

Therefore, the only remaining plausible mechanism is that suggested previously by Baumgarten et al.; this is essentially the same as that proposed originally by Cram and Hatch for the Neber rearrangement (Fig. 1).

Summary

N, N-Dichloro-1, 2-diphenylethylamine-1-^{14}C has been treated with sodium methoxide in methanol and then with hydrochloric acid to yield ^{14}C-labeled desylamine hydrochloride. Successive degradations have revealed that practically all the ^{14}C activity was found in the carbonyl carbon. From the ^{14}C distribution, it has been concluded that the reaction is essentially the same as that proposed for the Neber rearrangement, which involves the formation of the azirine ring intermediate.

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