[CONTRIBUTION FROM THE METCALF LABORATORIES, BROWN UNIVERSITY]

Alkylations with Alcohols and a Raney Nickel Catalyst[1]

LAURENCE T. PLANTE[2] AND LEALLYN B. CLAPP

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Alcohols (methanol, ethanol, and 2-propanol) can be used to convert piperazines (or their acyclic precursors) to N-alkylpiperazines in the presence of Raney nickel at 200°.

Alkylations of ammonia[3] and amines[4] with alcohols over alumina is a well-known reaction and the use of Raney nickel as a catalyst for such alkylations has received some attention.[5,6] Winans and Adkins[5] mentioned that methanol gave no appreciable alkylation of cyclohexylamine and it appears to be part of the folklore of organic chemists that methanol is a suitable solvent in which to carry out Raney nickel reductions. Paty and Barrans[7] have very recently found that hydrogen was liberated from methanol at 67.5° in the presence of Raney nickel and at elevated temperatures (190–272°) and pressures (90–200 atm.) methanol was reduced to methane. In this laboratory it has been found that methanol will alkylate 2,2,5,5-tetramethylpiperazine in the presence of Raney nickel at 200° to give 1,2,2,4,5,5-hexamethylpiperazine (46% yield). Under the same conditions 2,2,5,5-tetramethyl-2,3,4,5-tetrahydropyrazine is reduced and then alkylated to give the same piperazine (42% yield). Furthermore, under the same conditions, 5-amino-2,2,5-trimethyl-3-aza-1-hexanol yields 39% of the same piperazine. This last reaction is a cyclic alkylation[8] followed by reduction and another alkylation by the solvent, methanol.

Piperazine, itself, was also alkylated with methanol to about the same extent (47%) by the same procedure.

An interesting case of steric hindrance was observed in extending the alkylations to other alcohols. Whereas Winans and Adkins[5] found ethanol to be a good alkylating agent for piperidine, ethanol would not alkylate 2,2,5,5-tetramethyl-2,3,4,5-tetrahydropyrazine although hydrogen was removed from the ethanol to give 68% of the saturated piperazine. Isopropyl alcohol behaved similarly.

The failure of ethanol to alkylate the hindered tetrahydropyrazine was shown to be steric by successfully alkylating *trans*-2,5-dimethylpiperazine with ethanol to give 82% of 1,4-diethyl-2,5-dimethylpiperazine. The 2,5-dimethylpiperazine was also monoalkylated with isopropyl alcohol to the extent of 20%.

Ethanol also was used to alkylate the cyclization product of N-(2-hydroxyethyl)ethanediamine to yield 1,4-diethylpiperazine (24%).

EXPERIMENTAL PART[9]

1,2,2,4,5,5-Hexamethylpiperazine In an 1850-ml. stainless steel bomb, 33 g. of 5-amino-2,2,5-trimethyl-3-aza-1-hexanol,[10] m.p. 54°, was placed with 10 g. of Mozingo's nickel catalyst[11] and 220 ml. of absolute methanol. The bomb was heated to 200° and shaken for 22 hours at which time a gauge pressure of 600 p.s.i. had developed. Fractionation of the contents removed the methanol at 65°, and 26 g. of distillate containing water and 1,2,2,4,5,5-hexamethylpiperazine was collected at 75–100° (13 mm.). A residue of 6 g. remained which was not further identified. From the methanol, 1.6 g. of ammonium chloride was recovered by acidification and evaporation, indicating some deammonation accompanied the cyclization and reduction. The water solution of the piperazine was treated with ethanolic hydrogen chloride in which the piperazine hydrochloride was completely insoluble. Washing with absolute ethanol until colorless gave 20.6 g. of 1,2,2,4,5,5-hexamethylpiperazine hydrochloride. From this, 13.6 g. (39%) of 1,2,2,4,5,5-hexamethylpiperazine, b.p. 183–191°, was recovered by making a solution of the hydrochloride basic and extracting with ether. Another distillation gave an analytical sample, b.p. 189°, n_D^{25} 1.4540, d_4^{25} 0.8670.

Anal. Calc'd for $C_{10}H_{22}N_2$: C, 70.52; H, 13.03; N, 16.45; MR_D 54.06. Found: C, 70.32; H, 13.06; N, 16.46; MR_D 53.19.

A sample of the piperazine hydrochloride was recrystallized from water twice and sublimed at 150° (0.3 mm.). The compound did not melt below 300° in a closed tube but it sublimed in a flame.

Anal. Calc'd for $C_{10}H_{24}Cl_2N_2$: C, 49.38; H, 9.95; N, 11.52. Found: C, 49.01; H, 9.97; N, 11.58.

A quaternary ammonium iodide derivative was obtained with methyl iodide by a standard procedure. Three recrystallizations from absolute methanol and drying at 110° (0.3 mm.) for four hours gave an analytical sample of the monomethiodide; m.p. 296–297° dec.

Anal. Calc'd for $C_{11}H_{25}IN_2$: C, 42.31; H, 8.07; N, 8.97. Found: C, 42.25; H, 8.17; N, 9.20.

Similarly, reductive methylation of 8.5 g. of 2,2,5,5-

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(2) Eastman Kodak Fellow, 1953–1954.

(3) Goshorn, U. S. Patent 2,349,222 (1944) [*Chem. Abstr.*, **39**, 709 (1945)]; U. S. Patent 2,389,500 (1945) [*Chem. Abstr.*, **40**, 898 (1946)].

(4) Hill, Shipp, and Hill, *Ind. Eng. Chem.*, **43**, 1579 (1951).

(5) Winans and Adkins, *J. Am. Chem. Soc.*, **54**, 306 (1932).

(6) Metayer, *Bull. soc. chim. France*, [5] **15**, 1093 (1948).

(7) Paty and Barrans, *Compt. rend.*, **236**, 1286 (1953).

(8) Plante, Lloyd, Schilling, and Clapp, *J. Org. Chem.*, **21**, 82 (1956) preceding paper.

(9) Melting points given to tenths of a degree are corrected. Boiling points are uncorrected. Microanalyses by S. M. Nagy, Microchemical Laboratories, Massachusetts Institute of Technology, Cambridge, Massachusetts.

(10) Senkus, *J. Am. Chem. Soc.*, **68**, 10 (1946); Clapp, *J. Am. Chem. Soc.*, **70**, 184 (1948).

(11) Mozingo, *Org. Syntheses*, **21**, 15 (1941).

tetramethyl-2,3,4,5-tetrahydropyrazine[8] gave 4.9 g. (42%) of 1,2,2,4,5,5-hexamethylpiperazine (6.2 g. as hydrochloride). A small amount of the hydrochloride was neutralized with base, extracted with ether, and converted to the methiodide derivative with methyl iodide; m.p. 295°. A mixture m.p. with the methiodide previously prepared showed no depression.

1,2,2,4,5,5-Hexamethylpiperazine was also prepared by the reductive methylation of 5.6 g. of 2,2,5,5-tetramethylpiperazine as previously described. By distillation, there was obtained 3.1 g. (46%) of 1,2,2,4,5,5-hexamethylpiperazine, b.p. 185–189°. A small amount of the piperazine was converted to the methiodide; m.p. 295°.

1,4-Dimethylpiperazine. Anhydrous piperazine (20 g.), 10 g. of Mozingo's nickel catalyst, and 300 ml. of absolute methanol were sealed in a stainless steel bomb and heated at 200° for 60 hours. Distillation removed the methanol at 65°, and water and 1,4-dimethylpiperazine distilled at 90–110°. Treatment of the distillate with ethanolic hydrogen chloride gave 20.5 g. (47%) of 1,4-dimethylpiperazine dihydrochloride, m.p. 248–250°.[12,13]

When the above methylation was run at 180° for 24 hours, no alkylation took place and 80% of the piperazine was recovered unchanged.

Attempted ethylation of 2,2,5,5-tetramethyl-2,3,4,5-tetrahydropyrazine. 2,2,5,5-Tetramethyl-2,3,4,5-tetrahydropyrazine (18.7 g.), 10 g. of Mozingo's nickel catalyst, and 500 ml. of absolute ethanol were sealed in the stainless steel bomb and heated at 200° for 24 hours. Distillation gave 5.6 g. of 2,2,5,5-tetramethylpiperazine, b.p. 60° (15 mm.). From the forerun by treatment with alcoholic hydrogen chloride there was obtained 11.3 g. of 2,2,5,5-tetramethylpiperazine hydrochloride; total yield as the piperazine, 68%. The compound was identified as the dibenzamide; m.p. 268–270°. The mixture m.p. with an authentic sample[14] gave no depression.

Neither 2,2,5,5-tetramethyl-2,3,4,5-tetrahydropyrazine nor 5-amino-2,2,5-trimethyl-3-aza-1-hexanol could be alkylated with ethanol by the above procedure, even when the temperature was raised to 210°. In both cases, 2,2,5,5-tetramethylpiperazine was isolated.

Attempted alkylation of 2,2,5,5-tetramethyl-2,3,4,5-tetrahydropyrazine with 2-propanol gave only 2,2,5,5-tetramethylpiperazine (50.5%).

1,4-Diethyl-2,5-dimethylpiperazine. Recrystallized 2,5-dimethylpiperazine (15.7 g.), m.p.114–116°, 10 g. of Mozingo's nickel catalyst, and 300 ml. of absolute ethanol were sealed in the stainless steel bomb and heated at 190° for 24 hours. Fractionation gave 31.8 g. of distillate, b.p. 60–90° (5 mm.). The crude distillate was dissolved in ether, dried with calcium hydride, and redistilled, giving 19.3 g. (82%) of 1,4-diethyl-2,5-dimethylpiperazine, b.p. 60° (5 mm.). Four distillations gave an analytical sample, n_D^{25} 1.4569, having the same b.p.

Anal. Calc'd for $C_{10}H_{22}N_2$: C, 70.53; H, 13.02. Found: C, 70.09; H, 13.06.

A portion of the piperazine was converted to the *picrate.* Three recrystallizations from a large volume of absolute ethanol gave an analytical sample of 1,4-diethyl-2,5-dimethylpiperazine picrate; m.p. 212.8–214.0°.

Anal. Calc'd for $C_{22}H_{28}N_8O_{14}$: C, 42.04; H, 4.49; N, 17.83. Found: C, 41.92; H, 4.58; N, 18.04.

1-Isopropyl-2,5-dimethylpiperazine. Recrystallized 2,5-dimethylpiperazine (17.6 g.), m.p. 114–116° was treated as described above with 300 ml. of anhydrous 2-propanol and 10 g. of Raney nickel. Distillation removed the 2-propanol at 83°, and then 12 g. of distillate was collected; b.p. 75° (10 mm.). Nitrosation of the crude distillate gave a dinitroso derivative[15] of the unreacted starting compound (36%) which was insoluble in dilute sulfuric acid (6 *N*) but soluble in ether. The nitroso derivative of 1-isopropyl-2,5-dimethylpiperazine remained in the acid solution after ether extraction and was neutralized with base. Ether extraction followed by drying with calcium hydride gave 5.6 g. (20%) of 1-nitroso-2,5-dimethyl-4-isopropylpiperazine; b.p. 80° (0.4 mm.).

Anal. Calc'd for $C_9H_{19}N_3O$: C, 58.34; H, 10.33; N, 22.68. Found: C, 57.11; H, 10.62; N, 22.73.

A second analysis of this same sample gave: C, 54.68; H, 10.07, indicating rapid absorption of carbon dioxide and water.

The picrate derivative, however, was quite stable. Three recrystallizations from a large volume of absolute ethanol gave an analytical sample of 1-nitroso-2,5-dimethyl-4-isopropylpiperazine picrate; m.p. 181–182°.

Anal. Calc'd for $C_{15}H_{22}N_6O_8$: C, 43.47; H, 5.35; N, 20.28. Found: C, 43.49; H, 5.31; N, 20.38.

1,4-Diethylpiperazine. Redistilled aminoethylethanolamine (31.2 g.) was treated at 200° for 26 hours as previously described. 1,4-Diethylpiperazine (12.3 g., 24%) was obtained by distillation, b.p. 173–179°, identified as the dihydrochloride; m.p. 278–280°. Schmidt and Wichmann[12] report the m.p. of the dihydrochloride, 277° dec.

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(12) Schmidt and Wichmann, *Ber.*, **24**, 3237 (1891).

(13) von Braun, Kühn, and Goll, *Ber.*, **59**, 2330 (1926).

(14) McElvain and Pryde, *J. Am. Chem. Soc.*, **71**, 326 (1949).

(15) Godchot and Mousseron, *Compt. rend.*, **190**, 798 (1930).