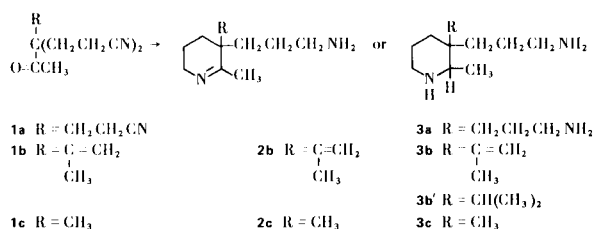


Amines by Reductive Cyclization of δ -Oxonitriles

Richard P. Welcher and Linda C. Mead

Industrial Chemicals Division, American Cyanamid Company

We wish to report the preparation of four new heterocyclic amines (**2b**, **3a**, **3b**, **3b'**) in 58-86% yield by the catalytic hydrogenation of δ -oxonitriles (**1**). The products, which were derivatives of tetrahydropyridine and piperidine, also contained at least one primary amine group (**1**).



The structure of the δ -oxonitrile greatly affected the degree of saturation of the final product. When hydrogenated over Raney cobalt at 120° the trinitrile (**1a**) gave a piperidine (**3a**), whereas the olefinic dinitrile (**1b**) formed a tetrahydropyridine (**2b**), still bearing the original isopropenyl group of **1b**.

With platinum oxide catalyst in methanol the ring double bond of **2b** was preferentially reduced, to give the isopropenyl piperidine (**3b**). Hydrogenation of **2b** over platinum oxide in acetic acid (2) was necessary to obtain the completely saturated piperidine (**3b'**). The sluggish reducibility of a shielded isopropenyl group has been pointed out by others (3).

In our hands the dinitrile (**1c**) was reduced to **3c** in high yield with Raney cobalt at 120°. By way of contrast, a Japanese team recently reported that **1c** was reduced only to the tetrahydropyridine (**2c**) with Raney nickel at 22° (4). They obtained the piperidine (**3c**) from **1c** in low yield in the presence of a mixed Raney nickel-palladium catalyst. Albertson, who first prepared compound **3c**, did not specify his starting material (5). In related work 3-acetobutyronitrile was chemically reduced to 2-pipecoline in 15% yield (6).

EXPERIMENTAL

All melting points are corrected. The ir spectra were recorded on a Perkin-Elmer Model 521 spectrophotometer. The nmr spectra were run on a Varian A-60 instrument at 60 Mc., and are

reported in parts per million, relative to tetramethylsilane as an internal standard. In general, vpc and ms measurements were unsatisfactory for determining the purity of the saturated amines. Loss of ammonia, and sometimes hydrogen, occurred, presumably in the injection blocks, causing spurious lower-boiling impurities to appear in compounds known to be pure by their nmr spectra.

The δ -oxonitriles were prepared by the base-catalyzed cyanoethylation of acetone (7), 4-methyl-3-penten-2-one (8) and 2-butanone (7).

The preparation and properties of the amines are summarized in Table I. In a typical experiment 26 g. of **1a**, 2 g. of Raney cobalt, 3 g. of ammonia and 50 ml. of 2B ethyl alcohol were hydrogenated at 725-1500 psi pressure for 4 hours at 120°. The uptake of hydrogen was approximately 73% of the expected seven-fold molar quantity. The catalyst was removed by filtration, the solvent by low-pressure distillation, and the residual liquid was fractionated to give **3a**. Hydrogenation of 19 g. of **2b**, 1 g. of platinum oxide and 20 ml. of 2B ethyl alcohol at 250-400 psi pressure for 6 hours at 60° led to 92% of the theoretical uptake of 1 mole of hydrogen, giving **3b**. Hydrogenation of 16 g. of **2b**, 0.5 g. of platinum oxide and 50 g. of glacial acetic acid for 13 hours at 30° led to 100% of the theoretical uptake of 2 moles. After removal of the catalyst and solvent, the amine was liberated with caustic, extracted with ether and dried before vacuum fractionation to give **3b'**.

The amines were identified by elemental analysis, neutralization equivalent weight, and their ir and nmr spectra. Significant peaks in the spectra are summarized in Tables II and III.

Acknowledgment.

We thank Mr. N. B. Colthup, Dr. J. E. Lancaster and Mrs. M. T. Neglia for their patient assistance in interpreting the ir and nmr spectra.

REFERENCES

- (1) Compounds: **1a**, 4-acetyl-4-(2-cyanoethyl)heptanedinitrile; **1b**, 4-acetyl-4-isopropenylheptanedinitrile; **1c**, 4-acetyl-4-methylheptanedinitrile; **2b**, 3-(3-aminopropyl)-3,4,5,6-tetrahydro-3-isopropenyl-2-pipecoline; **2c**, 3-(3-aminopropyl)-3,4,5,6-tetrahydro-2,3-dimethyl-2-pipecoline; **3a**, 3,3-bis(3-aminopropyl)-2-pipecoline; **3b**, 3-(3-aminopropyl)-3-isopropenyl-2-pipecoline; **3b'**, 3-(3-aminopropyl)-3-isopropyl-2-pipecoline; **3c**, 3-(3-aminopropyl)-2,3-dimethylpiperidine.
- (2) C. E. Larrabee and L. E. Craig, *J. Am. Chem. Soc.*, **73**, 5471 (1951).
- (3) E. M. Arnett, J. M. Bollinger and J. C. Sanda, *ibid.*, **87**, 2050 (1965).
- (4a) T. Takata, K. Sayama and M. Takigawa, *J. Chem. Soc. Japan, Pure Chemistry Section*, **85**, 237 (1964); (b) M. Takigawa,

TABLE I

Amine Product	Yield (%)	Preparation and Properties of the Amines		Analysis	Found
		Physical Properties (a)	Calcd.		
3a	74	b.p. 141-144°/0.6 mm n ²⁷ 1.5264 m.p. 53.5-55°	C ₁₂ H ₂₇ N ₃ C, 67.55 H, 12.76 N, 19.69 Equiv. wt. 71.1		67.52 11.03 19.57 68.8
2b	76	b.p. 122-125°/0.5 mm n ³¹ 1.5090	C ₁₂ H ₂₂ N ₂ C, 74.17 H, 11.41 N, 14.42 Equiv. wt. 97.7 Iodine No. 131 cg. I ₂ /g.		74.54 11.18 14.60 101.9 133
3b	86	b.p. 116-120°/0.8 mm n ²⁴ 1.5073			
3b'	58	b.p. 102-104°/0.2 mm n ²⁹ 1.4969	C ₁₂ H ₂₆ N ₂ N, 14.13 Equiv. wt. 99		14.19 101
3c	77(b)	b.p. 111-113°/8 mm (c) n ²⁵ 1.5006	C ₁₀ H ₂₂ N ₂ C, 70.53 H, 13.02 N, 16.45		71.25 12.39 16.32

(a) The amines were soluble in cold water and organic solvents. (b) Vpc analysis showed this compound to be at least 93% pure, with approximately 6.5% of two lower-boiling impurities. A Perkin-Elmer instrument was used, Model 154D, with a 1 meter column containing 20% Ucon Oil on 50-60 mesh Celite 545 diatomite, sodium hydroxide-coated; col. temp., 180°; He pressure, 10 psi; flow rate, 75 ml./min. See above for comment on vpc reliability. (c) Literature n²⁰ 1.4907; b.p. 98°/2 mm (4), n²⁵ 1.5031; b.p. 80°/1 mm (5).

TABLE II

Significant Peaks in the Infrared Spectra of the Amines

Compound	Peak Assignments (a)				
	C=CH ₂ CH ₃	C=N	CH(CH ₃) ₂	C-N-C	C=C
3a	Absent	Absent	Absent	1150 S	Absent
2b	3080 M	1650 S	Absent	1150 W	900 S
3b	3080 M	Absent	Absent	1140 M	888 S
3b'	Absent	Absent	1390-1380 S	1130 M	Absent
3c	Absent	1650 W (b)	Absent	1140 S	Absent
2c	Absent	1650 W (c)	-	1150 S	-

(a) Peak frequency units are given in cm⁻¹. Peak intensities: S (strong), M (medium), W (weak). (b) This band was caused by an estimated 5% of the tetrahydropyridine, **2c**. (c) These peak locations were estimated from the published ir spectrum (4a).

TABLE III

Significant Peaks in the Nmr Proton Spectra of Amines

Compound	Peak Assignments (a)					
	HCN- H ₂ CN-	HCN= H ₂ CN=	CH ₃ C=N	H ₂ C=	CH ₃ C=C	CH ₃ -C
3a	2.70	Absent	Absent	Absent	Absent	-(b)
2b	2.64	3.40	1.73	4.65 4.85	1.68	Absent
3b	2.75	Absent	Absent	4.68 4.85	1.64	0.95
3b'	2.65	Absent	Absent	Absent	Absent	0.90

(a) All chemical shifts are given in δ ; all the compounds showed peaks at 0.85 - 0.97 for HN- and H₂N-. (b) This peak did not show clearly where expected.

T. Takada and K. Sanukiyama (to Toho Rayon Company)
Japanese Patent 25,047 (1964), 11/7/64; Japanese Patent 1197
(1965), 1/22/65.

(5) N. F. Albertson, *J. Am. Chem. Soc.*, **72**, 2594 (1950).

(6) A. P. Terentyev and S. M. Gurvich, *J. Gen. Chem. USSR*,
21, 1789 (1951).

(7) H. A. Bruson and T. W. Reiner, *J. Am. Chem. Soc.*, **64**,
2850 (1942).

(8) H. A. Bruson and T. W. Reiner, *ibid.*, **65**, 18 (1943).

Received May 18, 1968

Stamford, Conn. 06904