125 cc. of ether for a period of 8 hours. A second and a third extraction, each involving 125 cc. of ether and carried out for an 8-hour period, brought all of the material in the thimble into solution. Concentration of the second ether extract afforded 0.77 g. of colorless crystals, m.p. 132.0–132.8°, $[\alpha]^{22}D$ +18.2° (*c* 0.275 in acetone), $[\alpha]^{26}D$ +41.9° (*c*, 0.691 in absolute ethanol). A mixed m.p. with tetrahydrodehydroemetine, described above, showed no depression.

The mother liquor from the methanol recrystallization was concentrated to a small volume, whereupon 0.19 g. of colorless needles, m.p. 196.2–197.2°, $[\alpha]^{26}D$ −392° (*c* 0.255 in absolute ethanol), was obtained. Openshaw and Wood[7e] report a m.p. of 197–198°, $[\alpha]^{15}D$ −395° (*c* 0.165 in acetone) for α-dihydrorubremetine. A mixed m.p. with isotetrahydrodehydroemetine, described above, showed no depression.

In a separate experiment, the hydrogenation of rubremetinium chloride was halted after the absorption of only one mole of hydrogen. The greenish-white suspension was filtered, and the filter cake extracted with hot absolute ethanol. Concentration and cooling of this solution afforded 0.40 g. of pale yellow crystals, m.p. 177–187°. Recrystallization from absolute ethanol gave colorless needles, m.p. 201.5–202.5°, $[\alpha]^{21}D$ +402° (*c* 0.189 in acetone). Openshaw and Wood[7e] reported a m.p. of 201–202° for β-dihydrorubremetine and $[\alpha]^{16}D$ +406.3° (*c* 0.148 in acetone). By working up the various mother liquors there was obtained a total of 0.45 g. of purified β-dihydrorubremetine. The β-dihydrorubremetine readily absorbed one mole of hydrogen in absolute ethanol containing 10% by volume of glacial acetic acid over Adams catalyst.

LAWRENCE, KANSAS

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, STANFORD UNIVERSITY]

Synthesis of Piperazines by Reductive Cyclization[1,2]

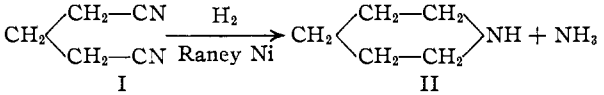
BY HARRY S. MOSHER, JOHN CORNELL, JR.,[3] OWEN L. STAFFORD[4] AND THORNDYKE ROE, JR.

RECEIVED JUNE 8, 1953

It has been shown that catalytic reduction of di-(cyanomethyl)-amine and its N-substituted derivative gives piperazine and mono-N-substituted piperazines. The N-acetyl, N-benzoyl, N-carbethoxy, N-diethylcarbamyl, N-methyl, N-ethyl and N-benzyl derivatives of di-(cyanomethyl)-amine (IV) have been prepared and reduced to the corresponding piperazines (V). This constitutes a new synthesis of piperazines which may be valuable in special cases since it inherently gives the mono-N-substituted products.

The formation of cyclic imines by the reduction of dinitriles is a particular intramolecular case of the formation of secondary amines which takes place during the reduction of nitriles. The term *reductive cyclization* has been applied to reactions of this kind in which the cyclic nitrogen bases are formed by reductive methods, and there are many known examples of the production of nitrogen ring compounds by this process.[5]

The best known example is the reduction of trimethylene cyanide I to give piperidine II as the major product along with a small yield of cadaverine III.[6] Mignonac[7] has postulated a satisfactory mechanism for the formation of secondary amines in the reduction of nitriles which can readily be applied to the above case.



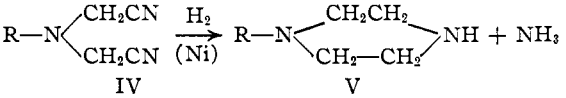
I II

and $H_2N-(CH_2)_5NH_2$

III

This process of reductive cyclization has been especially useful in the synthesis of piperidine,[5b] pyrrolidines,[5a] pyrrazolidines[5c] and octahydropyrrocolines[5c] but we have found no reference in the literature where this process has been used for the preparation of an heterocyclic compound containing more than one hetero atom in the ring.[8]

We therefore undertook a study of the reduction of di-(cyanomethyl)-amine and N-substituted di-(cyanomethyl)-amines to determine whether the reductive cyclization predicted by the following equation would be realized.



IV V

The first experiments on the high pressure Raney nickel catalyzed reduction of ethyldi-(cyanomethyl)-amine (IV, R = $-C_2H_5$) were unsuccessful.[9] It has been stated by Reihlen and co-workers[10] that α-aminonitriles on catalytic reduction readily eliminate hydrogen cyanide which poisons

(1) Presented in part at the International Congress of Pure and Applied Chemistry, New York, September, 1951.

(2) Abstracted from the Thesis submitted by J. H. C. in partial fulfillment of the requirements for the Ph.D to Stanford University, June, 1952.

(3) Parke Davis and Company Research Fellow 1950–1952.

(4) Parke Davis and Company Research Fellow 1950–1951.

(5) The references are far too numerous to review here but the following will indicate some of the most important work in this field: (a) H. Adkins, "The Reaction of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts," Univ. of Wisc. Press, Madison, Wis., 1937; (b) H. S. Mosher, "Piperidines" in Elderfield's "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 650–655; (c) N. J. Leonard, *et al.*, THIS JOURNAL, **71**, 1758 (1949), *et seq.*; (d) K. Smeykal and H. Dierichs, German Patent 730,235, Dec. 10, 1942; (e) J. Paden and H. Adkins, THIS JOURNAL, **58**, 2487 (1936).

(6) Reference 5a, pp. 53–55.

(7) G. Mignonac, *Ann. chim.*, [11] **2**, 225 (1934).

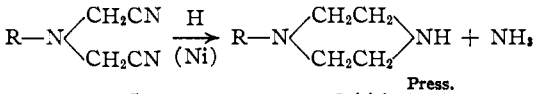
(8) (a) The only examples which might be considered to fall in this category are the reductions of the monoximes of α,β-diketones to give pyrazines reported by C. Winans and H. Adkins, THIS JOURNAL, **55**, 4167, 4170 (1933), and H. Adkins and E. Reeves, *ibid.*, **60**, 1328 (1938). Since the expected α-aminoketones spontaneously cyclize to pyrazines this seems to be a very special case. (b) P. L. Barrick, U. S. Patent 2,516,289 (July 25, 1950) reports the preparation of piperazines by the reduction of the monoxime of α,β-diketones using palladium catalysts at 20–150° and 50–200 p.s.i. (c) NOTE ADDED TO PROOF.—Since this paper was submitted, a patent (U. S. 2,605,263, July 29, 1952, by Martin J. Culver and Louis H. Bock) has come to our attention in which the reduction of di-(cyanomethyl)-amine to piperazine with hydrogen in the presence of acidified Raney nickel or cobalt is described.

(9) See R. B. Taylor, Ph.D. Thesis, The Pennsylvania State College, Feb. 1945, pp. 43–44, 133–136, and T. Roe, M.S. Thesis, Stanford University, Dec. 1949.

(10) H. Reihlen, G. von Hessling, W. Hühn and E. Weinbrenner, *Ann.*, **493**, 20–32 (1932).

TABLE I

HYDROGENATION OF SUBSTITUTED DI-(CYANOMETHYL)-AMINES



R	Mole	Catalyst, g.		Solvent	Concn., moles per l.	Temp., °C.	Time, hr.	Initial press., p.s.i.	Press. drop[a] theory, %	Yield, %	B.p., °C.	Product Press., mm.	Deriv., m.p., °C.
H[15,16]	0.1	Ni(R)[b]	18	Abs. alc.	0.67	36	2	47	94	40.7	135–150	760	188–190[d]
CH_3[19]	.1	Ni(Rp)[c]	6	Benzene	.67	24	2.5	47	91	7.6	15–145	760	129–130[e]
C_2H_5[20]	.1	Ni(Rpt)	6	Benzene	.67	44	2.5	48	95	15.8	165–185	760	243–244[f]
	.1	Ni(Rpt)	6	Dioxane	.67	25–45	5.5	46	88.4	9.6			93–95[g]
	.1	Ni(Rpt)	6	Abs. alc.	.67	45	5.5	48	89.0	8.1			124–125[e]
	.2	Ni(Rpt)	6	Benzene	2.0	25	0.5	2000	30	0			
$C_6H_5CH_2$[21]	.1	Ni(Rpt)	6	Benzene	2.0	65	7.2	47	67	32.9	88–121	1.5	161–163[h,i]
CH_3CO[22]	.1	Ni(Rpt)	6	Abs. alc.	0.75	60	1.0	45	73	41.5	95–105	0.5	218–221.5[j]
	.1	Co(R)	6	Dioxane	.33	120	6.0	2200	112	11.9	101–110	1	141–143[n]
	.1	Ni(R)	25	Abs. alc.	.72	68	2	45	72	40	105–115	2	
	.1	Ni(R)	10	Abs. alc.	1.14	115	1.5	1600	45	32	110–120	2	
	.1	Ni(R)	6	Dioxane	1.23	118	3	1350	47	20	104–108	1	
C_2H_5OCO	.1	Ni(Rpt)	6	Abs. alc.	0.67	30	5.0	47	101	15.4	103–110	2	115–116[e]
$(C_2H_5)_2NCO$	.11	Ni(Rpt)	6	Benzene	2.16	25	5.5	50	99	34.2	113–120	2	201–203.5[f,m]
													125–126[h]
C_6H_5CO[d]	.5	Ni(R)	12	Dioxane	0.62	95	1.5	1900	91	12.1	140–152	2	141.5–143[f,k]

[a] Percentage of the theoretical pressure drop disregarding any pressure which might be produced by the ammonia formed. [b] Ni(R) refers to W-2 Raney nickel; see ref. 12. [c] Ni(Rpt) refers to W-2 Raney nickel promoted with 0.07 of chloroplatinic acid; see ref. 12. [d] Benzyldi-(cyanomethyl)-amine, J. Bailey and D. Snyder, THIS JOURNAL, **37**, 940 (1915), and J. V. Dubsky and E. Hoher, *Ber.*, **54**, 2668 (1921). [e] Benzenesulfonamide, R. M. Jacob, U. S. Patent 2,507,408; *C. A.*, **44**, 7888 (1950). [f] Picrate. [g] *m*-Nitrobenzenesulfonamide; these three derivatives of N-ethylpiperazine gave undepressed melting points when mixed with samples from authentic N-ethylpiperazine made according to T. Moore, M. Boyle and V. Thorn, *J. Chem. Soc.*, 47 (1929). [h] Benzenesulfonamide. [i] Dihydrochloride, m.p. 235–242°. [j] Picrate; this product gave an undepressed melting point when mixed with an authentic sample.[22] [k] Hydrochloride, m.p. 269–272.5°, neut. equiv. calcd.: 226.7; found 226.6. See K. R. Jacobi, *Ber.*, **66**, 115 (1933). [l] Dibenzamide; mixed melting point with authentic sample undepressed. [m] Hydrochloride, m.p. 148–149°, H. Stequart and R. Turner, *et al.*, *J. Org. Chem.*, **13**, 135 (1948).

the catalyst. These workers found, however, that the α-aminonitriles were converted to the corresponding α,β-diacetamino compounds by reduction in acetic anhydride in the presence of platinum catalyst according to the method of Carothers and Jones.[11] In view of the accepted mechanism for secondary amine formation in the reduction of nitriles,[5a,7] it did not seem feasible to attempt the reductive cyclization under acetylation conditions. Adkins has reported,[5a] however, the successful reduction of methyleneaminoacetonitrile and diethylacetaminonitrile under non-acetylating conditions; accordingly further experiments were tried in which other conditions and catalysts were sought for the reductive cyclization.

It was found that by using Raney nickel catalyst with 1% chloroplatinic acid added as a promotor[12] with hydrogen pressures of 20–45 p.s.i. and 35–65°, the compounds listed in Table I were reduced to form the corresponding piperazines. Higher pressures and temperatures reduced the yields. Even under the best conditions found the yields were often erratic and did not in any case exceed 45%. Most of the remaining yield was a polymeric residue. Other catalysts were investigated for the reduction of acetyl di-(cyanomethyl)-amine including W-6 Raney nickel, platinum oxide, platinum black, palladium-on-barium sulfate, copper–chromium, molybdenum sulfide and an alloy skeleton cobalt catalyst but none were as effective as the W-2 Raney nickel. Although the addition of platinum slowed down the rate of reduction, it reduced poisoning of the catalyst and thus permitted completion of the reduction without addition of fresh catalyst.

When it was found that the acetyldi-(cyanomethyl)-amine (IV, R = $-COCH_3$) was reduced in much better yield than the ethyldi-(cyanoethyl)-amine (IV, R = C_2H_5), it was thought that it might be the basic nature of the alkyldi-(cyanomethyl)-amines which caused the low yields. The reasonable yield of piperazine obtained in the reduction of di-(cyanomethyl)-amine itself (IV, R = H) discounted this supposition however.

It has been shown[13] that diethylenetriamine can be cyclized to piperazine at 235° and that Raney nickel is a catalyst for this reaction[14] which permits the cyclization to go at 150°.

Diethylenetriamine cannot be considered an intermediate in the low temperature, low pressure reduction of dicyanomethylamine to piperazine, since an experiment in which diethylenetriamine was subjected to these conditions resulted in quantitative recovery of the diethylenetriamine.

The di-(cyanomethyl)-amine was prepared by a modification of the method of Eschweiler[15] and Dubsky[16] in 50–55% yield by the condensation of hexamethylenetetramine and potassium cyanide

(11) W. H. Carothers and G. A. Jones, THIS JOURNAL, **47**, 3051 (1925).

(12) See J. Reasenberg, E. Lieber and G. Smith, *ibid.*, **61**, 384 (1939). The Raney nickel catalyst used was W-2 catalyst prepared according to the directions in *Org. Syn.*, **21**, 15 (1941).

(13) L. P. Kyrides, U. S. Patent 2,267,686 (Dec. 23, 1941).

(14) W. B. Martin and A. E. Martell, THIS JOURNAL, **70**, 1817 (1948).

(15) W. Eschweiler, *Ann.*, **278**, 230 (1893).

(16) J. V. Dubsky and E. Dingemanse, *Ber.*, **54**, 2659 (1921).

in the presence of hydrochloric acid. Most of the derivatives of di-(cyanomethyl)-amine such as the acetyl, benzoyl, carbethoxy and diethylcarbamyl were obtained by direct substitution on the di-(cyanoethyl)-amine. Methyldi-(cyanomethyl)-amine and ethyldi-(cyanoethyl)-amine were made by the condensation of methylamine and ethylamine with glycolonitrile, and benzyldi-(cyanomethyl)-amine was prepared by the reaction of glycolonitrile on benzylcyanomethylamine.

Acknowledgment.—We wish to thank Parke, Davis and Company for the fellowship support which made this investigation possible.

Experimental[17]

The low pressure hydrogenations were conducted in a Parr hydrogenation apparatus which had a shaking frequency of 240 strokes per minute. The hydrogenation vessel was a 500-ml., electrically heated, asbestos-lagged, Pyrex centrifuge bottle.

Di-(cyanomethyl)-amine.—The following experiment, which is a modification of the method of Eschweiler[15] and Dubsky,[16] represents the optimum conditions found after many runs. Concentrated hydrochloric acid (10 moles) was added over a three-hour period to a stirred aqueous solution of hexamethylenetetramine (1.43 moles) and potassium cyanide (10 moles) in 2250 ml. of water which was kept at 10°. After stirring for ten hours the solution was subjected to continuous extraction with ethyl acetate. The extract was treated with Norit, concentrated to 300 ml., and the crystals which separated on cooling were recrystallized from ethanol to give 200 to 225 g. (50–55% yield), m.p. 75–77°. When the completion of the hydrochloric acid addition took one-half hour the yield dropped to 5% and an 18% yield of methylene-bis-di-(cyanomethyl)-amine[15] was isolated. Slower addition than three hours or temperatures above 10° caused reduced yields.

Piperazine.—Di-(cyanomethyl)-amine (9.5 g., 0.1 mole) was dissolved in 150 ml. of absolute ethanol and 6 g. of W-2 Raney nickel added. The hydrogenation was conducted at an initial pressure of 42.5 p.s.i. without external heating. When the absorption of hydrogen slowed, the hydrogen was vented, an additional 6 g. of catalyst added and the hydrogenation continued; this procedure was repeated until 18 g. of catalyst had been added and the pressure drop corresponded to 93.7% of the theoretical amount. In other runs when 1% chloroplatinic acid was added, the catalyst was not poisoned so rapidly and the initial 6 g. was sufficient for the reduction. The reaction mixture was filtered, the catalyst removed by filtration, washed three times with 20-ml. portions of ethanol, and the solvent removed from the filtrate by distillation. Distillation of the residue gave 3.5 g. of a fraction, b.p. 135–150° (760 mm.), which crystallized. Benzoylation gave a product, m.p. 188–190°, which showed no depression of the melting point when mixed with an authentic sample of dibenzoylpiperazine.[18]

Methyldi-(cyanomethyl)-amine.—This was prepared according to Eschweiler[19] from glycolonitrile and methylamine in 32% yield, b.p. 145–146° (26 mm.), 186–188 (105 mm.). The boiling point given by Eschweiler,[19] 70° (45 mm.), was apparently a misprint. The above boiling point was confirmed by synthesis of a sample by methylating dicyanomethylamine with dimethyl sulfate.

Ethyldi-(cyanomethyl)-amine.—By the substitution of a 50% aqueous solution of glycolonitrile for a mixture of formalin, sodium bisulfite and potassium cyanide, the method of Knoevenagel and Mercklin[20] was modified to give a 70% yield of ethyldi-(cyanomethyl)-amine.

Benzyldi-(cyanomethyl)-amine.—Although benzyldi-(cyanomethyl)-amine has been made by the treatment of di-(cyanomethyl)-amine with benzyl chloride,[16] in the present work it was much more satisfactorily prepared by the action of glycolonitrile on benzyl-(cyanomethyl)-amine.[21] A mixture of 50% aqueous solution of glycolonitrile (47.3 g., 0.414 mole) benzyl-(cyanomethyl)-amine[21] (60.5 g., 0.414 mole) and two drops of concentrated sulfuric acid were heated on the steam-bath with vigorous stirring for five hours. The product was extracted from the reaction mixture with ether and the ether layer dried over Drierite. After removing the ether, the residue was distilled and the fraction, b.p. 142–165° (2 mm.), allowed to crystallize. Washing of these crystals with a small amount of cold methanol gave 47 g. (61% yield), m.p. 41–41.5° of benzyldi-(cyanomethyl)-amine.

Reduction of Benzyldi-(cyanomethyl)-amine.—Benzyldi-(cyanomethyl)-amine was reduced as indicated in Table I in benzene solution. An ethanolic solution of chloroplatinic acid (0.7 ml. containing 0.1 g./ml.) was added as a catalyst promoter.[13] The reaction mixture was filtered, the solvent removed by distillation and the residue distilled to give two fractions as well as considerable residue. The first fraction, 5.8 g., b.p. 88–121° (1.5 mm.), gave a benzenesulfonamide, m.p. 161–163°, and a hydrochloride, m.p. 235–242° dec., corresponding in analysis to the dihydrochloride of benzylpiperazine.

Anal. Calcd. for $C_{11}H_{18}N_2Cl_2$: C, 53.02; H, 7.28; N, 11.25. Found: C, 53.17; H, 7.15; N, 10.75.

The second fraction, 0.9 g., b.p. 121–185° (1.5 mm.), melted at 149–150° after recrystallization from methanol and corresponded in analysis to 4-benzyl-2-ketopiperazine.

Anal. Calcd. for C, 69.44; H, 7.41; N, 14.73. Found: C, 69.32, 69.41; H, 7.03, 7.13; N, 14.81, 14.98.

Acetyldi-(cyanomethyl)-amine.[22]—This was prepared in 97% yield by heating di-(cyanomethyl)-amine with a three molar quantity of acetic anhydride for four hours on the steam-bath. The product crystallized to a low melting solid after distillation, b.p. 174° (3 mm.); it was reduced as indicated in Table I.

Carbethoxydi-(cyanomethyl)-amine.—This was obtained in 57% yield by the method employed by Jongkees[22] for the preparation of the carbomethoxy derivative; b.p. 133.5–137° (1 mm.), $n^{3.0}$D 1.4543.

Diethylcarbamyldi-(cyanomethyl)-amine.—Diethylcarbamyl chloride[23] (13.6 g., 0.1 mole) was treated with di-(cyanomethyl)-amine (9.5 g., 0.1 mole) in dry pyridine (20 ml.) for 2.5 hours on the steam-bath. The reaction mixture was poured into 50 ml. of water and extracted with benzene; the benzene layer was successively washed with dilute hydrochloric acid, sodium carbonate solution and water. The benzene extract was then dried over Drierite and distilled to give 11.8 g. (60%) of product, b.p. 174–176.5° (2 mm.), n^{20}D 1.4789. This was reduced as indicated in Table I.

Benzenesulfonyldi-(cyanomethyl)-amine.—Di-(cyanomethyl)-amine (19.0 g., 0.2 mole) was dissolved in 40 ml. of pyridine and benzenesulfonyl chloride (36 g., 0.2 mole) added portionwise with stirring; the temperature rose from 25 to 105°. The mixture was poured onto water; the oil which separated solidified and was recrystallized from ethanol after Norit treatment to give 39.6 g. (84% yield), m.p. 88.5–90°, of the benzene–sulfonamide. An attempt to reduce this led only to tars.

STANFORD, CALIF.

(17) All melting points and boiling points are uncorrected. Analyses by Charles Koch, Microchemical Specialties Co., Berkeley, Calif.

(18) A. Franchimont and E. Kramer, *Rec. trav. chim.*, **31**, 69 (1912).

(19) W. Eschweiler, *Ann.*, **279**, 41 (1894).

(20) E. Knoevenagel and E. Mercklin, *Ber.*, **37**, 4093 (1904).

(21) W. Baker, W. Ollis and V. Poole, *J. Chem. Soc.*, 312 (1949).

(22) W. J. A. Jongkees, *Rec. trav. chim.*, **27**, 310, 313 (1908).

(23) A. Lumiere and F. Perrin, *Bull. soc. chim.*, [3] **31**, 689 (1904).