THE MECHANISM OF THE HOFMANN-MARTIUS REARRANGEMENT OF N-ALKYLANILINE

by

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DEDICATION

To My Parents

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INTRODUCTION

The rearrangement of N-alkylanilines, a reaction discovered by Hofmann and Martius in 1871 (21, p. 742-748), has been the center of studies in several laboratories. The findings of these investigations resulted in the proposal of several mechanisms for this rearrangement; nevertheless, up to the present time a satisfactory understanding of all the observed pertinent facts is yet to be realized.

It was reported by Hofmann and Martius in 1871 (21, p. 742-748) that when aniline hydrochloride was methylated with methanol, ring methylation as well as methylation of the amino nitrogen atom was observed. It was further revealed (22, p. 704-719; 23, p. 720-722) that upon heating N-alkylaniline hydroiodide or hydrochloride at 220-335°, a rearrangement occurred giving rise to the formation of xylidines, toluidines, cumidines and multiple ring methylated compounds. The rearrangement was regarded then as an intramolecular type, although no conclusive supporting evidence was presented by the original investigators. A similar rearrangement, involving ethyl groups, was reported by Benz (4, p. 1650-1651)

in which p-aminoethylbenzene was obtained as the principal product in the ethylation of aniline hydrochloride with ethanol. Michael, in a note (29, p. 2107) published in 1881, suggested that the Hofmann-Martius rearrangement may have involved the formation of an alkyl halide as the key intermediate.

The mechanism of this rearrangement was examined again, forty years later, by Reilly and Hickinbottom (33, p. 103-136). In a series of experiments, these authors demonstrated the important role played by the hydrohalide moiety of the aniline salt, as well as some metal halides such as cobalt chloride, zinc chloride, or cadmium chloride in facilitating the rearrangement. Other salts in the nature of calcium sulfate or sodium chloride and silicon dioxide were described as completely inactive as catalysts for the rearrangement. In a subsequent experiment by these workers (19, p. 1281-1290), significant amounts of butylene and n-butyl chloride were isolated as side products in the pyrolytic rearrangement of N-n-butylaniline hydrochloride; however, butylene was considered not necessarily a key intermediate on the ground that only a trace amount of p-amino-sec-butylbenzene was ever isolated for the same reaction mixture. The authors also observed that the rate of the rearrangement was

significantly faster with the N-n-butyl group as compared to that with the N-methyl group (33, p. 129-136).

A number of investigators including Hickinbottom and coworkers, Chapman, Michael, Kon, Beckmann, Correns, Bennett, Chapman, Dewar, Howard, Derick, Hughes and Ingold have since examined the nature of this rearrangement more thoroughly. The findings, covering a great variety of experiments, soon led to the proposal of several speculative mechanisms. These proposed mechanisms are briefly reviewed below, according to their basic natures.

The intramolecular nature of the rearrangement was suspected by several investigators. The intramolecular nature of the metal halide catalyzed rearrangement was first suspected by Hickinbottom (13, p. 64-67) on the ground that the formation of alkyl halides and alkenes called for by an intermolecular mechanism was not detected when N-alkylaniline was heated in the presence of metal halides. Moreover, metal oxide, a speculative side product proposed by Chapman in a suggested intermolecular mechanism (6, p. 186), was also not detected in the reaction mixture (13, p. 64-67).

Dewar (7, p. 227) believed that the rearrangement could be readily explained by the theory of π complex formation, which involves the interaction of the N-alkyl

substituent with the π electrons of the benzene ring, followed by an intramolecular migration of the alkyl group to the para position. The observation of the lack of multiple ring alkylation in a typical rearrangement of this type was cited as the key evidence, although polyalkylations were indeed observed in several laboratories.

Contrary to the foregoing propositions, the intermolecular nature of the rearrangement was recognized by several other groups of investigators. It should be pointed out that in the earlier studies on this subject, the uncertain role played by metal halides in the Hofmann-Martius rearrangement caused considerable confusion in understanding the mechanism of the rearrangement. In fact, it had long been suspected by workers that different mechanisms were involved in the superficially similar rearrangement reactions, when it was carried out in the presence of metal halides or in the presence of the hydrogen halides.

The intermediary formation of alkyl halides was firmly believed by several workers proposing intermolecular mechanisms for this rearrangement. In 1922, Beckmann and Correns (2, p. 852-856) reported the isolation of primary, secondary, and tertiary

N-alkylanilines when N-alkylaniline hydrochloride was subjected to the rearrangement conditions. These findings were interpreted by these authors to indicate the formation of alkyl halides in the rearrangement process.

Howard and Derick (24, p. 166-167) stated that experiments with the rearrangement of acylanilines indicated that the cleavage of acyl groups in the acyl derivatives of aniline requires the formation of diacylaniline as an intermediary step. It was also found that the ionization constants of these disubstituted compounds were ten thousand times as great as the product of the rearrangement. The authors, therefore, postulated that a similar situation may have existed in the alkylaniline hydrochloride rearrangement. By examining the ionization constants of the organic bases presumably involved in the rearrangement of N-methylaniline hydrochloride, it was found that the compound which possesses a large enough ionization constant to be an intermediate in the rearrangement would have to be a quaternary ammonium base, in this case trimethylphenylammonium chloride. The authors reported that by carrying out the reaction at a temperature of 300° the formation of a small amount of trimethylphenylammonium chloride was indeed detected.

This fact together with the previous understanding of the mechanism associated with the acylaniline rearrangement led these authors to conclude that the rearrangement was basically intermolecular in nature (24, p. 175-177).

In 1930 Hickinbottom and Preston (18, p. 1566-1571) reported that whereas p-amino-tert-butylbenzene was formed, almost exclusively, when isobutylaniline hydrobromide was heated under the rearrangement conditions, p-aminoisobutylbenzene was the principal product of the rearrangement of isobutylaniline treated in a similar manner except the addition of metal halide. These authors, therefore, suggested that a different mechanism involving different intermediates was associated with the metal halide catalyzed rearrangement. The authors further stated that the rearrangement catalyzed by metal halides could be considered as a true isomerization process.

Bennett and Chapman (3, p. 123-124), in explaining an observation made by Hickinbottom and Preston in 1930 (18, p. 1566-1571) in which p-amino-tert-butylbenzene was produced as the major product when isobutylaniline hydrobromide was heated at 220-300°, proposed an intermolecular rearrangement mechanism for this rearrangement. These authors visualized that isobutyl bromide may

have been rapidly eliminated when isobutylaniline hydrobromide was subjected to the rearrangement conditions. This was followed by the isomerization of the isobutyl bromide to tert-butyl bromide, which in turn reacted with the benzene ring to yield the rearrangement product, p-amino-tert-butylbenzene. The fact that extensive isomerization was not observed in the case of the rearrangement carried out in the presence of metal halides was explained on the basis that ring alkylation occurred prior to the isomerization of the alkyl group under the catalytic effect of the metal halide.

Contrary to Reilly and Hickinbottom's earlier findings (33, p. 103-136), Hickinbottom and Ryder, in 1931 (19, p. 1281-1290), reported the extensive formation of olefins in the rearrangement of N-alkylaniline hydrobromides particularly when the alkyl groups were the higher members of a homologous series. It should be noted that this conclusion did not support the proposition of Bennett and Chapman (3, p. 123-124) which called for the elimination of alkyl halide from N-alkylaniline hydrobromide as the key step of the rearrangement without the involvement of olefins whatsoever. Hickinbottom, however, states that there was a "notable" amount of alkyl halide formed when alkylaniline hydrobromides were placed under

the rearrangement conditions (15, p. 1700) particularly in the case of propyl or ethyl derivatives. Moreover, triphenylmethyl chloride when reacted with dimethylaniline yielded p-trityldimethylaniline (15, p. 1700). The finding was used by the author to conclude that alkyl halides were capable of alkylating the benzenoid moiety of aniline without the presence of a metal halide catalyst. Hickinbottom further reported (15, p. 1700) that a small amount of methyl bromide was produced when N-methylaniline hydrobromide was rearranged to p-aminomethylbenzene in an open tube. Analogous results were observed (15, p. 1700) also with N-methylaniline hydroiodide with the formation of o-aminomethylbenzene in addition to p-aminomethylbenzene as the rearrangement products. These findings were cited in supporting an intermolecular mechanism for the rearrangement in question.

Following the isolation of trimethylethylene, an olefin, for the rearrangement of N-<u>iso</u>butylaniline hydrobromide (14, p. 2396-2400), the direct ring alkylation of aniline with olefins was successfully demonstrated by Hickinbottom (14, p. 2396-2400) under conditions comparable to the usual rearrangement conditions. That the ring alkylation did not proceed by way of an

alkylation of the amino nitrogen atom followed by the Hofmann-Martius rearrangement was derived from the observation that N-alkylaniline, isolated as a side product from the reaction mixture, failed to undergo the rearrangement under similar conditions to yield the corresponding p-aminoalkylbenzene.

It is obvious that the accumulation of a vast amount of information on the Hofmann-Martius rearrangement during that period caused considerable confusion in the basic understanding of the mechanism in question. However, subsequent careful examination of these findings eventually led several investigators to propose a more solid mechanism which involved the intermediary formation of carbonium ions, carbanions or free radicals.

Kon in 1933 (28, p. 186-187) proposed that the Hofmann-Martius rearrangement may have proceeded by way of a mechanism similar to that suggested by Whitmore (34, p. 3274-3283) for the isomerization of the neopentyl halides which involves the formation of either a carbonium ion or a carbanion as the intermediate. In the latter case, the configuration of the neopentyl group was preserved in the rearrangement reaction. This view was concurred by Hickinbottom (15, p. 1700-1705), who added that the proposed ionic mechanism was also in agreement

with the observed formation of alkyl halide and olefin, two side products detected in the reaction mixture of a typical Hofmann-Martius rearrangement. In fact, Hickinbottom also implied the possibility that the olefin derived from the carbonium ion may have been a direct intermediate in the alkylation of the benzenoid structure.

In 1952, Hughes and Ingold (25, p. 43-45) pointed out the discrepancy between the ionic mechanism and the observation that, whereas isomerization occurs with the olefins and the alkyl moiety of the C-alkylaniline, retention of configuration was the rule with alkyl halides isolated in the same reaction mixture. By combining the previously proposed mechanisms of Michael and Hickinbottom and taking into consideration the modern understanding of aromatic substitution, Hughes and Ingold proposed a revised mechanism which consists of a series of intermediary steps indicated in the following scheme:

$$\mathrm{Ph\overset{+}{N}H_2R} + \mathrm{H\bar{a}l} \rightarrow \mathrm{PhNH_2} + \mathrm{RHal}$$

$$\mathrm{RHal} \rightleftarrows \mathrm{R^+} + \mathrm{Hal^-}$$

$$\mathrm{R^+} + \mathrm{PhNH_2} \rightleftarrows \mathrm{Olefin} + \mathrm{PhNH_3^+}$$

$$\mathrm{R^+} + \mathrm{PhNH_2} \rightarrow \mathrm{R{\cdot}C_6H_4{\cdot}NH_2} + \mathrm{H^+}$$

$$\mathrm{H^+} + \mathrm{PhNH_2} \rightleftarrows \mathrm{PhNH_3^+}$$

According to this mechanism the first step involved the fission of the alkylaniline hydrohalide, catalyzed by the prevailing strongly polar medium, into aniline and alkyl halide. This is then followed by the alkylation of the benzene ring by an alkyl carbonium ion derived from the newly formed alkyl halide via a S_n1 mechanism. These authors further indicated that since the olefins are presumably derived from the alkyl carbonium ion, consequently isomerization occurs to both olefin and the ring alkyl group whenever the carbonium ion is susceptible to isomerization (25, p. 43-45). The latter process should not in any way affect the configuration of the parent compound of the carbonium ion, the alkyl halide.

A careful review of the previously described mechanisms proposed by workers in the field revealed that these mechanisms failed to account for the retention of alkyl group's configuration in the rearrangement of N-n-alkylaniline hydrochloride. Thus, when N-n-butylaniline hydrochloride is subjected to the rearrangement conditions, one finds the principal product is p-amino-n-butylbenzene. According to either the olefin mechanism or the carbonium ion mechanism it is hard to visualize that the key intermediate, in the nature of butene-1 or primary butyl carbonium ion, will retain its configuration during the

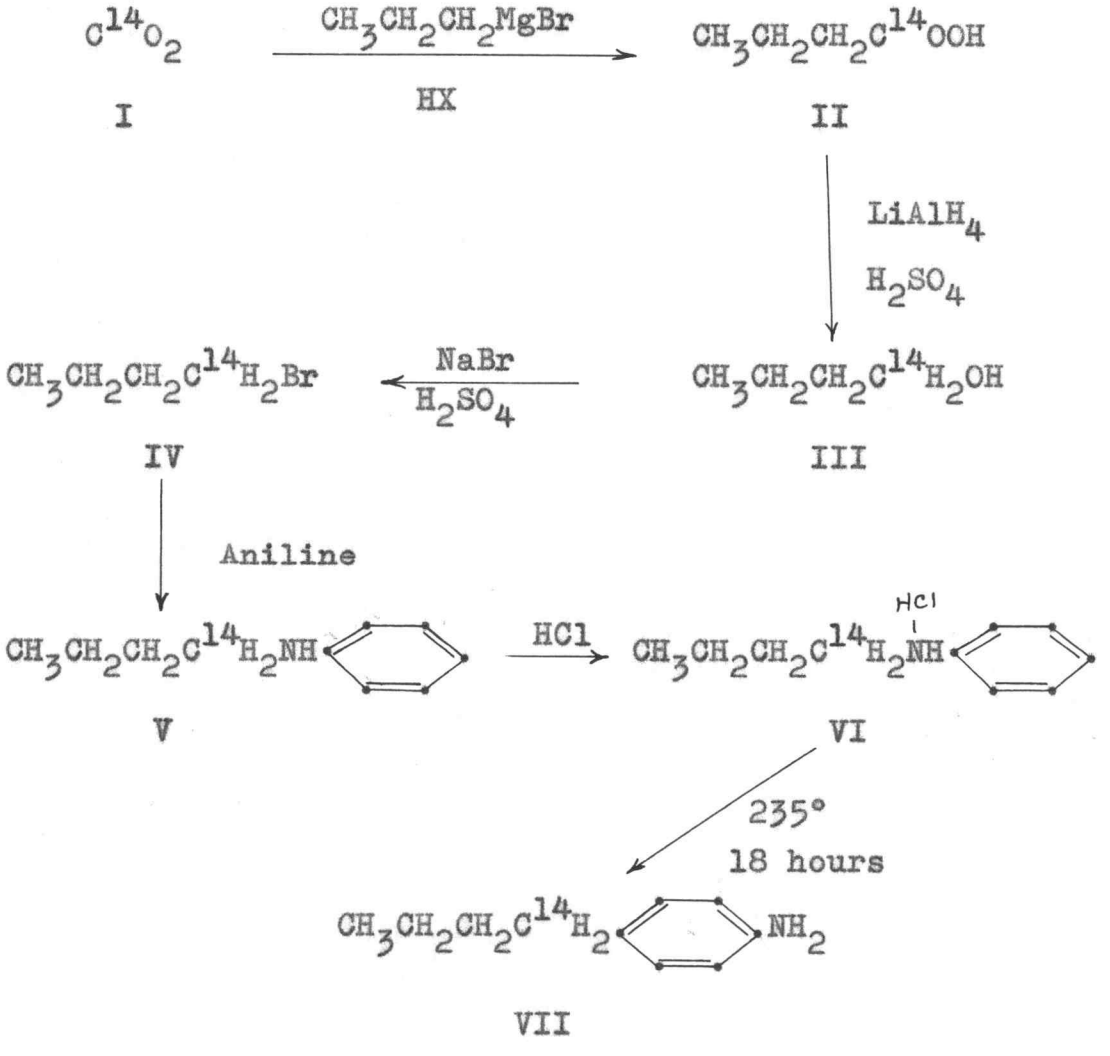
ring alkylation process inasmuch as the isomerization of butene-1 or primary butyl carbonium ion to the more stable structure, i.e., butene-2 or sec-butyl carbonium ion, have been well established in recent years.

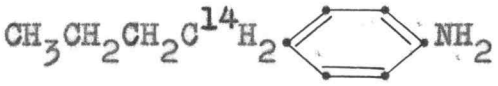
In order to understand better the basic nature of the Hofmann-Martius rearrangement, radiotracer methods have been employed in the present work to obtain information on the rearrangement of N-n-butylaniline hydrochloride. No attempt has been made to study the rearrangement in the presence of metal halides inasmuch as the latter may involve a completely different mechanism, hence, a completely different issue insofar as experimental designs are concerned.

EXPERIMENTAL

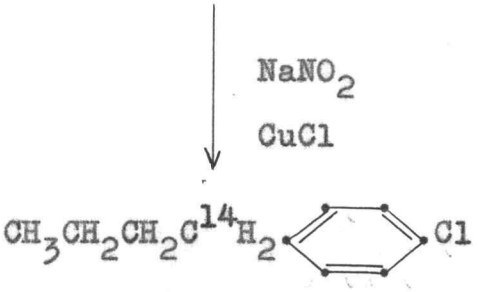
Simple Rearrangement

Below is the sequence of reactions for the preparation of the N-(n-butyl-1-C^{14})-aniline hydrochloride and the equations to identify the position of C^{14} radioactivity after the simple rearrangement:

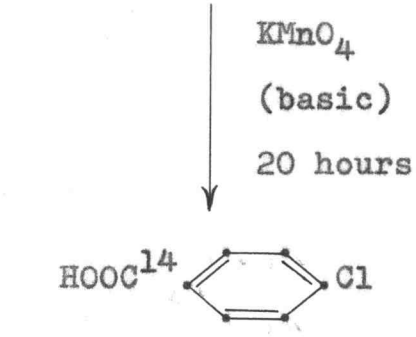




VII



VIII



IX

Butanoic-1-C^{14} acid (II). -- Butanoic-1-C^{14} acid was prepared according to the method of van Bruggen, Claycomb and Hutchens (35, p. 45-48), originally developed for the synthesis of acetic-1-C^{14} acid. Carbon-C^{14}-dioxide, liberated from one millimole (197.37 mg, 1.023 mc) of barium carbonate-C^{14} with 1.0 ml of 40% perchloric acid, was reacted with 4.0 ml of a solution, 1.33 molar in concentration, of propyl magnesium bromide in ether, prepared according to the method of Gilman, Zoellner and

Dickey (10, p. 1576-1583). Upon completion of the carbonation reaction the ethereal solution was acidified with 0.5 ml of 6N sulfuric acid and was subsequently transferred to a 100 ml three-necked flask, from which the organic acid was recovered by steam distillation. The progress of the distillation was checked by continuously titrating the distillate with standard (0.020N) sodium hydroxide, using phenolphthalein as the indicator. Calculation of the results of the titration and also by weighing the dried sodium salt indicated there were 80.0 mg (0.73 mM) produced corresponding to a yield of 73%. A portion of the sodium salt, 56.300 mg, was placed in a 100 ml volumetric flask and to which was added 0.30 ml of reagent grade n-butyric acid and 0.30 ml of concentrated hydrochloric acid to completely liberate all the butyric-1-C^{14} acid. Enough ethyl ether was added to produce 100 ml of solution and the mixture was dried over 4.0 g of anhydrous sodium sulfate for 24 hours. One tenth ml samples were taken for radiochemical assay which revealed there were 398 uc in the ethereal solution or a specific activity of 7.08 uc/mg for the sodium butyrate-1-C^{14}.

Butanol-1-C^{14} (III). -- The butyric-1-C^{14} acid in an ethereal solution was converted to butanol-1-C^{14} according to the reduction method of Nystrom and Brown (32, p. 2548-2549). One gram of lithium aluminum hydride was dissolved in 45 ml of anhydrous ether and refluxed and stirred for 4 hours, after which length of time, 100 ml of ethereal solution of butyric-1-C^{14} acid was introduced into the lithium aluminum hydride solution over a period of one hour. The solution was stirred for one additional hour, followed by the addition of 20-30 ml of water to decompose the excess hydride. Carrier, reagent grade, n-butyl alcohol (39.2 ml, 0.43 mole) was added prior to the addition of 45 ml of 10% sulfuric acid solution to decompose the complex salt formed during the reduction. The labeled n-butyl alcohol was exhaustively extracted with ethyl ether in a continuous liquid-liquid extraction apparatus. The ethereal solution of butanol-1-C^{14} was made up to a volume of 250.0 ml from which 0.10 ml samples were taken for radioactive assay. The radiochemical yield was 365 uc or 91.5%. The remaining solution was distilled to remove the ether.

1-Bromobutane-1-C^{14} (IV). -- 1-Bromobutane-1-C^{14} was prepared from the butanol-1-C^{14} by the sodium

bromide-sulfuric acid method (5, p. 28-29). The yield of 1-bromobutane-1-C^{14} was 46 g or 78%. Seventh-five grams of reagent grade 1-bromobutane was added as a carrier, giving rise to 121 g of the labeled compound.

N-(n-Butyl-1-C^{14})-aniline (V). -- 1-Bromobutane-1-C^{14} (121 g, 0.87 mole) prepared by the foregoing reactions was reacted with aniline (221 g, 2.37 moles) for three hours on a boiling water bath according to the method of Hickinbottom (11, p. 992-994). The reaction mixture was cooled to room temperature and made basic with ammonium hydroxide. To the cooled basic solution was added 146 g of fused zinc chloride in 146 ml of water to remove the primary amines which form an insoluble complex salt. After standing for 12 hours, the mixture was filtered and washed with water to remove the excess zinc chloride. The mixture of solid amine complex salts was extracted with ethyl ether to remove the N-(n-butyl-1-C^{14})-aniline from the mixture, since a secondary amine does not form the amine complex.

N-(n-Butyl-1-C^{14})-aniline hydrochloride (VI). -- The ethereal solution of N-(n-butyl-1-C^{14})-aniline obtained in the foregoing section was made sharply acidic with concentrated hydrochloric acid. The acidic solution

was then concentrated, cooled and the crystallized N-(n-butyl-1-C^{14})-aniline hydrochloride, isolated by filtration, was recrystallized from benzene. The amine salt was dried in vacuo and gave a melting point of 107-110°C (uncorrected). Radiochemical assay indicated a specific activity of 0.25 uc/mM. The chemical yield was 56 g or 70%, corresponding to a radiochemical yield of 38% based on the butanol-1-C^{14}.

Rearrangement of N-(n-butyl-1-C^{14})-aniline hydrochloride. -- A portion of N-(n-butyl-1-C^{14})-aniline hydrochloride having a specific activity of 0.25 uc/mM was sealed into two sets of Carius tubes. Each set of tubes consisted of 4 tubes with 10.16 g (0.05 mole) of salt in one set and 11.03 g (0.06 mole) of salt in the second set. The tubes were placed into a warm (150-190°C) Carius oven and the temperature was raised to 235±10°C over a 2 hour period of time. The tubes were left in the oven at this temperature for 18-20 hours and then removed from the oven. The tubes were cooled and opened and any gaseous products were collected in 100 ml of toluene, cooled to -78°C. A 1.0 ml sample of the toluene solution was radiochemically assayed with a result corresponding to 1.53 uc of radioactivity in the solution. When the toluene solution was warmed to 25°C

the radiochemical assay indicated there was 1.34 uc of radioactivity in the solution. After the removal of the gaseous products, methanol was added to each of the reaction tubes to remove the solid reaction residue. The methanolic solution was diluted to 100 ml and samples were assayed for radioactivity which indicated an activity of 17.1 uc of radioactivity in the solution.

Isolation of p-amino-(n-butyl-X-C^{14})-benzene (VII). -- One ml of concentrated hydrochloric acid was added to the previously obtained methanolic solution and the resulting solution was evaporated to dryness in vacuo on a rotary evaporator. The residue so obtained was made basic with the addition of 25 ml of 17% sodium hydroxide solution and then extracted with ether. The ethereal solution of amines was dried over sodium hydroxide pellets for 12 hours and the ether was removed by distillation. The mixed amines were separated by vacuum distillation. Two fractions of the amines were obtained: 2.7 ml at 63-72°/12 mm (uncorrected) and 6.5 ml at 94-99°/12 mm(uncorrected). Both fractions were assayed for radioactivity which gave results that indicated the specific activity of the two fractions was, respectively, 0.044 uc/mM and 0.26 mc/mM.

p-Chloro-(n-butyl-X-C^{14})-benzene (VIII). -- A portion of the higher boiling fraction which corresponds to p-amino-(n-butyl-X-C^{14})-benzene (0.8676 g) was dissolved in 5 ml of concentrated hydrochloric acid. Four ml of a 20% solution of sodium nitrite was slowly added to the above acid solution of amines. This solution of diazotized amines was added to a 25% solution of cuprous chloride in 3 ml of 12N hydrochloric acid, as in the conventional Sandmeyer reaction. The solution was allowed to warm up and to stand at room temperature for 5 hours. This was followed by steam distillation while 125 ml of distillate were collected. The distillate was extracted, sequentially, with a saturated aqueous solution of sodium bicarbonate, 6N sulfuric acid and finally water to remove any undesirable components. The ethereal solution was dried over calcium chloride for 12 hours and concentrated; it yielded 93 mg of p-chloro-(butyl-X-C^{14})-benzene upon microdistillation. A radiochemical assay of the material indicated a psecific activity of 0.26 mc/mM.

p-Chloro-benzoic-X-C^{14} acid (IX). -- p-Chloro-(n-butyl-X-C^{14})-benzene, 66 mg (0.59 mM), was placed in a 50 ml flask, together with 0.40 g of potassium permanganate, 0.10 ml of 10% sodium hydroxide and 8 ml of

water. The reaction mixture was refluxed with stirring for 20 hours. The reaction mixture was cooled to room temperature and extracted with ethyl ether to remove any starting material. The solution was extracted again with ether, after acidification with 1.0 ml of concentrated sulfuric acid, with a liquid-liquid extraction apparatus. The ethereal solution was distilled to remove the solvent and 22 mg (0.14 mM, 24% yield) of crude p-chloro-benzoic-X-C^{14} was obtained. This was purified by recrystallization and sublimation, yielding a product with a melting point of 235-237° and a specific activity of 0.26 uc/mM.

Mixed Rearrangement

Transalkylation of m-toluidine hydrochloride with N-(n-butyl-1-C^{14})-aniline hydrochloride. -- A ratio of 3.38 g (0.023 mole) of meta toluidine hydrochloride to 5.0 g (0.027 mole) of N-(n-butyl-1-C^{14})-aniline hydrochloride were mixed together. The mixture was sealed into three Carius tubes and in a separate Carius tube was placed 3.278 g of N-(n-butyl-1-C^{14})-aniline hydrochlrride. (The single tube was used as a check at each step of the way.) The respective tubes were heated at 235±10° for 18 to 20 hours. After which time, the tubes were cooled, their seals opened and the respective

contents were made basic by the addition of a portion of 50 ml of 10% sodium hydroxide to each tube. The resulting mixture was extracted with ethyl ether. The ethereal solutions of the free amines were subjected to gas chromatographic analysis; the findings revealed the presence of one additional component in the mixed rearrangement mixture in comparision with that of the simple rearrangement products.

The respective ethereal solutions were concentrated and to each of the residues was added 9.0 ml of concentrated hydrochloric acid. To this solution was added 3 ml of 33% aqueous sodium nitrite; this combined solution was added to a 20% solution of cuprous chloride in 9 ml of 8N hydrochloric acid, as in the manner described for the conventional Sandmeyer reaction. The reaction mixtures were allowed to stand at room temperature for 3 hours before being subjected to steam distillation. The mixed chloroalkylbenzenes in the distillate were isolated from the distillate by means of ether extraction. This was followed by the removal of any undesirable components in the ether solution by a sequence of extractions with aqueous sodium bicarbonate, 6N sulfuric acid and water. The resulting ethereal solutions were analyzed by means of a gas chromatograph which once

again revealed an additional component in the mixed chloroalkylbenzenes derived from the mixed rearrangement mixture in comparison with the products of the simple rearrangement.

The solvent of the respective ethereal solutions of the mixed chloroalkylbenzenes was removed by evaporation. The respective residues (mixed one yielded 0.38 g and simple one yielded 0.27 g) so obtained were subjected to permanganate oxidation using 5% alkaline permanganate. The oxidation products, mixed chlorobenzoic acids, from each of the two reaction mixtures were recovered from the oxidation mixture by means of acidification and ether extraction. Upon removal of the solvent of the ethereal solutions, there was obtained from the mixed experiment 135 mg and from simple experiment 36 mg. In view of the low concentration of the unknown component in the mixed rearrangement mixture, isotopic dilution technique was applied to isolate the unknown compound. This was carried out by the addition of 4-chlorophthalic acid (100 mg, Delta Chemical Works and purified by recrystallization), a possible product called for by the mechanism designed as the working assumption. Inasmuch as the mixed chlorobenzoic acids are presumably of the nature of p- and m-chlorobenzoic acids, both fairly insoluble

in water in contrast to 4-chlorophthalic acid which is fairly soluble in water, use was made of these characteristics for the isolation of 4-chlorophthalic acid. The crude 4-chlorophthalic acid so isolated was recrystallized repeatedly from a mixture of ethanol and benzene yielding 50 mg with a melting point of 148-152°. Radioactive assays of the compound prior to each successive recrystallization revealed that the product carried a constant specific activity of 0.007 uc/mM.

In order to determine the exact amount and specific activity of the 4-chlorophthalic acid produced in the mixed rearrangement experiment, a double isotopic dilution was carried out using unlabeled 4-chlorophthalic acid as the carrier. An amount (2.4 g) of the mixed chloroalkyl compounds obtained from the mixed rearrangement reaction mixture in an identical manner as described previously was oxidized with alkaline permanganate and the mixed chlorobenzoic acids, 0.9 g, were isolated from the acidified reaction mixture by ether extraction.

To two equal portions of acids, 312 mg, carrier 4-chlorophthalic acid was added in the amounts of 50 mg and 200 mg, respectively. The labeled 4-chlorophthalic acid samples were isolated from the respective mixtures in the manner as described previously, yielding two

specimens of pure labeled 4-chlorophthalic acid having a specific activity of 207.9 cpm (0.0315 uc/mM) and 55.3 cpm (0.0075 uc/mM) from the 50 mg and 200 mg experiments, respectively, where cpm is counts per minute. The definition of specific activity is a disintegration rate per unit of mass which leads to the following equations,

$$A_1 = \frac{CS}{C + X} \qquad (1)$$

and

$$A_2 = \frac{CS}{C + Y} \qquad (2)$$

In the equations, A_1 cpm (55.3 cpm) and A_2 cpm (207.9 cpm) are the counting rates per minute of dilution of X mg (200 mg) and Y mg (50 mg) respectively, and C is the mass of radioactive material of a specific activity (S) in the equal samples. Performing algebraic manipulations the following equation may be obtained,

$$C = \frac{A_2Y - A_1X}{A_1 - A_2} \qquad (3)$$

Equation (1) may be rewritten in the following form to calculate the specific activity (S) of the original radioactive material,

$$S = \frac{A_1 (C + X)}{C} \qquad (4)$$

Using the values and equations given above, the mass of radioactive material may be calculated to be 4.4 mg and the specific activity of it is 0.35 uc/mM.

Measurement of Radioactivity

Radioactivity determinations throughout the present work were carried out by use of a liquid scintillation counter, employing a Packard Tri-Carb Liquid Scintillation Spectrometer. The optimum operating voltage was determined as 1220 volts and the window widths were set at 10 to 100 and 10 to ∞ volts. Counting samples, usually 15 ml in size, were prepared in toluene as the primary solvent; however, in the case of 4-chlorophthalic acid a 1 to 3, ethanol to toluene, mixture was used as a mixed solvent. 2,5-Diphenyloxazole, 0.40% (w/v) in concentration with respect to the solvent, and p-bis(2-[5-phenyloxazoyl])-benzene, 0.05% (w/v) in concentration with respect to the solvent, were employed respectively as the phosphor scintillator and wave shifter. The counter efficiency for each type of counting sample was established by adding to the respective scintillation sample solutions a given amount of

radioactive benzoic-7-C^{14} acid. Whenever severe quenching was suspected a quenching curve was prepared for efficiency correction. The curve was established by the counting of a series of samples containing various amounts of the compound under consideration. Countings were carried out to a standard deviation of no greater than 2% with respect to the counting rates of background and sample.

DISCUSSION

It can be seen from the literature review given in the introductory section that several important facets in connection with the mechanism of the Hofmann-Martius rearrangement are yet to be fully elucidated. The proposed mechanisms, either intramolecular or intermolecular, cannot explain all the experimental findings so far observed. The intramolecular mechanism proposed by Dewar relies heavily on the absence of polyalkylation in the typical rearrangement, yet it is known that dibutylaniline is one of the products in the pyrolytic rearrangement of N-n-butylaniline hydrochloride (33, p. 123). The intermolecular mechanism proposed earlier by Michael (29, p. 2107) and later by Hickinbottom (15, p. 1700-1705) calls for the formation of alkyl halide as the key intermediate. The latter process is believed by Hughes and Ingold (25, p. 43-45) to be in the nature of a S_n2 mechanism. This is followed by a S_n1 cleavage, giving rise to a carbonium ion which is in turn engaged in either ring alkylation or dehydrohalogenation which gives rise to the formation of the observed side products, olefins. The intermolecular mechanism, although explaining most of the experimental findings, is not consistent with several basic understandings of reactions of this

type. Firstly, the alkylation of aniline under the rearrangement conditions was demonstrated by Hickinbottom with an unusually reactive alkyl halide, i.e., triphenylmethyl chloride, but not any other alkyl halide. Secondly, it is difficult to visualize that the configuration of a primary alkyl group can be preserved in the ring alkylation process. The extensive isomerization of the n-butyl group in the typical Freidel-Crafts reaction has been reported previously in the literature (1, p. 363-368). One would expect that if a carbonium ion is involved in the pyrolytic rearrangement of N-n-alkylaniline hydrohalide the prevailing strongly polar medium would undoubtedly cause extensive isomerization of the n-alkyl groups, such as the n-butyl or n-amyl groups, prior to ring alkylation.

In the present work, efforts have been devoted exclusively to the study of the pyrolytic rearrangement of N-(n-butyl-1-C^{14})-aniline hydrochloride. Radiotracer methods have been used as the major tool to elucidate the nature of the rearrangement. It is understood that the findings may not necessarily lead to a general mechanism applicable to all the rearrangements of the Hofmann-Martius type. This is particularly true in view of the possible involvement of several mechanisms in the

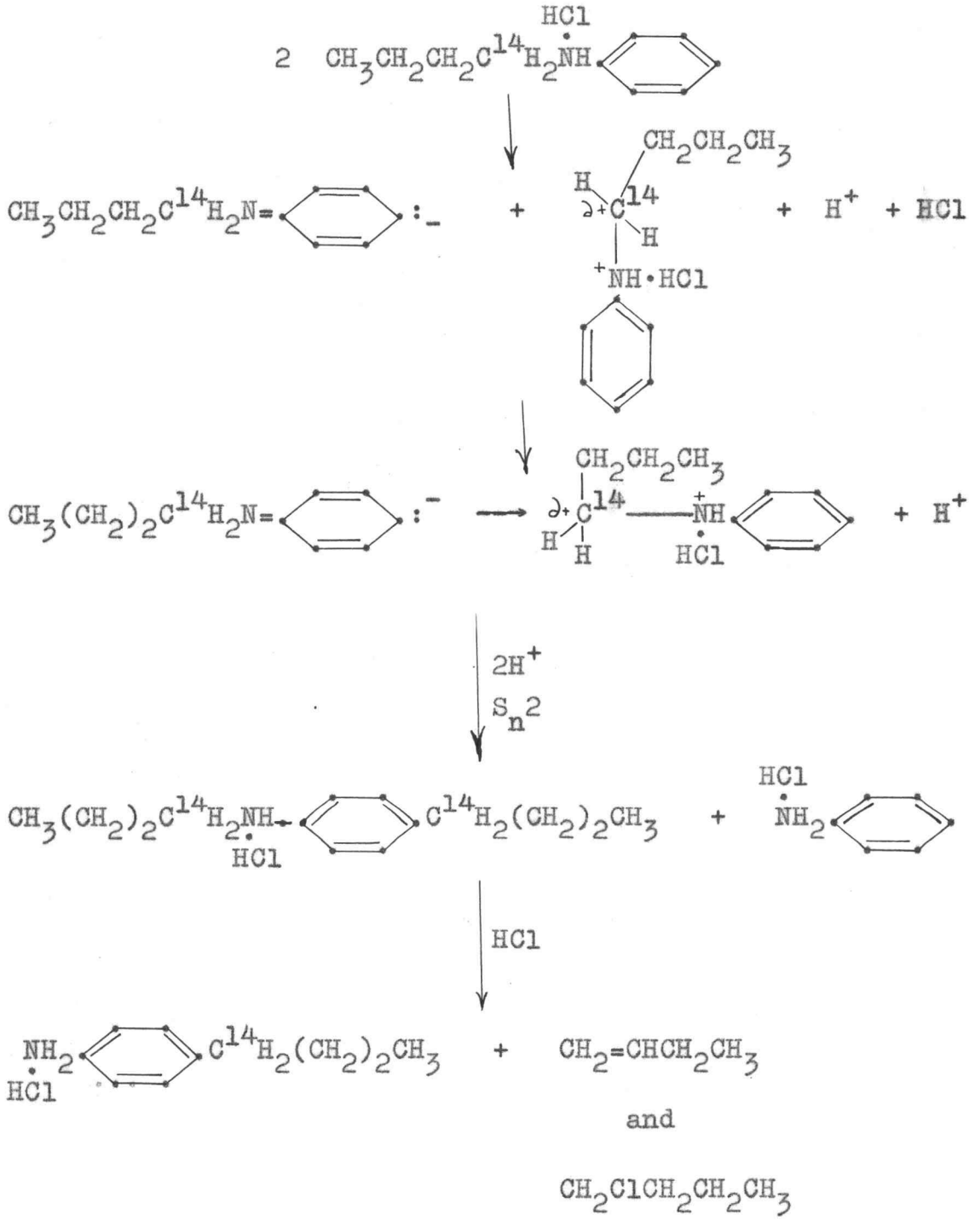
various versions of this rearrangement. However, it is hoped that the information obtained in the present work will shed some light on the basic understanding of this unique pyrolytic rearrangement.

When N-(n-butyl-1-C^{14})-aniline hydrochloride was subjected to the rearrangement conditions, the products, although in rather modest yield, were definitely identified to be aniline and p-butylaniline by means of gas chromatography and other physical means. A more interesting finding was the fact that the specific activity, expressed as microcuries per millimole of compound, of the mono-alkylated product was essentially as that of the starting material, N-(n-butyl-1-C^{14})-aniline hydrochloride. In view of the known mechanism of the degradation reactions employed in the present work, namely diazotization and side chain oxidation, it is reasonable to assume that no randomization of the alkyl group has occurred during the degradation study. This being the case, the finding thus provides one with conclusive evidence that the Hofmann-Martius rearrangement involves an alkylation step in which the carbon atom in the alkyl group attached to the amino nitrogen atom is the one engaged in the ring alkylation process. Superficially the latter fact tends to lend support to the intramolecular mechanism of Dewar, in which the interaction

of the alkyl group with the π electrons of the benzenoid structure would have resulted in the migration of a n-alkyl group without chain randomization. On the other hand, it is equally possible that an intermolecular mechanism could have given rise to the same findings, if one takes into consideration that the nucleophylic nature of an external benzenoid structure may have played an important role in the pyrolytic fission of the C-N bond in the N-alkylaniline molecule. In this regard one can visualize that the interaction of the para carbon atom of one molecule of N-alkylaniline, being elevated in electron density through a mesomeric mechanism, with the carbon atom bonded to the nitrogen atom of another molecule of N-alkylaniline resulting in a substitution of the S_n2 type. Subsequent cleavage of the N-alkyl group from the N-butyl-p-butylaniline would then give rise to the observed labeling pattern of p-butylaniline. The speculative scheme is described in the following figure.

In order to differentiate the two foregoing alternative mechanisms, the rearrangement of N-(n-butyl-1-C^{14}) -aniline hydrochloride in the presence of unlabeled m-toluidine hydrochloride was therefore designed and carried out. m-Toluidine was chosen as the unlabeled

Figure 1


HCl
2 CH3CH2CH2C14H2NH
CH2CH2CH3
CH3CH2CH2C14H2N=
:-
+
H
∂+C14
H
+NH·HCl
+ H+ + HCl
CH3(CH2)2C14H2N=
:-
CH2CH2CH3
∂+C14
H
H
NH
HCl
+ H+
2H+
Sn2
CH3(CH2)2C14H2NH
HCl
C14H2(CH2)2CH3
+
HCl
NH2
HCl
HCl
NH2
C14H2(CH2)2CH3
+
CH2=CHCH2CH3
and
CH2ClCH2CH2CH3

component for the obvious reason that the para carbon atom of this compound is highly activated toward undergoing electrophylic aromatic substitution and should, therefore, enhance the ring alkylation with respect to the labeled group of N-(n-butyl-1-C^{14})-aniline hydrochloride as the alkylating reagent under typical pyrolytic rearrangement conditions.

As described in the experimental section, the product anticipated from the intermolecular mechanism, 3-methyl-4-butylaniline, was indeed formed as evidenced by the detection of 4-chlorophthalic acid after diazotization and oxidation of the rearrangement products. More significantly, the specific activity of the 4-chlorophthalic acid as determined by the double isotopic dilution method was found to be in the same order of magnitude as the reactant. This finding implies that no randomization of the labeled alkyl group has occurred in the mixed rearrangement experiment. This fact, thus, renders strong support to the belief that the Hofmann-Martius rearrangement is indeed intermolecular in nature and proceeds according to the intermolecular mechanism previously described in Figure 1.

SUMMARY

Based on the radiotracer study of the Hofmann-Martius rearrangement of N-(n-butyl-1-C^{14})-aniline hydrochloride and the isolation and subsequent degradation studies of the product, p-amino-n-butyl-1-C^{14}-benzene, it can be stated that the butyl group migrated with full retention of its configuration.

In order to determine whether the mechanism was of an intermolecular or intramolecular type, N-(n-butyl-1-C^{14})-aniline hydrochloride was subjected to identical rearrangement conditions as before in the presence of unlabeled m-toluidine hydrochloride. Transfer of the labeled butyl group onto the para position of m-toluidine was accomplished. Through degradation studies it was revealed that the labeled carbon atom was directly attached to the benzenoid ring. On the basis of these findings, an intermolecular mechanism involving an S_n2 displacement of the C-1 of the butyl group in N-(n-butyl-1-C^{14})-aniline hydrochloride has been proposed.

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