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The Reductive Alkylation of Primary Aromatic Amines with Raney Nickel and Alcohols

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Secondary amines form readily from primary aromatic amines, primary or secondary alcohols and relatively large amounts of Raney nickel. Aniline, 2,5-dimethoxyaniline and 2-naphthylamine represent the amines successfully employed while ethyl, *n*- and isopropyl, *n*-butyl, cyclohexyl and benzyl alcohols represent the alcohols that were used. The reaction takes place at steam-bath temperature and yields of pure secondary amines are generally satisfactory. Benzylamine and 2-phenylethylamine with excess Raney nickel in ethyl alcohol gave dibenzylamine and di-(2-phenylethyl)-amine, respectively.

During investigation of the cleavage of carboxylic acid hydrazides with Raney nickel,[1] it was found that 1-*n*-butyryl-2-phenylhydrazine (I) with *excess* Raney nickel in ethyl alcohol yielded *n*-butyramide. The basic fraction, however, was not aniline but proved to be N-ethylaniline.

$$\underset{\text{I}}{CH_3CH_2CH_2CONHNHC_6H_5} + C_2H_5OH \xrightarrow[\text{Ni}]{\text{Raney}} CH_3CH_2CH_2CONH_2 + C_6H_5NHC_2H_5$$

As a result of this finding, aniline and about three parts of moist Raney nickel[2] in ethyl alcohol were heated on the steam-bath for two hours, and N-ethylaniline[3] was obtained in 80% yield. If one-tenth part Raney nickel was used under these conditions no alkylation resulted and aniline was recovered.

Other examples of this reaction were studied to determine its value as a means of preparing pure secondary amines under mild conditions.[4] First, the alcohol employed in the alkylation reaction was varied. The findings were essentially the same as those reported recently by Rice and Kohn (ref. 3), *i.e.*, N-alkylanilines were formed readily from primary alcohols such as *n*-propyl and *n*-butyl alcohols when heated with aniline and a relatively large amount of Raney nickel catalyst. No alkylation took place when methyl or isopropyl alcohols were used under similar conditions and aniline was recovered.

Next, various amines were tried. Raney nickel in ethyl alcohol with 2-naphthylamine and 2,5-dimethoxyaniline formed N-ethyl-2-naphthylamine and N-ethyl-2,5-dimethoxyaniline in about 80 and 60% yields, respectively. When 2-aminopyridine or 5-aminotetrazole was used, no alkylation occurred, and starting materials were recovered.

The reaction scheme which suggested itself was the same as that given by Rice and Kohn. It involved the dehydrogenation of the alcohol by Raney nickel to give aldehyde, followed by Schiff base formation and subsequent reduction to alkylated amine. Schiff base formation appears to be the limiting step in the conversion. This is based on the observation that 2-aminopyridine and 5-aminotetrazole, which did not undergo reductive alkylation in this reaction, likewise, do not appear to form Schiff bases readily.[5] Also, the failure of isopropyl alcohol in the reaction must be attributed to slow Schiff base formation, since acetone is readily obtained from a mixture of isopropyl alcohol and excess Raney nickel heated under reflux.[6] Furthermore, aniline, isopropyl alcohol and excess Raney nickel heated on the steam-bath *overnight*, rather than for only two hours, gave a 50% yield of N-isopropylaniline. The rapid disproportionation of formaldehyde by Raney nickel[7] may explain the failure of methyl alcohol as an alkylating agent in this reaction.

The reaction of Raney nickel and alcohols with primary aliphatic amines appears to be more complex. When 2-phenylethylamine, ethyl alcohol and Raney nickel were heated on the steam-bath for 30 minutes di-(2-phenylethyl)-amine[8] formed in 50% conversion. Similarly, benzylamine with excess Raney nickel gave dibenzylamine.[8b]

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Experimental

1-*n*-Butyryl-2-phenylhydrazine and Raney Nickel.—A stirred mixture of 4 g. of 1-*n*-butyryl-2-phenylhydrazine,[9] about 12 g. of moist Raney nickel and 100 ml. of 95% ethyl alcohol was heated under reflux for 3 hours. After removal of the nickel by filtration, the alcohol was evaporated on the steam-bath. The residue was dissolved in ether and extracted with 50 ml. of 1 *N* hydrochloric acid. Evaporation of the aqueous extract gave 1.3 g. of product which was identified as N-ethylaniline hydrochloride since it had the same melting point and infrared absorption as authentic material.

The ether layer was dried and after evaporation of the ether about 1 g. of product remained. This material was shown to be butyramide by mixed melting point determination and comparison of infrared absorption with authentic material.

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(1) C. Ainsworth, THIS JOURNAL, **76**, 5774 (1954).

(2) The Raney nickel used throughout these studies was "Raney Catalyst in Water" supplied by the Raney Catalyst Co., Chattanooga, Tennessee. The commercial material was slurried several times with 95% ethanol and stored under ethanol.

(3) Since the completion of our work, R. G. Rice and E. J. Kohn, THIS JOURNAL, **77**, 4052 (1955), reported the N-alkylation of aniline and benzidine with alcohols using about an equal weight of Raney nickel. The reaction mixture was heated for a longer time than that used here.

(4) C. F. Winans and H. Adkins, *ibid.*, **54**, 306 (1932), observed alkylation when aniline, ethanol and a catalytic amount of Raney nickel with hydrogen under pressure were heated to a minimum of 175°. E. F. Pratt and E. J. Frazza, *ibid.*, **76**, 6174 (1954), prepared N-benzylanilines from aniline, benzyl alcohols and U. O. P. nickel in the presence of potassium benzylate.

(5) A. Kirpal and E. Reiter, *Ber.*, **60**, 664 (1927); E. Bures and F. Barsi, *Casopis Ceskoslov. Lekarnictva*, **14**, 345 (1934) [*C. A.*, **29**, 4765 (1935)].

(6) R. Paul, *Bull. soc. chim. France*, **8**, 507 (1941).

(7) M. Delepine and A. Horeau, *ibid.*, **4**, 1524 (1937).

(8) (a) E. C. Kornfeld, *J. Org. Chem.*, **16**, 131 (1951), obtained the same product from phenyl thioacetamide and excess Raney nickel. (b) K. Kindler, *Ann.*, **485**, 113 (1931), showed that hydrogen and palladium converted benzylamine and 2-phenylethylamine to the corresponding diamines. A mechanism for the formation was proposed.

(9) T. Vahle, *Ber.*, **27**, 1513 (1894).

Aniline and Raney Nickel.—(a) A stirred mixture of 9.3 g. (0.1 mole) of aniline, 100 ml. of 95% ethyl alcohol and about 30 g. of moist Raney nickel was heated under reflux for 2 hours. The nickel was removed by filtration and the filtrate was concentrated by heating on the steam-bath. The residue was distilled under reduced pressure and 9.5 g. (about 80% yield) of N-ethylaniline, b.p. 84° (10 mm.), $n^{25}_{\rm D}$ 1.5568, was obtained.

(b) A stirred mixture of 9.3 g. of aniline, 100 ml. of 95% ethyl alcohol and 1 g. of Raney nickel catalyst was treated as in procedure a. The product obtained (about 8 g.) was unchanged aniline.

Using procedure a as the general method, aniline and *n*-propyl, *n*-butyl, cyclohexyl and benzyl alcohols with Raney nickel (previously washed with the appropriate alcohol to remove ethanol) gave N-*n*-propyl, N-*n*-butyl, N-cyclohexyl and N-benzylaniline in 70, 81, 22 and 50% yields, respectively.

2-Naphthylamine and Raney Nickel.—A stirred mixture of 14.3 g. (0.1 mole) of 2-naphthylamine 100 ml. of 95% ethyl alcohol and about 40 g. of moist Raney nickel was heated under reflux for 4 hours. The nickel was removed by filtration and the filtrate distilled under reduced pressure. Following a forerun of alcohol 14 g. (82% yield) of N-ethyl-2-naphthylamine came over as a colorless oil, b.p. 162° (12 mm.), $n^{25}_{\rm D}$ 1.6402.

N-Ethyl-2,5-dimethoxyaniline.—A stirred mixture of 10 g. of 2,5-dimethoxyaniline, about 30 g. of moist Raney nickel and 100 ml. of 95% ethyl alcohol was heated under reflux for 4 hours. After removal of the nickel by filtration the filtrate was heated on the steam-bath to remove alcohol. The residue was distilled under reduced pressure. N-Ethyl-2,5-dimethoxyaniline came over as a colorless oil, b.p. 138° (15 mm.), $n^{25}_{\rm D}$ 1.5501. The yield was 7.3 g. (61%).

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.23; H, 8.36; N, 8.05.

Aniline, Isopropyl Alcohol and Raney Nickel.—(a) A stirred mixture of 9.3 g. (0.1 mole) of aniline, about 30 g. of moist Raney nickel (washed with isopropyl alcohol to remove ethanol) and 100 ml. of isopropyl alcohol was heated overnight on the steam-bath. The nickel was removed by filtration and the filtrate distilled at atmospheric pressure. About 7.5 g. (50% yield) of N-isopropylaniline was obtained, b.p. 198–206° (lit.[10] b.p. 206–208°), $n^{25}_{\rm D}$ 1.5380.

Anal. Calcd. for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.72; H, 9.48; N, 10.63.

(b) A stirred mixture of 9.3 g. of aniline, about 30 g. of moist Raney nickel (washed with isopropyl alcohol) and 100 ml. of isopropyl alcohol was heated under reflux for 2 hours. After removal of the nickel by filtration 7 g. of aniline was recovered from the filtrate.

Aniline, Methyl Alcohol and Raney Nickel.—A stirred mixture of 9.3 g. of aniline, about 30 g. of moist Raney nickel (washed with methyl alcohol to remove ethanol) and 100 ml. of methyl alcohol was heated under reflux for 3 hours. After removal of the nickel by filtration, the filtrate was concentrated on the steam-bath. The residue was distilled and 8 g. of aniline recovered.

Attempted Alkylation of 2-Aminopyridine and 5-Aminotetrazole with Raney Nickel and Ethyl Alcohol.—(a) A mixture of 5 g. of 2-aminopyridine and about 15 g. of moist Raney nickel in 100 ml. of ethyl alcohol was heated under reflux for 4 hours. The nickel was removed by filtration and evaporation of the alcohol left 4 g. of starting material.

(b) A mixture of 5 g. of 5-aminotetrazole, about 15 g. of moist Raney nickel and 100 ml. of 95% ethyl alcohol was treated as in procedure a. About 4 g. of unchanged starting material was recovered.

2-Phenylethylamine and Raney Nickel.—A stirred mixture of 20 g. of 2-phenylethylamine, about 50 g. of moist Raney nickel and 100 ml. of ethyl alcohol was heated under reflux for 0.5 hour. The nickel was removed by filtration and the filtrate concentrated by heating on the steam-bath. Following a forerun of 9 g. of 2-phenylethylamine, about 9 g. of di-(2-phenylethyl)-amine came over, b.p. 190° (15 mm.) (lit.[11] b.p. 335° (603 mm.)), $n^{25}_{\rm D}$ 1.5550.

Anal. Calcd. for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 85.10; H, 8.47; N, 6.37.

A sample was converted to the hydrobromide salt and shown by infrared absorption to be identical with authentic material.

Benzylamine and Raney Nickel.—A stirred mixture of 10 g. of benzylamine, about 20 g. of moist Raney nickel and 100 ml. of 95% ethyl alcohol was heated under reflux for 2 hours. After removal of the nickel by filtration, the alcohol was evaporated on the steam-bath. The residue was distilled under reduced pressure. Following a forerun boiling between 70 and 120° (5 mm.) about 5 g. of constant boiling product came over, b.p. 160° (5 mm.). It was shown to be dibenzylamine by comparison of the infrared absorption curve with that of authentic material.

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(10) W. J. Hickinbottom, *J. Chem. Soc.*, **133**, 992 (1930).

(11) P. Spica, *Gazz. chim. ital.*, **9**, 555 (1879); *J. Chem. Soc. Ab.*, **38**, 241 (1880).

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Hydrogenolysis of the Nitrogen–Nitrogen Bond with Raney Nickel

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Twelve compounds representing a variety of types but all containing nitrogen–nitrogen bonds have been subjected to the action of a large excess of Raney nickel in the absence of atmospheric hydrogen. In ten of the twelve examples the nitrogen–nitrogen bond was cleaved and the products were identified.

The conversion of carboxylic acid hydrazides to amides with excess Raney nickel was reported[1] recently from this Laboratory. Hydrogenolysis of some other compounds containing nitrogen–nitrogen bonds with excess Raney nickel is now reported.

Adkins,[2] in an early communication on Raney nickel, noted that the catalyst readily converted nitrobenzene into azo- and azoxybenzene. This observation is interesting since the over-all reaction represents the *formation* of a nitrogen–nitrogen bonded compound. Later[3] it was shown that the reaction of azoxybenzene and hydrazobenzene with excess Raney nickel in boiling ethyl alcohol gave rise to N-ethylaniline. This involved the *cleavage* of a nitrogen–nitrogen bonded compound, such reaction being followed by alkylation.[4–6]

Our interest in this cleavage reaction arose from the observation that treatment of 2-(β-benzamido-

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(1) C. Ainsworth, THIS JOURNAL, **76**, 5774 (1954). Also, S. Akabori and K. Narita, *Proc. Japan Acad.*, **29**, 264 (1953); *C. A.*, **49**, 864 (1955), employed Raney nickel in the conversion of L-glutamic γ-hydrazide to L-glutamine.

(2) L. W. Covert and H. Adkins, THIS JOURNAL, **54**, 4116 (1932).

(3) R. Mozingo, C. Spencer and K. Folkers, *ibid.*, **66**, 1859 (1944).

(4) K. H. Shah, B. D. Tilak and K. Venkataraman, *Proc. Indian Acad. Sci.*, **28A**, 145 (1948); *C. A.*, **44**, 3958 (1950).

(5) R. G. Rice and E. J. Kohn, THIS JOURNAL, **77**, 4052 (1955).

(6) C. Ainsworth, *ibid.*, **78**, 1635 (1956).