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Hydrogenation of Basic Nitriles with Raney Nickel

BY WOLFGANG HUBER

According to von Braun[1] the hydrogenation of a nitrile is expressed by the following series of reactions

$$RCN + H_2 \longrightarrow RCH{=}NH \qquad (1)$$

$$RCH{=}NH + H_2 \longrightarrow RCH_2NH_2 \qquad (2)$$

$$RCH{=}NH + RCH_2NH_2 \longrightarrow RCH(NH_2)NHCH_2R \qquad (3)$$

$$RCH(NH_2)NHCH_2R + H_2 \longrightarrow RCH_2NHCH_2R + NH_3 \qquad (4)$$

Numerous procedures have been described in the literature to minimize the formation of secondary amines according to equations 3 and 4. Thus, Carothers[2] hydrogenated benzonitrile to benzylamine with platinum oxide in good yields using acetic anhydride as solvent, and attributed the high yield to the fact that the primary amine is quickly acetylated and therefore protected against interaction with the intermediate imine. Hartung[3] used alcohol containing one mole of hydrochloric acid and palladized charcoal in the hydrogenation of aromatic nitriles, and Kindler[4] used glacial acetic acid containing one mole of concentrated sulfuric acid and palladium sponge to hydrogenate nitriles to the corresponding β-arylethylamines. The high yield of primary amines in these reactions is attributed to the removal of the base from the reaction equilibrium by salt formation, thus preventing the possible interaction with the intermediary imine according to equation 3.

In connection with other work it was of interest to develop a method for the reduction of basic heterocyclic nitriles to the corresponding primary amines exclusively. It was found that such nitriles, and for that matter basic nitriles in general, cannot be hydrogenated in good yields to the corresponding primary amines by any of the aforesaid methods. It is obvious that basic nitriles in the presence of acids or acetic anhydride will undergo salt formation or acetylation, the latter products being considerably less soluble than the parent nitriles in the non-aqueous solvents generally used in hydrogenations. The resulting heterogeneous reaction mixture slows the hydrogenation speed and the subsequent coating of undissolved nitrile salt with primary amine salt, precipitating from the solution, tends to slow further and eventually inhibit the reduction. The poisoning effect of anhydrous mineral acids on catalysts such as platinum oxide, palladized charcoal and palladium on zirconium oxide is an additional factor which tends to slow the smooth and speedy reduction of basic nitriles. In the hydrogenation of 2-methyl-4-aminopyrimidine-5-nitrile with either one of the aforesaid catalysts the formation of secondary amine is thus always considerable or even predominant, the reduction time is markedly increased and often, due to catalyst poisoning, the hydrogenation is incomplete. Data illustrating this behavior are listed in Table I.

The hydrogenation of basic nitriles to the corresponding primary amines, however, can be carried out smoothly and with excellent yields with Raney nickel in organic solvents and in the presence of ammonia. Schwoegler and Adkins[5] were the first to use Raney nickel and ammonia in the hydrogenation of aliphatic nitriles, thus obtaining *n*-pentyl- and *n*-heptylamine in excellent yields. The results of this study seem to confirm their assumption that it is the ammonia rather than the primary amine which will react with the imine formed according to equation 1 of the von Braun scheme, thus giving rise to the formation of additional primary amine according to the equations

$$RCH{=}NH + NH_3 \longrightarrow RCH(NH_2)_2 \qquad (5)$$

$$RCH(NH_2)_2 + H_2 \longrightarrow RCH_2NH_2 + NH_3$$

The yields, in all reactions studied, were found to be nearly quantitative. Secondary amines, if found at all, were rarely present in excess of 5%. The presence of ammonia, however, is essential since reduction with Raney nickel alone always leads to the formation of large amounts of secondary amines. Indeed, a rather high concentration of ammonia is desirable; generally 3-4 moles of ammonia were used per mole of nitrile. Using less than 2.5 moles of ammonia per mole of nitrile seems to cause a competitive reaction between ammonia-imine and primary amine-imine in equation 5, thus increasing the formation of secondary amine. With all compounds investigated, the reduction proceeded smoothly at room temperature with hydrogen pressures ranging from 60 to 200 lb./sq. in. Vigorous shaking of the autoclave seems to be essential for a smooth reduction at these pressures, since it was found that in slowly shaking autoclaves considerably higher hydrogen pressures were necessary to insure a smooth hydrogenation. A variety of organic solvents has been used including methanol, ethanol, 2-propanol, butanol, dioxane, *n*-butyl ether and formamide. For all practical purposes methanol was found to be an excellent solvent, whereas in water or in aqueous solvents the amounts of secondary amines present were always considerable. The hydrogenation proceeds very quickly, the average time for 0.5 mole

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[1] von Braun, Blessing and Zobel, *Ber.*, **56**, 1988 (1923).

[2] Carothers and Jones, THIS JOURNAL, **47**, 3051 (1925).

[3] Hartung, *ibid.*, **50**, 3370 (1928).

[4] Kindler, Peschke and Brandt, *Ber.*, **68**, 2241 (1935).

[5] Schwoegler and Adkins, THIS JOURNAL, **61**, 3499 (1939).

TABLE I

HYDROGENATION OF 2-METHYL-4-AMINOPYRIMIDINE-5-NITRILE[6] WITH VARIOUS SOLVENTS AND CATALYSTS

Size of batch, mole	Catalyst	Solvent	Pressure, lb.	Temp., °C.	Reduction time, hours	Primary[a] amine, % yield	Secondary[b] amine, % yield	Uptake of[c] hydrogen, % of theory
0.1	Palladium on zirconium oxide[d]	Ac_2O	60	28	18	47	49	96
.1	Palladium on zicronium oxide[d]	EtOH-HCl	60	28	9.5	74	24.5	100
1.0	Palladium on zirconium oxide[d]	EtOH-HCl	60	55	37	32	60	88
0.1	Palladium on zirconium oxide[d]	EtOH-H_2SO_4	55	29	11.5	38	30	74
.1	Palladium on zirconium oxide[d]	AcOH-HCl	80	55	8.5	70	29	102
.1	Palladium on zirconium oxide[d]	AcOH-H_2SO_4	80	26	13	62	36.5	99
.1	Palladized charcoal	Ac_2O	60	25	14.5	42	41	86
.1	Palladized charcoal	EtOH-HCl	80	25	11	58	36	96
.4	Palladized charcoal	EtOH-HCl	80	55	26	34	50	85
.05	Palladized charcoal	EtOH-H_2SO_4	80	31	6.5	64	34	104
.1	Palladized charcoal	AcOH-HCl	80	29	10	61	30	94
.1	Pt_2O Adams catalyst	Ac_2O	80	55	9.5	69	30	100
.1	Pt_2O Adams catalyst	EtOH-HCl	60	29	9.5	52	46	107
.1	Pt_2O Adams catalyst	EtOH-H_2SO_4	60	29	14	44	43	87

[a] The % of primary amine present was determined by condensation of the free base wtih potassium dithioformate (see Huber, THIS JOURNAL, 65, 2225 (1943)) and subsequent weighing of the precipitated 2-methyl-4-amino-5-thioformylaminomethylpyrimidine. [b] The % of secondary amine present was determined from the weight of the 2-methyl-4-amino-5-hydroxymethylpyrimidine obtained by the treatment of the secondary amine salt with dilute alkali. For details see experimental part. [c] In the case of very slow hydrogen uptake fresh catalyst was always added; generally, however this had no lasting beneficiary effect. [d] Addition of small amounts of a 5% aqueous $PdCl_2$ solution did not improve the rate or the speed of the hydrogenation.

TABLE II

HYDROGENATION OF BASIC NITRILES

Nitrile	Product	B. p., °C. (mm.)	M. p., °C.	Yield, %	Reduction time, min.	Batch size, mole	Average pressure, lb.	Amount of catalyst, g.
2-Methyl-4-aminopyrimidine-5-nitrile[7]	2-Methyl-4-amino-5-aminomethylpyrimidine.[7] As Dihydrochloride.		262, dec.	93.3	80	2.0	125	50
	Di-(2-methyl-4-amino-5-pyrimethyl) amine.[a]			4.2	80	2.0	125	50
2,4-Diaminopyrimidine-5-nitrile[8]	2,4-Diamino-5-aminomethyl-pyrimidine.[8] As dihydrochloride		258, dec.	94.0	50	.5	200	25
	Di-(2,4-diamino-5-pyrimethyl)amine[a]			4.1	50	.5	200	25
N-Benzyl-4-phenylpiperidine-4-nitrile[9]	N-Benzyl-4-phenyl-4-aminomethylpiperidine	224–26 (1)	71–72	91	90	.5	125	29
Pyridine-3-nitrile	3-pyridylmethylamine	98–99 (12)		89	55	.5	100	25
	Di-(3-pyridylmethyl)-amine			8	55	.5	100	25
4-Methyl-5-cyanomethylthiazole[10]	4-Methyl-5-β-aminoethylthiazole[10]	79–80 (1)		92	80	.5	125	29
4-Diethylaminobutyronitrile[11]	4-Diethylamino-butylamine[12]			97	65	2.0	100	55
	Di-(4-diethylaminobutyl)-amine			2	65	2.0	100	55
Furan-2-nitrile[b]	2-Furyl-methylamine	49–50 (10)		84	76	1.0	125	45
	Di-(2-furylmethyl)-amine	126–28 (10)		11	76	1.0	125	45

[a] Determined as 2-methyl-4-amino-5-oxymethylpyrimidine. [b] Although not a basic nitrile, this method gave excellent yields of the primary amine which were considerably in excess of those reported in the literature.[5,13]

batches being from thirty to eighty minutes. Compounds hydrogenated include pyrimidine, piperidine, pyridine, thiazole, furan and aliphatic basic nitriles. In each reduction the corresponding primary amine was obtained in excellent yields. A summary of the results is found in Table II. The description of the apparatus and a detailed procedure are given in the experimental part.

It is believed that in the preparation of primary amines from basic nitriles in general and from heterocyclic basic nitriles in particular the hydrogenation with Raney nickel in the presence of ammonia will often suggest itself as the method of choice.

Experimental

Apparatus.—The reduction vessel was an ordinary steel cylinder, 9 × 6 inches with rounded bottom and flanged top with lead gasket. A pressure gage and an inlet valve were welded onto the side wall of the vessel, the valve being connected with a copper spiral to a hydrogen tank. The necessary agitation was provided by a Schaerr type shaker into which the reduction vessel was placed. The total capacity of the vessel was 4 liters. After calibration the hydrogen consumption was measured by the pressure drop as indicated by the pressure gage. The copper spiral between reduction vessel and hydrogen tank was made flexible enough to stay on during the shaking to facilitate quick recharging in cases where the size of the batch required hydrogen in excess of the volume available.

Method.—Average pressures as given in Table II were calculated as the mean between highest and lowest pressure

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(6) Grewe, *Z. physiol. Chem.*, **242**, 89 (1936).
(7) Grewe, *ibid.*, **242**, 89 (1936).
(8) Huber, THIS JOURNAL, **65**, 2222 (1943).
(9) Eisleb, *Ber.*, **74**, 1433 (1941).
(10) Price and Pickel, THIS JOURNAL, **63**, 1069 (1941).
(11) Strukov, *Khim. Farm. Prom.*, 332 (1933).
(12) von Braun and Lemke, *Ber.*, **55**, 3634 (1922).
(13) Paul, *Bull. soc. chim.*, [5] **4**, 1121 (1937).

as indicated by the side wall gage. For example, if the pressure at the beginning of the hydrogenation was 200 lb./sq. in. and dropped during the course of the reduction to 150 lb./sq. in., to be recharged then to 200 lb./sq. in. again, the average pressure was taken as 175 lb./sq. in.

The Raney nickel was prepared according to the method of Covert and Adkins.[14] The catalyst was washed with water till free of alkali, the water replaced by methanol and the catalyst kept under methanol till ready for use. In none of the experiments had the Raney nickel been stored for more than three weeks. Although the same catalyst can be used several times, it is better to use fresh Raney nickel each time in order to insure a good reduction speed.

The hydrogen was the ordinary commercial product which gave satisfactory results without purification.

The nitriles, prepared according to the literature, were purified until their physical characteristics were constant.

In a typical experiment anhydrous ammonia (4 moles) was incorporated with cooling into anhydrous methanol (35 moles) and the solution filled into the reduction vessel. Nitrile (1 mole) and Raney nickel (1.5 moles)[15] were then added with final attachment of gasket and flange to give a pressure tight seal. The size of the reaction vessel and the volume of the charge were adjusted so that a pressure drop of 50 lb. was equivalent to an uptake of 0.33 mole of hydrogen. The vessel was charged with hydrogen to the maximum pressure necessary and shaking started thereafter. After the uptake of hydrogen equivalent to a 50 lb. pressure drop, fresh hydrogen was charged up to the initial pressure level. This operation was repeated until the calculated amount of hydrogen had been consumed. In all the experiments in this study the hydrogenation stopped after two moles of hydrogen had been consumed, indicating that reduction under these conditions is limited to the nitrile group. The spent catalyst was removed by filtration, washed with methanol and the filtrate decolorized with charcoal, if necessary. After removal of the solvent the residue was freed from unchanged nitrile, if any, and the primary amine purified by distillation, recrystallization, or via its salts. Secondary amine, when present, was isolated by fractional distillation or crystallization.

N-Benzyl-4-phenyl-4-(aminomethyl)-piperidine.—One hundred thirty-one grams of N-benzyl-4-phenylpiperidine-4-nitrile[16] in 560 cc. of methanol containing 34 g. of anhydrous ammonia and 29 g. of Raney nickel took up the calculated amount of hydrogen in ninety minutes at an average pressure of 125 lb./sq. in. From the oily residue, obtained after removal of the solvent, N-benzyl-4-phenyl-4-(aminomethyl)-piperidine was secured by vacuum distillation; b. p. 224–26° (1 mm.); yield, 121 g. or 91%; m. p. 71–72°.

Anal. Calcd. for $C_{19}H_{24}N_2$: N, 10.00. Found: N, 9.84.

On titration the base consumed two moles of hydrochloric acid. The dihydrochloride was recrystallized from acetone–ethanol; m. p. 202–204° (dec.).

Anal. Calcd. for $C_{19}H_{24}N_2Cl_2$: Cl, 20.11. Found: Cl, 19.68.

The dipicrate melts at 229–30°.

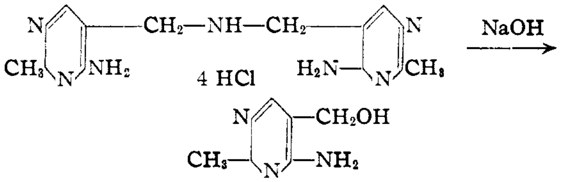
Di-(2-methyl-4-amino-5-pyrimethyl)-amine.—Seven grams of 2-methyl-4-aminopyrimidine-5-nitrile was dissolved in 150 cc. of water containing two mols of hydrochloric acid and 100 mg. of moderately active palladized charcoal. The reduction was performed in a Parr-Burgess hydrogenator and the theoretical amount of hydrogen had been taken up after sixteen hours of shaking at room temperature under a pressure of 60 lb./sq. in. After removal of the catalyst, the filtrate was concentrated to a small volume and the reduction product precipitated with excess ethanol containing some hydrochloric acid. The di-(2-methyl-4-amino-5-pyrimethyl)-amine tetrahydrochloride thus obtained was purified by recrystallization from 85% ethanol. Small amounts of 2-methyl-4-amino-5-aminomethylpyrimidine dihydrochloride which were present stayed in solution due to the greater solubility of this compound in 85% ethanol. The tetrahydrochloride melted at 357° (dec.).

Anal. Calcd. for $C_{12}H_{21}N_7Cl_4$: N, 24.19; Cl, 35.06. Found: N, 24.25; Cl, 35.20.

The picrate as obtained from the hydrochloride crystallizes from water; m. p. 269–70° dec.

The free secondary amine is unstable. Even on addition of the calculated amount of dilute alkali to a chilled solution of the tetrahydrochloride the carbon–nitrogen bond is broken with evolution of ammonia and formation of 2-methyl-4-amino-5-hydroxymethylpyrimidine. The latter proved to be identical in all respects with an authentic sample prepared according to the literature.[17] Table III shows the respective data of the two specimens and their derivatives. This instability of the carbon–nitrogen linkage to hydrolysis is not uncommon[18] and accounts also for the fact that the small amounts of di-(2-methyl-4-amino-5-pyrimethyl)-amine formed during the reduction of 2-methyl-4-aminopyrimidine-5-nitrile with Raney nickel in the presence of ammonia are often not found as such but in the form of 2-methyl-4-amino-5-(hydroxymethyl)-pyrimidine.

TABLE III



	M. p., °C.	M. p. (lit.), °C.	Mixed m. p., °C.
Alcohol	192–193	194	191–193
Hydrochloride	220–222	224	223–224
Picrate	194–195	194–196	194–196

Anal. Calcd. for $C_6H_{10}ON_3Cl$: N, 23.93; Cl, 20.22. Found: N, 23.76; Cl, 20.37.

Di-(4-diethylaminobutyl)-amine.—This secondary amine was obtained by vacuum fractionation of the still foots from the preparation of 4-diethylaminobutylamine. If the primary amine is prepared by the reduction of the corresponding nitrile with Raney nickel in the presence of ammonia the amount of secondary amine does not usually exceed 2–3%; b. p. 125–26° (2 mm.).

Anal. Calcd. for $C_{16}H_{37}N_3$: N, 15.49. Found: N, 15.36.

The hydrochloride as obtained with ethanolic hydrogen chloride and precipitated with ether is very hygroscopic and cannot be conveniently purified.

A crystalline, non-hygroscopic picrate was obtained from an alcoholic solution of the base with alcoholic picric acid in the presence of two moles of hydrochloric acid, m. p. 90–93°.

Anal. Calcd. for $C_{24}H_{43}O_{14}N_9$: C, 42.27; H, 6.36. Found: C, 42.51; H, 6.19.

Summary

Basic nitriles cannot be hydrogenated to the

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[14] Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

[15] In large batches considerably less Raney nickel is necessary.

[16] Eisleb, *Ber.*, **74**, 1433 (1941); *C. A.*, **36**, 5465 (1942). The nitrile and the N-benzyl-4-phenyl-4-(aminomethyl)-piperidine dihydrochloride were kindly prepared by Dr. C. E. Kwartler of this Laboratory.

[17] Andersag and Westphal, *Ber.*, **70**, 2035 (1937).

[18] Kharasch and Howard, THIS JOURNAL, **56**, 1370 (1934); Huber, *ibid.*, **65**, 2222 (1943). For a summary, see Houben-Weyl, "Die Methoden der organischen Chemie," second ed., 1924, Vol. 4, pp. 446–469.

corresponding primary amines in good yields by methods involving the use of acidic solvents and palladium or platinum type catalysts.

The hydrogenation with Raney nickel in the presence of ammonia, however, results in the formation of primary amines in nearly quantitative yields. Compounds hydrogenated include pyrimidine, piperidine, pyridine, thiazole and aliphatic basic nitriles.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF RICHMOND]

Tris-(hydroxymethyl)-aminomethane Derivatives. I. Polyhydroxyamines[1,2]

BY J. STANTON PIERCE AND JOHN WOTIZ[3]

Polyfunctional compounds are of particular interest as they afford opportunities for the synthesis of substances with varied properties, many of which are of practical importance. The ethanolamines have been found to be particularly useful, due to their solubility properties, ease of preparation and low cost. A large and interesting field for the synthesis of more highly polar amino alcohols than the ethanolamines was opened by the recent commercial synthesis of tris-(hydroxymethyl)-aminomethane, $(HOCH_2)_3CNH_2$,[4] (A). In 1897, Piloty and Ruff[5] prepared (A) by the reduction of tris-(hydroxymethyl)-nitromethane which had been prepared two years previously by Henry,[6] by the reaction of nitromethane and formaldehyde.

Various investigators have combined two primary or secondary amino groups by reaction with epichlorohydrin,[7] α,ω-dihalohydrins[8] or α,ω-dihalogenalkanes.[9] This paper takes up the synthesis of polyhydroxyamines by the union of two molecules of (A), mainly through methylene or methylene and hydroxymethylene groups, by the union of (A) with other amino alcohols through methylene and hydroxymethylene groups, and by the alkylation of (A) with chlorohydrins. A subsequent paper will take up the preparation of alkyl and alkaryl derivatives of (A).

The symmetrical polyhydroxydisecondary amines described in this paper usually were prepared by heating (A) with an α,ω-dihalide, in most cases the bromide. The reactions were carried out under reflux, with no solvent or with alcohol as solvent, and in sealed tubes, with alcohol as solvent. The asymmetrical diamines, all of which are derivatives of 2-propanol, were prepared by treating a secondary amine with epichlorohydrin at a temperature not exceeding 30° and by the reaction of the product thus formed with (A) at elevated temperature, with alcohol as solvent. Also, two molecules of (A) reacted with epichlorohydrin, to form a symmetrical derivative. Monoalkylation products of (A) were prepared by reaction with halohydrins.

The greatest difficulty in the preparation of the polyhydroxyamines described in this paper was their isolation and purification. Since the free bases, as obtained, showed no tendency to crystallize, they were converted to hydrobromides or hydrochlorides for identification and analysis. A typical mixture in the preparation of a symmetrical disecondary amine likely contained dihalide, (A), the monoalkylation product of (A) and the desired disecondary amine, the latter three compounds being present both as the free bases and as the halogen acid salts. Usually, excess halogen acid was added to convert all of the free bases to their salts. The unreacted alkylene dihalide was removed by evaporation or extraction with ether. Finally, purification was effected by fractional crystallization or by selective extraction with two solvents, evaporation of the solvent, if necessary, and trituration of the oily residue with alcohol or acetone or a mixture of the two solvents. Since this purification involved so much loss of material, the yield is given only in the case of 1,3-bis-[tris-(hydroxymethyl)-methylamino]-2-propanol, the compound which was studied most fully.

The polyhydroxyamines described in this paper are characterized by their very high water solubility, both as the free bases and in the form of their salts with hydrochloric or hydrobromic acid. Some of these derivatives of (A) have a great tendency to hold ferric hydroxide, bismuth hydroxide and some other metallic hydroxides in solution. The solubilizing action of the derivatives of (A) is being studied with the view to technical and pharmaceutical applications and will be reported elsewhere. Each of these compounds has one or two secondary amino groups. The high proportion of hydroxyl groups and likely their spatial arrangement makes difficult some of the reactions

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(3) Taken from the thesis submitted by John Wotiz in partial fulfillment for the degree of Master of Science. Present address, Department of Chemistry, The Ohio State University, Columbus, Ohio.

(4) C. L. Gabriel, *Ind. Eng. Chem.*, **32**, 891 (1940).

(5) O. Piloty and O. Ruff, *Ber.*, **30**, 1665, 2062 (1897).

(6) Henry, *Bull. soc. chim.*, [3] **13**, 1001 (1895).

(7) O. Eisleb, U. S. Patent 1,790,042 (1931); Groggins and Stirton, *Ind. Eng. Chem.*, **29**, 1359 (1937).

(8) J. F. Olin, U. S. Patent 2,042,621 (1936); V. Kartaschoff, U. S. Patent 2,149,527 (1939).

(9) I. G. Farbenindustrie A. G., British Patent 459,746 (1937).