93. *Reduction of α-Amino-nitriles.*

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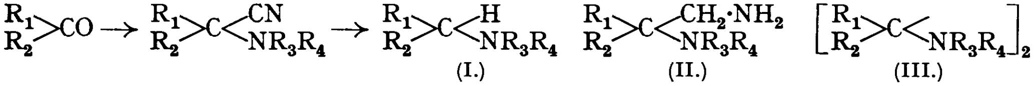
MUCH dimethyl-*n*-propylamine results from the action of "atomised" sodium on α-dimethylamino-*n*-butyronitrile in dry ether. (The hydrogen produced by the action of sodium on a part of the nitrile no doubt serves to reduce a further portion.) The reduction of a number of α-amino-nitriles has therefore been studied, in order to test the preparative utility of the following route from aldehyde or ketone to amine (I):



$$\begin{matrix}R_1\\R_2\end{matrix}\!>\!CO \rightarrow \begin{matrix}R_1\\R_2\end{matrix}\!>\!C\!<\!\begin{matrix}CN\\NR_3R_4\end{matrix} \rightarrow \begin{matrix}R_1\\R_2\end{matrix}\!>\!C\!<\!\begin{matrix}H\\NR_3R_4\end{matrix} \quad \begin{matrix}R_1\\R_2\end{matrix}\!>\!C\!<\!\begin{matrix}CH_2{\cdot}NH_2\\NR_3R_4\end{matrix} \quad \left[\begin{matrix}R_1\\R_2\end{matrix}\!>\!C\!<\!NR_3R_4\right]_2$$

(I.) (II.) (III.)

As several of the conventional reducing agents proved unsatisfactory, the original experiment was repeated, using moist ether [method (1)]. Moderate yields of the desired products were obtained in the three cases tried, although the reaction was too violent for easy manipulation. Better results were attained by adding sodium in slices to the nitrile dissolved in ether floating on potassium bicarbonate solution [method (2)]. These two very similar processes do not always lead to the same result (cf. Table I); for method

(2) appears to yield product (I) only if R_1 or R_2 is an aryl radical, otherwise the nitrile group is not replaced, but reduced *in situ* (II). Phenylation on the nitrogen atom has no effect.

These two types of reduction have already been encountered by Gulewitsch and Wasmus (*Ber.*, 1906, **39**, 1184), who obtained a little *iso*propylamine (type I) by reducing α-amino-*iso*butyronitrile with sodium and alcohol; and by Purgotti (*Gazzetta*, 1894, **24**, ii, 427), who reduced α-aminophenylacetonitrile to phenylethylenediamine (type II) with zinc and hydrochloric acid. Considered along with the present results, these suggest that formation of product (I) is favoured by alkaline conditions, and that of (II) by acids.

TABLE I.

			Method (1).		Method (2).	
	R_1,R_2.	R_3,R_4.	Product.	Yield %.	Product.	Yield %.
A	Et,H	Me,Me	I	30–40	II	39
B	Me,Me	Me,Me	I	30–40	II	22
C	Me,Me	H,H	—	—	decomp.	—
D	Me,H	Ph,Et	—	—	II	55
E	Ph,H	Me,Me	I	50	I	57
F	Ph,H	C_5H_{10}	—	—	I	85
G	Ph,H	Me,H	—	—	I	19 *
H	Ph,H	H,H	—	—	I	46
I	Ph,H	Ph,Me	—	—	I	50
K	Ph,Me	Ph,H	—	—	I	55

* Calculated on the crude nitrile, which cannot be purified.

The results of reduction by method (2) may be compared with those of the interaction of α-dimethylamino-nitriles and the Grignard reagent (Thomson and Stevens, J., 1932, 2607). In the former case α-phenylation of the nitrile causes replacement of the cyanogen by hydrogen, while in the latter it leads to suppression of the normal reaction of ketone formation in favour of the displacement of the nitrile group by the radical of the Grignard reagent—*e.g.*, $CHPh(NMe_2){\cdot}CN + PhMgBr \longrightarrow CHPh_2(NMe_2) + MgBrCN$.

A Fittig–Wurtz synthesis, resulting in the formation of (III), which some amino-nitriles undergo when treated with the Grignard reagent, has not been encountered in these reduction experiments.

EXPERIMENTAL.

Except where otherwise stated, the amino-nitriles were prepared by addition of amine hydrochloride in H_2O to aldehyde or ketone and KCN in H_2O, or of AcOH to aldehyde or ketone, KCN, and amine in H_2O. Low-melting, solid amino-nitriles were prepared at 0°, and the crude material then needed no further purification, though the yield was somewhat diminished. The known compounds had the properties ascribed to them by the authorities cited.

In method (1) the amino-nitrile, dissolved in Et_2O, was added gradually to Na (5—6 atoms) atomised under toluene. The reaction having subsided, EtOH and H_2O were added, and the product extracted with Et_2O. In method (2) 20 mols. $KHCO_3$ and 20 atoms Na were used, the reduction conducted so as to maintain gentle ebullition, and the product finally extracted with Et_2O. Water-soluble bases were salted out by K_2CO_3 before extraction. In each case the dried Et_2O solution was distilled (column; water-bath), giving the " distillate " and " residue " referred to below.

The following reducing agents were tried in the preliminary expts., mostly with α-dimethylaminophenylacetonitrile: Zn–AcOH, Al amalgam–EtOH, Na amalgam–EtOH, and Na–EtOH. In every case the yield of (I) was negligible, the main product being $NHMe_2$. In method (1) the replacement of moist Et_2O by Et_2O containing EtOH (moderate excess, calc. on Na used) led to no improvement.

(A) α-Dimethylamino-*n*-butyronitrile, colourless liquid, b. p. 156—158°; the *picrate*, yellow prismatic needles, m. p. 148° (decomp.; change at 142°) (Found: $C_6H_3O_7N_3$, 67·2. $C_6H_{12}N_2,C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 67·1%), yielded dimethylamine picrate, m. p. and mixed m. p. 157°, on boiling with EtOH.

(1) The distillate gave dimethyl-*n*-propylamine picrate, m. p. and mixed m. p. 108—109° (Hanhart and Ingold, J., 1927, 1007), together with a trace of dimethylamine picrate.

(2) The distillate gave no picrate. From the residue there was obtained α-amino-β-dimethyl-

aminobutane picrate, fine yellow needles, m. p. 176° (decomp.; change at 170°), from acetone, slightly sol. in EtOH, easily in acetone; *dihydrochloride*, slightly deliquescent, m. p. 169°, from EtOH (Found: HCl, 38·2. $C_6H_{16}N_2,2HCl$ requires HCl, 38·6%).

(B) α-Dimethylamino*iso*butyronitrile (Henry and Dewael, *Bull. Acad. roy. Belg.*, 1904, 741).

(1) The distillate gave dimethyl*iso*propylamine picrate, m. p. 240—241° (decomp.) (Thomson and Stevens, *loc. cit.*) (Found: $C_6H_3O_7N_3$, 72·7. Calc. for $C_5H_{13}N,C_6H_3O_7N_3$: $C_6H_3O_7N_3$, 72·5%).

(2) The distillate gave no picrate. The residue yielded α-amino-β-dimethylamino-β-methylpropane picrate, fine yellow needles, m. p. 184°, from acetone–EtOH, easily sol. in acetone, slightly in EtOH; *dihydrochloride*, slightly deliquescent, m. p. 256—258°, from EtOH (Found: HCl, 38·5%).

(C) α-Amino*iso*butyronitrile (Gulewitsch and Wasmus, *loc. cit.*).

(2) No picrate was obtained. Since the nitrile decomposes fairly rapidly on standing, it probably did so under the experimental conditions, the basic products escaping.

(D) *α-Ethylanilinopropionitrile*, liquid, b. p. 133—134°/10 mm. (Found: N, 16·2. $C_{11}H_{14}N_2$ requires N, 16·1%).

(2) The residue gave α-amino-β-ethylanilinopropane picrate, yellow prisms, m. p. 164°, from acetone–EtOH, easily sol. in acetone, less sol. in EtOH; *dihydrochloride*, m. p. 199—200°, from EtOH (Found: HCl, 29·4. $C_{11}H_{18}N_2,2HCl$ requires HCl, 29·1%).

(E) α-Dimethylaminophenylacetonitrile (Stevens, Cowan, and MacKinnon, J., 1931, 2568).

(1) Traces of dimethylamine picrate were obtained from the distillate. From the residue there was isolated benzyldimethylamine picrate, m. p. and mixed m. p. 94°.

(2) The residue was steam-distilled, and the distillate gave benzyldimethylamine picrate, m. p. and mixed m. p. 94°.

(F) α-Piperidinophenylacetonitrile (Knoevenagel, *Ber.*, 1904, **37**, 4086).

(2) After reduction, the Et_2O layer was washed thoroughly with H_2O to remove piperidine, and dried. It yielded 1-benzylpiperidine picrate, stout yellow prisms, m. p. 176—177°, from acetone; phenacylobromide, m. p. and mixed m. p. 135—138° (slight efferv.) (Stevens, J., 1930, 2117).

(G) α-Methylaminophenylacetonitrile (von Miller and Plöchl, *Ber.*, 1898, **31**, 2717) was obtained mixed with a considerable quantity of a neutral cryst. solid, m. p. 183°, from EtOH; the nitrile was extracted from this by Et_2O, and no further purification was attempted.

(2) The procedure of case E(2) gave *benzylmethylamine picrate*, masses of long yellow needles, m. p. 117—118°, from EtOH (Found: $C_6H_3O_7N_3$, 66·1. $C_8H_{11}N,C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 65·4%).

(H) α-Aminophenylacetonitrile (Minovici, *Ber.*, 1896, **29**, 2103).

(2) The residue gave benzylamine picrate, m. p. and mixed m. p. 194° (Jerusalem, J., 1909, **95**, 1283).

(I) α-Methylanilinophenylacetonitrile (Sachs and Goldmann, *Ber.*, 1902, **35**, 3351).

(2) The residue was steam-distilled, leaving benzylmethylaniline; picrate, m. p. and mixed m. p. 104° (Komatsu, *Mem. Coll. Sci. Kyoto*, 1912, **3**, 371).

(K) α-Anilino-α-phenylpropionitrile, prepared as described by Bucherer and Grolée (*Ber.*, 1906, **39**, 992).

(2) Owing to the low solubility of the nitrile in Et_2O, the reduction had to be carried out in dil. solution, and a considerable quantity was recovered unchanged (mixed m. p.). The product was steam-distilled, the residue extracted with Et_2O, and the solvent evaporated. A solution of the remaining liquid in hot dil. HCl deposited α-phenylethylaniline hydrochloride, m. p. 185—186° (Busch, *Ber.*, 1904, **37**, 2691) (Found: HCl, 15·7. Calc. for $C_{14}H_{15}N,HCl$: HCl, 15·6%).

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