BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 2917—2920 (1969)

The Mechanism of the Base-Promoted Rearrangement of *N,N*-Dichlorocyclohexylamine to 2-Aminocyclohexanone and the Deaminative Diazotization of 2-Aminocyclohexanone

Mamoru NAKAI,[*1] Naomichi FURUKAWA and Shigeru OAE

Department of Applied Chemistry, Faculty of Engineering, Osaka City University, Sugimoto-cho, Sumiyoshi-ku, Osaka

(Received February 21, 1969)

N,N-Dichlorocyclohexylamine-1-^{14}C has been treated with sodium methoxide in methanol and then with hydrochloric acid to yield ^{14}C-labeled 2-aminocyclohexanone hydrochloride. Successive degradations have revealed that practically all the ^{14}C activity was found in the carbonyl carbon of the original aminoketone. From the ^{14}C distribution, it has been concluded that the reaction is essentially the same as that proposed for the Neber rearrangement. As a part of the degradation of 2-aminocyclohexanone, deaminative diazotization was employed to obtain cyclopentanecarboxylic acid together with other minor products. The ^{14}C tracer work revealed that the carbonyl group of the acid is originated from the carbonyl group of the 2-amino-ketone.

Baumgarten and his coworkers[1] reported that when *N,N*-dichlorocyclohexylamine is reacted with sodium methoxide and then treated with aqueous hydrochloric acid 2-aminocyclohexanone hydrochloride is formed, analogous to the Neber rearrangement of the corresponding oxime tosylate.[2,3] They have extended this reaction to other various *N,N*-dichloro-*s*-alkylamines.[4] A similar rearrangement of *N,N*-dichlorocyclohexylamine to 2-aminocyclohexanone hydrochloride has also been recently reported.[5] Meanwhile the rearrangement of *N,N*-dichlorodiphenylethylamine to desylamine was investigated by us using ^{14}C-labeled compound and revealed to proceed according to the mechanism similar to the Neber rearrangement as shown below[6] (Fig. 1).

Although the same mechanism may hold for the reaction of *N,N*-dichlorocyclohexylamine with sodium methoxide, the reaction could proceed *via* other mechanistic routes, since the Neber type rearrangement involves a very highly strained bicyclic azirine bearing a double bond at the bridge-head position, and other possibilities such as that involving the prior *gem*-dichlorination followed by hydrolysis could occur (Fig. 2). Thus

---

[*1] Ube Industries Ltd., Ube, Yamaguchi.

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

[2] D. J. Cram and M. S. Hatch, *ibid.*, **75**, 33 (1953).

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

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

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

[6] S. Oae and N. Furukawa, This Bulletin, **38**, 62 (1965).

a similar ^{14}C tracer work is quite desirable. However, the same degradative procedure gave rather obscure results. Hence other better degradative methods have been tried. Among a few methods employed, a degradative diazotization of 2-aminocyclohexanone has been proved to be very promising since it gives the rearranged cyclopentanecarboxylic acid in yields always exceeding 35%. However, this degradative procedure must be examined at first, because it is not known whether or not this procedure changes the sequence of carbon skeleton, nor has it been clarified that the carbon dioxide formed during the rearrangement originates from the carbonyl carbon of 2-aminocyclohexanone.

We have accumulated data of the ^{14}C tracer experiments on these reactions. This paper will describe the results in detail.

N,N-dichlorocyclohexylamine-1-^{14}C has been synthesized, and a series of successive degradation has been carried out.

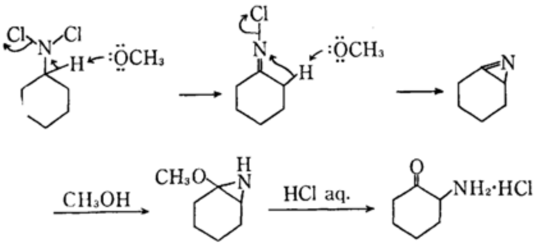


Fig. 1

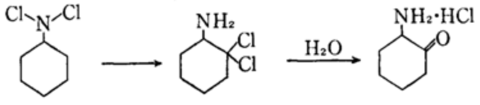
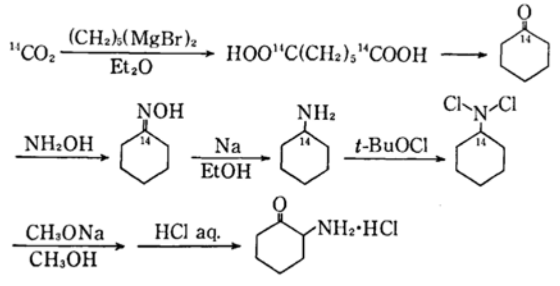


Fig. 2

Synthetic Method



Degradative Mothod

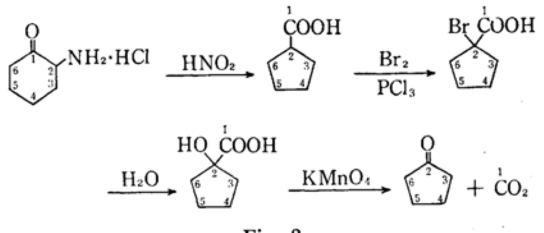


Fig. 3

Both the synthetic and degradative procedures are shown below (Fig. 3).

Experimental

Preparation of *N,N*-Dichlorocyclohexylamine-1-^{14}C. Pimeric acid-1,7-^{14}C was obtained by the carbonation of pentamethylene magnesium bromide which was prepared from 0.9 g of magnesium and 4.0 g of pentamethylene dibromide, with $^{14}CO_2$ generated from 7.0 g (1 mCi) of barium carbonate. The crude product was recrystallized from benzene; yield 2.0 g (70%), mp 104°C.

A mixture of 1.8 g of pimeric acid-1,7-^{14}C and 0.1 g of barium carbonate was gradually heated in a metallic bath up to about 320°C and the distillate was collected. The crude cyclohexanone-1-^{14}C (0.9 g) was purified by distillation (bp 155°C).

The above cyclohexanone-1-^{14}C (2.5 g) was added to a solution containing 2.2 g of hydroxylamine hydrochloride in 5 m*l* of water, into which a solution containing 1.7 g of sodium carbonate in 5 m*l* of water was added. The mixture was filtered to collect the precipitate which was then washed with cold water and recrystallized from 50% ethanol. The yield of cyclohexanone oxime-1-^{14}C was 1.9 g in 75%; mp 91°C.

Strips of sodium (6 g) were added to a solution of cyclohexanone oxime-1-^{14}C (2.0 g) in 60 m*l* of absolute ethanol. From the reaction mixture, cyclohexylamine-1-^{14}C (1.3 g) was obtained in 75% yield; bp 132°C.

Cyclohexylamine-1-^{14}C (6.5 g) was chlorinated with 15 g of *t*-butyl hypochlorite in anhydrous benzene. *N,N*-Dichlorocyclohexylamine-1-^{14}C thus obtained was not isolated; the solution was used directly for the preparation of 2-aminocyclohexanone hydrochloride-*x*-^{14}C, as in the experiments of previous workers.[4]

Rearrangement of *N,N*-Dichlorocyclohexylamine-1-^{14}C. The rearrangement of *N,N*-dichlorocyclohexylamine-1-^{14}C was carried out by the following procedure used previously;[4] the benzene solution of *N,N*-dichlorocyclohexylamine-1-^{14}C prepared from 6.5 g of cyclohexylamine was treated with a methanolic sodium methoxide prepared from 4.8 g of sodium and 50 m*l* of methanol. The reaction mixture became very dark when the reaction ended. The aqueous acid extract was tan to red-brown, but most of the color could be removed by repeated treatments with active charcoal. The resulting, crude 2-amino-cyclohexanone hydrochloride-*x*-^{14}C was recrystallized from absolute methanol, then washed with a mixture of isopropanol and methanol to give a pure substance; yield 4.6 g (47%), nearly colorless crystals, mp 158°C.

Degradation of 2-Aminocyclohexanone Hydrochloride-*x*-^{14}C. Deamination of 2-aminocyclohexanone hydrochloride was reported by Edwards and Lesage,[7] who revealed that the reaction affords cyclopentanecarboxylic acid, bicyclo[3,1,0]hexane-2-one and 2-methyl-2-cyclopentene-1-one as the products from 2-aminocyclohexanone.

We also carried out the deaminative diazotization in a similar way. 2-Aminocyclohexanone hydrochloride-*x*-^{14}C (1.60 g) was dissolved in 9 m*l* of 6 N hydrochloric acid, and to this solution cooled in an ice-salt bath was

---

[7] O. E. Edwards and M. Lesage, *Can. J. Chem.*, **41**, 1592 (1963).

added a solution of 3.6 g of sodium nitrite in 9 m*l* of water dropwise with stirring. The reaction mixture turned to blue. After the addition was complete the contents of the flask was stirred for 1 hr while keeping the temperature below 0°C, and then for 1 hr at room temperature, followed by heating for 1/2 hr at 50°C. It was then made alkaline with sodium carbonate and extracted with ether to remove neutral and acidic substances. The aqueous solution was acidified with hydrochloric acid and extracted with ether. This etheral solution was dried over anhydrous sodium sulfate and distilled, affording 0.8 g of acidic materials, *i. e.*, cyclopentanecarboxylic and adipic acids which were identified by comparing their infrared spectra with those of authentic samples. The latter acid was further confirmed by the mixed melting point determination with the authentic sample of adipic acid. Thus cyclopentanecarboxylic acid-*x*-^{14}C was obtained in about 35% yield based on the data of the isotopic dilution method; bp 103—105°C/8 mmHg.

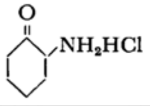
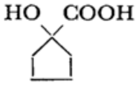
The method of Loftfield was used to degradate cyclopentanecarboxylic acid-*x*-^{14}C[8]. This acid (2.3 g), bromine (1.1 m*l*) and phosphorus trichloride (0.15 m*l*) were heated to 100°C for one hour in a sealed tube. 1-Bromocyclopentanecarboxylic acid-*x*-^{14}C was dissolved in a mixture of 30 m*l* of acetone, 30 m*l* of water, 2.5 m*l* of acetic acid and 2 g of sodium acetate and then allowed to stand for 16 hr at room temperature. The resulting 1-hydroxycyclopentanecarboxylic acid-*x*-^{14}C (1.0 g) was obtained in 38% yield; mp 103°C.

In a distillation flask, a solution of 0.2 g of the hydroxy acid-*x*-^{14}C and 0.12 g of potassium permanganate in 30 m*l* of water was gradually heated to boiling. A stream of nitrogen was bubbled through the solution and the carbon dioxide released was introduced into a barium hydroxide trap. From the distillate (6.5 m*l*) was obtained cyclopentanone; the conversion was about 60%. One-third of this distillate was used to prepare cyclopentanone semicarbazone which was recrystallized from water; mp 207°C.

Measurement of the Activities. The activities of the samples were measured with a JRC Aloka 2π-gas flow G-M counter using Q gas. 1-Hydroxycyclopentanecarboxylic acid-*x*-^{14}C was used as the standard sample of the total activity. An aliquot of a sample was thoroughly oxidized by the Van Slyke-Folch Method, and all the carbon dioxide formed was converted to a barium carbonate tablet which was then subjected to ^{14}C counting.

The counting data obtained are shown in Table 1.

TABLE 1. THE ^{14}C COUNTING DATA

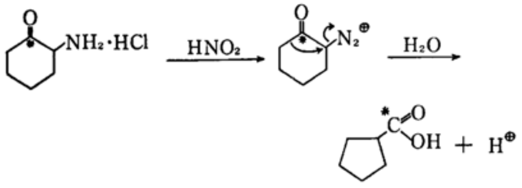
			 a)
Run 1	1240 cpm	278 cpm (100%)	7±3 cpm (∼2.5%)
Run 2	17200 cpm	3650 cpm (100%)	63 cpm (1.7%)

a) Assayed as semicarbazone.

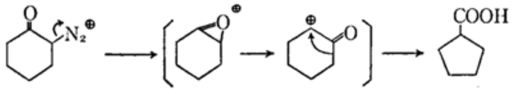
Results and Discussion

1-Hydroxycyclopentanecarboxylic acid was used as the standard sample of 2-aminocyclohexanone, and the ^{14}C total activities were counted. The value which substracts the ^{14}C activity of cyclopentanone from that of 1-hydroxycyclopentanecarboxylic acid may be regarded as the ^{14}C activity of carbonyl carbon of original 2-aminocyclohexanone. Thus semicarbazone of cyclopentanone obtained can be counted for the activity of all the positions except carbonyl carbon of aminoketone. As shown in Table 1, the ^{14}C activity (1.7%) of cyclopentanone carries only a very small portion of the original activity of 2-aminocyclohexanone. Therefore, carbonyl carbon of the original aminoketone carries essentially all the ^{14}C activity.

All the synthetic procedures used for the ^{14}C compounds are quite common ones that have often been tested in the past, and it is known that no rearrangement is involved in any step of the total synthesis of *N*,*N*-dichlorocyclohexylamine-1-^{14}C. Meanwhile the degradation of cyclopentanecarboxylic acid has also been carried out by a well-known procedure involving no skeletal rearrangement. A serious problem lies, however, in the step of deaminative diazotization of 2-aminocyclohexanone, since it involves the rearrangement of the carbon skeleton. However, since nearly all the carbon-14 activity was found to be concentrated at the resulting carboxyl group of cyclopentanecarboxylic acid, the formation of cyclopentanecarboxylic acid from 2-aminocyclohexanone appears to proceed through a simple Wagner-Meerwein type rearrangement as shown below.



Thus, other possible routes such as that analogous to the one involved in the hydrolysis of α-halocyclohexanone,[9] shown below are excluded.

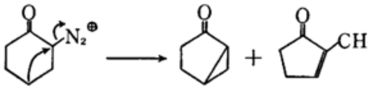


Although degradation was not performed for the other two products, namely 2-methyl-2-cyclopentene-1-one and bicyclo[3.1.0]hexane-2-one,[7] these are undoubtedly formed by the initial 1,2-shift from 4-position as shown below.

---

8) R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951).

9) T. Masuike, N. Furukawa and S. Oae, unpublished.



The formation of a substantial amount of cyclopentanecarboxylic acid (35%) is interesting in connection with the highly energy-recoiled carbonium ion formed by the deaminative diazotization. Here again, the migration of the carbon-skeleton took place rather indiscriminately regardless of the electronic nature of β-methylene groups which undergo 1,2-shift.

The results of the degradation revealed that nearly all the ^{14}C activity originally placed at 1-position of *N,N*-dichlorocyclohexylamine was found in the carbonyl carbon of 2-aminocyclohexanone formed, similar to the previous case with *N,N*-dichlorodiphenylethylamine.

Therefore, the plausible mechanism for this reaction is that suggested previously by Banmgarten *et al.*; this is essentially the same as that proposed originally by Cram and Hatch for the Neber rearrangement.