[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY, UNIVERSITY OF WISCONSIN]

THE ALKYLATION OF AMINES AS CATALYZED BY NICKEL

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RECEIVED AUGUST 14, 1931 PUBLISHED JANUARY 7, 1932

The catalytic hydrogenation of various nitrogen containing organic compounds such as primary arylamines, cyanides, oximes, anils, nitro and nitroso compounds often results in the formation of secondary and tertiary amines as well as of the desired primary amines. The further study of these processes seems worth while for several reasons: first, to ascertain how to exercise a better control of the competitive reactions, second because of the interest in the mechanisms of these transformations and third because of the paucity of available information as to reactions other than hydrogenation induced by nickel.

Alkylation of Amines by Alcohols.—Ethylcyclohexylamine was recently obtained in an excellent yield by the hydrogenation of aniline in an ethanol solution using nickel as a catalyst.[1] This result suggested that nickel is a catalyst for the reaction of amines with alcohols according to equation I

$$C_6H_{11}NH_2 + C_2H_5OH = C_6H_{11}NHC_2H_5 + H_2O \qquad (I)$$

This supposition has been confirmed by the fact that the reaction indicated does not occur to any appreciable extent if the reactants are heated at 200° in the absence of active nickel. However, when 0.55 mole of cyclohexylamine, 1.2 mole of ethanol and 4 g. of a nickel catalyst were heated under a pressure of 75 atmospheres of hydrogen at 200° for three and one-half hours, the fractionation of the products showed 8.6 g. of cyclohexylamine, 42.0 g. of ethylcyclohexylamine, 6 g. of diethylcylcohexylamine and 2.0 g. of dicyclohexylamine. If the reactants were heated at 150° with a nickel catalyst no reaction occurred, but at 175° only 52% of the cyclohexylamine was recovered unchanged. In general the same factors seem to govern the activity of nickel for the catalysis of the alkylation of amines as govern its activity for hydrogenation, since a preparation of catalyst which was rather inactive for hydrogenation was also rather inactive for alkylation.

Piperidine and α-methylpiperidine reacted with ethanol, butanol and cyclohexanol at 200° in a similar way, the yields of the corresponding tertiary amines being 76 to 80%. Mechanical losses account for about one-third of the remainder, while under the conditions used there was 13 to 17% of unreacted secondary amine. At temperatures lower than 165° piperidine and some of its derivatives do not react with ethanol in the presence of nickel. This is shown by the fact that recently α- and

[1] Adkins and Cramer, THIS JOURNAL, **52**, 4354 (1930).

β-pyridylphenylethylene and α-benzylpyridine were hydrogenated in ethanol solution at 150–165° to α- and β-piperidylphenylethane and α-benzylpiperidine without any appreciable amount of alkylation.[1]

Since the same yields of alkylated amine were obtained in an atmosphere of nitrogen as were obtained in an atmosphere of hydrogen it is obvious that the latter plays no part in the reaction.

Cyclohexylamine did not react to any appreciable extent with methanol, propanol-2 or ethylene glycol. Tertiary butyl alcohol did not react with piperidine, nor did ethanol react with aniline under the conditions used for the successful alkylations described above. β-Phenylethylamine reacted with butanol-1, as did amylamine with ethanol, but such a variety of products resulted that the method seems to have little preparational value.

Alkylation of Amines by Amines.—Rosenmund and Jordan,[2] and more recently Kindler,[3] showed that over palladium benzylamine and β-phenylethylamine in boiling xylene or alcohol were converted in excellent yields to the corresponding secondary amines with the evolution of ammonia. It has been found that nickel also catalyzes this type of alkylation under suitable conditions.

$$2C_6H_5CH_2CH_2NH_2 = (C_6H_5CH_2CH_2)_2NH + NH_3 \qquad (II)$$

Cyclohexylamine did not undergo reaction II rapidly but β-phenylethylamine was converted completely to di-β-phenylethylamine in three and one-half hours at 200° over a nickel catalyst. In a similar way *n*-amylamine was completely converted into di-*n*-amylamine. Aniline did not form diphenylamine under similar conditions.

It is noteworthy that the alkylation formulated in equation II proceeded only as far as the secondary amine, since no tertiary amine was isolated from any of the experiments referred to above. This behavior is in marked contrast to the alkylation of primary amines with alcohols, which usually results in the formation of some tertiary amine.

Alkylation of Amines during Hydrogenation.—Having as a background a knowledge of the conditions inducing the two types of alkylation of amines referred to above, it is possible to consider more conclusively the nature of the reactions which result in the formation of secondary and tertiary amines during the reduction of aryl amines, cyanides, etc. Under the most advantageous conditions so far used in this Laboratory for the hydrogenation of aniline there was produced 1 part of dicyclohexylamine for 9 parts of cyclohexylamine, while with less active catalysts (with a resultant longer period of hydrogenation) the proportion of the secondary amine was increased to 1 part for 2 parts of primary amine. Similarly in the hydrogenation of benzyl cyanide there was produced under the most advantageous conditions 1 part of di-β-phenylethylamine for 6 parts of

[2] Rosenmund and Jordan, *Ber.*, **58B**, 51 (1925).

[3] Kindler, *Ann.*, **485**, 113 (1931).

β-phenylethylamine, while in the hydrogenation of butyl cyanide the ratio of secondary to primary amine was 1 to 3. The formation of the secondary amine in the hydrogenation of aniline is certainly the result of an alkylation in the sense of equation II. However, this reaction cannot account for the formation of secondary amines in the hydrogenation of cyanides for reaction II did not occur at temperatures below about 160–170°, while the cyanides were hydrogenated at 125° or lower.

Mignonac[4] proposed the hypothesis that the formation of dibenzylamine in the hydrogenation of phenyl cyanide depended upon the intermediate formation of hydrobenzamide from benzalimine as shown in equations III to V.

$$RC{\equiv}N + H_2 \longrightarrow RCH{=}NH \quad \text{(III)}$$

$$3RCH{=}NH \longrightarrow RCH(N{=}CHR)_2 + NH_3 \quad \text{(IV)}$$

$$RCH(N{=}CHR)_2 + H_2 \longrightarrow RCH_2NH_2 + (RCH_2)_2NH \quad \text{(V)}$$

Rupe and Glenz[5] also postulated a compound of the hydrobenzamide type as an intermediate in the formation of secondary amines from cyanides although according to their scheme it results from the reaction of ammonia with an aldehyde produced by hydrolysis of an aldimine.

Von Braun[6] suggested that the formation of secondary amines in the hydrogenation of cyanides was due to the interaction of an aldimine (formed as in equation III) with a primary amine as shown in equations VI and VII, VIII (or VI and VIIa, VIIIa).

$$RCH{=}NH + H_2 = RCH_2NH_2 \quad \text{(VI)}$$

$$RCH{=}NH + RCH_2NH_2 = RCH{=}NCH_2R + NH_3 \quad \text{(VII)}$$

$$RCH{=}NCH_2R + H_2 = (RCH_2)_2NH \quad \text{(VIII)}$$

$$RCH{=}NH + RCH_2NH_2 = RCH(NH_2)NHCH_2R \quad \text{(VIIa)}$$

$$RCH(NH_2)NHCH_2R + H_2 = (RCH_2)_2NH + NH_3 \quad \text{(VIIIa)}$$

Kindler[3] considers that the aldimine is hydrolyzed to an aldehyde which then reacts with primary amine to give the anil which is hydrogenated to the secondary amine.

The formulations of Rupe and Glenz and of Kindler are of no significance in connection with the hydrogenations reported in this paper for our results were obtained in most cases under anhydrous conditions, although it was shown that the ratio of primary and secondary amines produced in the hydrogenation of benzyl cyanide was the same irrespective of whether or not water was present in the reaction medium.

The salient facts in regard to the mechanism of the reaction seem to be as follows:

1. Benzalimine (as the hydrochloride) reacts with aniline to give benzalaniline as indicated in equation VII for the reaction of an imine

[4] Mignonac, *Compt. rend.*, **171**, 114 (1930).

[5] Rupe and Glenz, *Helv. Chim. Acta*, **5**, 937 (1922).

[6] Von Braun, *Ber.*, **56**, 1988 (1923).

and an amine. This reaction was discovered by Busch[7] and has given a 67% yield of benzalaniline in this Laboratory.

2. Benzalaniline is almost quantitatively hydrogenated to the corresponding secondary amine.

3. Benzalimine reacts with itself to give hydrobenzamide as indicated in equation IV.

4. Hydrobenzamide upon hydrogenation gave a 94% yield of benzylamine and a 96% yield of dibenzylamine as calculated on the basis of equation V. Mignonac obtained much higher yields of dibenzylamine with corresponding lower yields of the primary amine. The results here reported are thus in better accord with his formulation than were his own experiments. This better agreement of experiment with hypothesis is no doubt due to the greater activity of our catalyst, which minimized the importance of side reaction.

5. Hydrobenzamide as shown by Busch and confirmed in this Laboratory is readily converted into benzalimine even at 5° according to equation XI.

$$C_6H_5CH(N{=}CHC_6H_5)_2 + 2C_2H_5OH + 2HCl = 2C_6H_5CH{=}NHHCl + C_6H_5CH(OC_2H_5)_2 \quad (XI)$$

The facts listed as 1 and 2 are in accord with von Braun's hypothesis as to the mechanism of the formation of secondary amines in the hydrogenation of cyanides, while facts 3 and 4 are in harmony with Mignonac's hypothesis. However, in view of fact 5 there seems to be no reason to assume that both a synthesis and a cleavage occur, such as is involved in the latter hypothesis. von Braun's hypothesis seems to be entirely adequate to explain the results obtained.

The above discussion of the reactions resulting in the formation of secondary amines in the hydrogenation of cyanides is also pertinent to the formation of secondary amines in the hydrogenation of oximes, nitro and nitroso derivatives, since highly reactive imines would also be formed in the course of these hydrogenations.

Alkylation of Amines with Aldehydes and Ketones.—Another method for the catalytic alkylation of ammonia and amines is that discovered by Mignonac[8] and applied among others by Skita and Kiel[9] and Manske and Johnson.[10] This method involves the reaction of an aldehyde or ketone with ammonia or an amine in a solvent followed immediately by hydrogenation. The method is illustrated in equations XII and XIII.

$$C_6H_{11}NH_2 + C_3H_7CHO = (C_3H_7CH(OH)NHC_6H_{11}) \text{ or } (C_3H_7CH{=}NHC_6H_{11} + H_2O) \quad (XII)$$

$$C_3H_7CH{=}NHC_6H_{11} + H_2 = C_4H_9NHC_6H_{11} \quad (XIII)$$

[7] Busch, *Ber.*, **29**, 2114 (1896).

[8] Mignonac, *Compt. rend.*, **172**, 223 (1921).

[9] Skita and Kiel, *Ber.*, **61B**, 1682 (1928).

[10] Manske and Johnson, THIS JOURNAL, **51**, 580 (1929).

This method has proved to be very satisfactory in this Laboratory in the preparation over a nickel catalyst of cyclohexyl-*n*-butylamine, *n*-butyl-β-phenylethylamine, dicyclohexylamine and N-*n*-butylpiperidine.

Experimental Results

The nickel catalysts were prepared and used as previously described.[1] Unless stated otherwise the reactions were carried out at 200° under a pressure of approximately 100 atmospheres of hydrogen.

There are listed in Table I for certain alkylation experiments the names and amounts in moles of reactants, the time of heating, the weight of catalyst, the weights and boiling ranges of the more important fractions and such information or modification of the procedure and identification and analysis of products as is necessary.

TABLE I

SUMMARY OF EXPERIMENTAL RESULTS IN SIMPLE ALKYLATIONS

Amines	Moles	Alcohol	Moles	Time, hrs.	Catalyst, g.	Products
Cyclohexylamine	0.55	Ethanol	1.2	4.5	4	Cyclohexylamine 8.6 g. (130–140°) (16%) N-Ethylcyclohexylamine 31.5 g. (46%) (155–160°)[a] N-Diethylcyclohexylamine 6.0 g. (14%) (190–210°)
Piperidine	.5	Ethanol[b]	1.0	3.5	2	N-Ethylpiperidine 44.5 g. (80%) (125–129°)[c]
α-Methylpiperidine	.5	Ethanol	1.0	7.0	3	N-Ethyl-α-methylpiperidine 53 g. (84%) (145–147°)[d]
β-Phenylethylamine	.33	Butanol-1[b]	0.68	4	4	β-Phenylethylamine 17 g. (78–85°) (10 mm.) (43%) N-*n*-Butylphenylethylamine 20 g. (125–130°) (10 mm.) (34%) N-Di-*n*-butylphenylethylamine 10 g. (160–170°) (10 mm.) (13%) Di-β-phenylethylamine 6.2 g. (195–205°) (10 mm.) (9%)
α-Methylpiperidine	.5	Butanol-1[b]	1.0	3.5	3	N-*n*-Butyl-α-methylpiperidine 60 g. (78%) (185–190°)[e]
Piperidine	.5	Ethanol	1.0	3.5	2	N-Ethylpiperidine 42.7 g. (78%) (125–129°)[c]
Piperidine	.45	Butanol-1	0.5	3.5	3	N-*n*-Butylpiperidine 22.1 g. (35%) (167–172°)[f]
n-Amylamine	.5	Butanol-1 (or ethanol)	1.0	3.5	3	*n*-Amylamine 20.2 g. (100–105°) (47%) Di-*n*-amylamine 12 g. (200–205°) (36%)
Piperidine	.45	Cyclohexanol	0.9	7.8	4	N-Cyclohexylpiperidine 57 g. (76%) (98–100°) (10 mm.)[g]
α-Methylpiperidine	.21	Ethanol	0.5	3	1	N-Ethyl-α-methylpiperidine 16 g. (145–147°) (60%)
n-Amylamine	.29	None	...	3.5	1	Ammonia and di-*n*-amylamine
Cyclohexylamine	.25	None	...	3.5	1	Cyclohexylamine 15 g. (130–134°) (60%) Dicyclohexylamine 8 g. (245–253°) (36%)

[a] The m. p. of the phenylisocyanate derivative 124–125°; *cf.* Sabatier and Senderens.

Compt. rend., **138**, 457, 1257 (1904). [b] The alkylation was made under nitrogen. [c] The m. p. of picrate 165–166°; *cf.* Evans, *J. Chem. Soc.*, **71**, 522 (1897). [d] The m. p. of the picrate from alcohol 188–189°; *cf.* Ladenburg, *Ann.*, **304**, 56 (1899). [e] M. p. of picrate 113–114°. The hydrochloride was prepared in ether solution. *Anal.* Calcd. for $C_{10}H_{22}NCl$: Cl, 18.54. Found: Cl, 18.61. [f] The low yield was due to the smaller amount of alcohol. M. p. of the picrate of the secondary amine 132°. *Cf.* von Braun, *Ber.*, **40**, 3930 (1908). [g] M. p. of picrate 127–127.5°. Hydrochloride. *Anal.* Calcd. for $C_{11}H_{22}NCl$: Cl, 17.45. Found: Cl, 17.48.

There are summarized in Table II the more significant data in the hydrogenation of various compounds.

TABLE II

HYDROGENATION OF VARIOUS COMPOUNDS

Hydrogen acceptor	Moles	Temp., °C.	Time, hours	Catalyst, g.	Products
Benzyl cyanide	1.0	125	2	5	β-Phenylethylamine 90 g. (74%) Di-β-phenylethylamine 28 g. (25%)
Butyl cyanide	0.96	150	2	5	*n*-Amylamine 50 g. (100–105°) (60%) Di-*n*-amylamine 14.5 (200–208°) (20%)
Butyl cyanide (50 cc. ether)	.5	125	2.5	2	*n*-Amylamine 25.1 g. (56%) (102–106°) Di-*n*-amylamine 8.8 (22%) (200–208°)
Butyl cyanide (60 cc. ethanol)	.5	150	4	3	*n*-Amylamine 14.5 g. (32.5%) (102–106°)[a] Di-*n*-amylamine 8.9 (22.3%) (200–208°)
Benzyl cyanide (50 cc. β-phenylethylamine	.6	125	1.7	3	β-Phenylethylamine (solvent and product) Di-β-phenylethylamine (0.07 mole) (23%)
Hydrobenzamide (in 110 cc. of ethanol)	.16	100	0.6	4	Benzylamine 16.8 g. (60–64°) (4 mm.) (94%)[b] Di-benzylamine 31.8 (120–123°) (1 mm.) (96%)
Benzalaniline (in 50 cc. of ethanol)	.077	70	0.25	1	Benzylaniline 13.5 g. (96.5%) (144–146°) (1 mm.)
α-Benzaldoxime (in 80 cc. of ethanol)	.33	100	0.75	3	Benzylamine 27.2 g. (77%) (47–50°) (1 mm.) Dibenzylamine 6.2 g. (19%) (160–164°) (1 mm.)
α,β-Cinnamaldoxime (in 70 cc. ether)	.33	100	2	3	γ-Phenylpropylamine 20.8 g. (75–80°) (1 mm.) (42%)
Sodium *p*-dimethylaminoazobenzene sulfonate in 100 cc. of water	.185	100	1	4	*p*-Aminodimethylaniline 17.6 g. (87%) (95–100°) (1 mm.) *p*-Sulfanilic acid 23 g. (72%)
(Cyclohexylamine) (Cyclohexanone)	.4 .4	125	2	4	Cyclohexanol 11.2 g. (155–165°) (28%) Dicyclohexylamine 50.3 g. (70%) (115–120°) (10 mm.)[c]
Cyclohexylamine Butyraldehyde	.5 .55	125	1	4	N-*n*-Butylcyclohexylamine 70.1 g. (200–204°) (91%)[d]
Piperidine Butyraldehyde	.45 .5	125	2	4	N-*n*-butylpiperidine 55 g. (93%) (170–174°)[e]
β-Phenylethylamine Butyraldehyde	.41 .42	125	1	4	β-Phenylethylamine 10.3 g. 80–85° (10 mm.) (21%) N-*n*-Butyl-β-phenylethylamine 26.2 g., 130–135° (10 mm.)[f] (36%) N-Di-*n*-butyl-β-phenylethylamine 10 g. 162–168° (10 mm.)[g] (11%)

[a] The low yield is due to the loss of amine in the distillation of the alcohol. [b] M. p. of benzoyl derivative 106°. [c] M. p. of hydrochloride 333°. *Anal.* Calcd. for $C_{12}H_{24}$-

NCl: Cl, 16.29. Found: Cl, 16.16. [d] Hydrochloride. *Anal.* Calcd. for $C_{10}H_{22}NCl$: Cl, 18.53. Found: Cl, 18.41. [e] M. p. of picrate 131–132°; *cf.* v. Braun, *Ber.*, **40**, 3930 (1908). [f] Hydrochloride. *Anal.* Calcd. for $C_{12}H_{20}NCl$: Cl, 16.61. Found: Cl, 16.72. [g] Hydrochloride, *Anal.* Calcd. for $C_{16}H_{28}NCl$: Cl, 13.18. Found: Cl, 13.01.

Summary

The formation of secondary amines from primary amines or during the hydrogenation of cyanides, oximes, etc., over a nickel catalyst may result from three types of reactions: (1) reaction of amines with alcohol with the elimination of water; (2) reaction of two molecules of an amine with elimination of ammonia; (3) reaction of alkylidene imines with themselves or with amines. Reactions of types 1 and 2 are induced by the nickel catalyst used in this Laboratory at temperatures above 160–170°. These reactions account in whole or in part for the secondary amines formed in hydrogenations carried out above this range of temperature. Reactions of type 3 do not require a catalyst and occur spontaneously at room temperature. Reactions of this type account for the formation of secondary amines in the hydrogenation of cyanides and oximes and probably of other nitrogenous compounds which can be hydrogenated below approximately 175°. The amount of material entering into these three types of "side" reactions may be minimized by the use of more active nickel catalysts.

The following transformations have been carried out sufficiently successfully with a nickel catalyst so that the methods used seem to merit consideration for preparing these and similar compounds: N-ethylcyclohexylamine from ethanol and cyclohexylamine, N-ethylpiperidine from ethanol and piperidine, N-ethyl-α-methylpiperidine from ethanol and α-methylpiperidine, N-butyl-β-phenylethylamine from butanol and β-phenylethylamine, N-butyl-α-methylpiperidine from butanol and α-methylpiperidine, N-cyclohexylpiperidine from cyclohexanol and piperidine, N-butylpiperidine from butyraldehyde and piperidine, dicyclohexylamine from cyclohexylamine and cyclohexanone, N-butylcyclohexylamine from butyraldehyde and cyclohexylamine, N-*n*-butyl-β-phenylethylamine from butyraldehyde and β-phenylethylamine, diamyl and dicyclohexylamine from the corresponding primary amines, *n*-amyl and di-*n*-amylamine from butyl cyanide, benzyl and dibenzylamines from hydrobenzamide, *p*-aminodimethylaniline from methyl orange, benzylamine from benzaldoxime and γ-phenylpropylamine from cinnamaldoxime.

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