294. *Aliphatic Nitro-compounds. Part XV. Preparation of Heterocyclic Bases by Reduction of 3-Nitroalkyl Cyanides.**

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Reduction of 3-nitro-3-methyl-*n*-butyl cyanide (I) with iron and hydrochloric acid gives a mixture of 5-amino-2 : 2-dimethylpyrroline *N*-oxide (II) [or its tautomeride (II*a*)], with 5-amino-2 : 2-dimethylpyrrolidine (III) [or its tautomeride (III*a*)]. The structure of (III) is established by formation from it of mono- and di-benzoyl derivatives, and by its hydrolysis to 5 : 5-dimethyl-2-pyrrolidone (V) by water and Raney nickel. The structure of the *N*-oxide (II) follows from its reduction to (III) by zinc-dust distillation and to 2 : 2-dimethylpyrrolidine (IV) on catalytic hydrogenation. Similar reactions with analogues of (I) are described, and possible mechanisms are discussed.

With a view to the synthesis of 3-amino-3-methyl-*n*-butyl cyanide, 3-nitro-3-methyl-*n*-butyl cyanide (I) was reduced with iron and hydrochloric acid. Two products were obtained : (*a*) a crystalline solid, $C_6H_{12}ON_2$, m. p. 238° (17% yield), and (*b*) a crystalline volatile base, $C_6H_{12}N_2$, (30% yield), with a formula and equivalent weight in agreement with those of the expected amino-cyanide, but with properties which excluded this structure.

The base, $C_6H_{12}N_2$, with 0·5 mol. of benzoyl chloride in ether gave a weakly basic monobenzoyl derivative which formed a picrate and was precipitated unchanged from its hydrochloric acid solution by addition of ammonia.

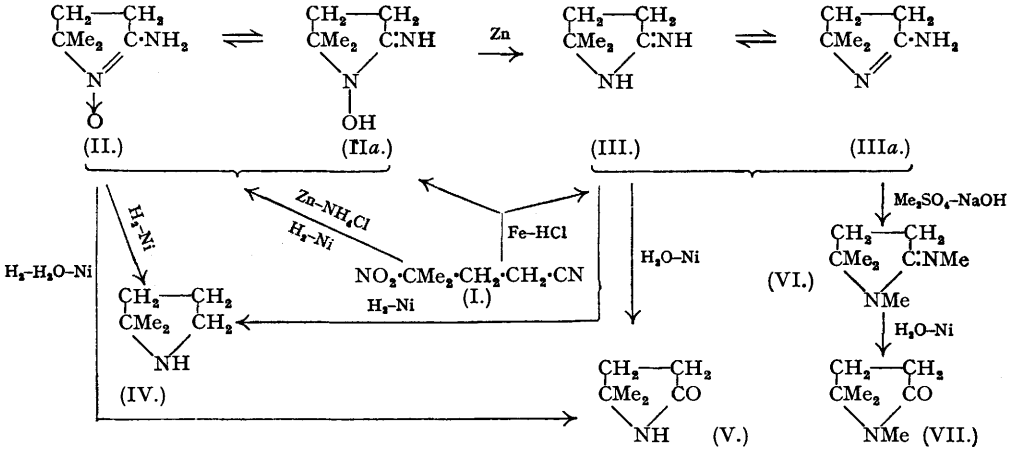
Benzoylation with excess of benzoyl chloride (Schotten–Baumann) gave both the *monobenzoyl* derivative and an acid-insoluble *dibenzoyl* derivative. This suggested that the base was the internal amidine 5-*imino*-2 : 2-*dimethylpyrrolidine* (III) [or 5-amino-2 : 2-dimethylpyrroline (III*a*)]. This was confirmed by the behaviour of the base on hydrolysis, reduction, and methylation. It was extremely resistant to acid or alkaline hydrolysis, but on boiling it with water in the presence of a little Raney nickel, ammonia was evolved and a crystalline, water-soluble solid $C_6H_{11}ON$, having the expected properties of 2 : 2-*dimethyl*-5-*pyrrolidone* (V), was formed. Reduction of the imine (III) with sodium and alcohol was difficult, but gave a small yield of 2 : 2-*dimethylpyrrolidine* (IV), also formed in good yield by catalytic reduction at 100°/100 atms. with Raney nickel under anhydrous conditions. Methylation of (III) with methyl sulphate and sodium hydroxide gave a dimethyl derivative, shown to be 5-*methylimino*-1 : 2 : 2-*trimethylpyrrolidine* (VI), by hydrolysis with water and Raney nickel to methylamine

* Patent application pending.

and 1 : 2 : 2-*trimethyl*-5-*pyrrolidone* (VII). The evidence in favour of the internal amidine structure (III) or (III*a*) is therefore conclusive.

Attention was then directed to the structure of the base $C_6H_{12}ON_2$ (above). This material was the main product when 3-nitro-3-methyl-*n*-butyl cyanide (I) was reduced with zinc dust and ammonium chloride under conditions which normally would be expected to reduce an aliphatic nitro-compound to the hydroxylamine, and was formed in 75% yield by reduction of (I) with hydrogen and Raney nickel at ordinary temperature and pressure. The base was weak; it gave a hydrochloride but would not react with benzoyl chloride, acetic anhydride, phenyl *iso*cyanate, or *N*-nitro-*N'*-2 : 4-dinitrophenylurea. It contained two active hydrogen atoms (Zerewitinoff). Distillation with zinc dust gave the iminopyrrolidine (III), and reduction with sodium and alcohol gave a mixture of (III) and 2 : 2-dimethylpyrrolidine (IV). The latter was also formed by catalytic hydrogenation of the base $C_6H_{12}ON_2$ under anhydrous conditions at 100°/100 atms., but in the presence of water the pyrrolidone (V) was obtained in good yield, presumably by hydrolysis of the first-formed imine (III). Attempts to hydrolyse the base itself by boiling it with water and Raney nickel were unsuccessful.

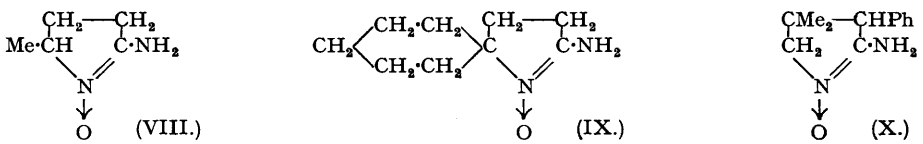
On this evidence the compound was formulated as 5-*amino*-2 : 2-*dimethylpyrroline* N-*oxide* (II) [or the tautomeric 5-*imino*-1-*hydroxy*-2 : 2-*dimethylpyrrolidine* (II*a*)], and its formation is ascribed to cyclisation of the first-formed 3-hydroxylamino-3-methyl-*n*-butyl cyanide. A similar case has been reported by Bauer (*Ber.*, 1938, **71**, 2226), who hydrogenated *o*-nitrostyryl cyanide over a palladium catalyst and obtained 2-aminoquinoline *N*-oxide in 60% yield.



In the reduction of the nitro-cyanide (I) with iron and hydrochloric acid, the iminopyrrolidine (III) might be formed either by reduction of the *N*-oxide (II) or by reduction of the nitro-cyanide to amino-cyanide, followed by cyclisation. Although difficult to prove conclusively, the former appears to be the more probable route; a careful search failed to reveal any amino-cyanide in the reduction products of (I), and it has been shown that the *N*-oxide (II) is, in fact, slowly reduced to the iminopyrrolidine (III) by iron and hydrochloric acid.

Attempts to reduce 3-nitro-3-methyl-*n*-butyl cyanide with platinum or palladium catalysts in the presence of mineral acids were unsuccessful, and use of stannous chloride and hydrochloric acid resulted in hydrolysis. It was concluded, therefore, that the preparation of 3-amino-3-methyl-*n*-butyl cyanide by reduction of the nitro-cyanide was impracticable.

Analogues of (I) were obtained, usually in good yield, by catalytic reduction of other 3-nitroalkyl cyanides. 3-Nitro-*n*-butyl cyanide gave 5-*amino*-2-*methylpyrroline* N-*oxide* (VIII), 1-nitro-1-(2-cyanoethyl)*cyclo*hexane gave 5-*amino*-2 : 2-*pentamethylenepyrroline* N-*oxide* (IX),



and 3-nitro-1-phenyl-2 : 2-dimethyl-*n*-propyl cyanide gave 2-*amino*-3-*phenyl*-4 : 4-*dimethylpyrroline* N-*oxide* (X). Results of hydrogenations at 100 atms. were similar to those obtained

at atmospheric pressure. Raney nickel and palladised calcium carbonate appeared to be equally effective as catalysts, but Adams's platinum oxide gave inferior yields.

Experimental.

Analyses are by Mr. E. S. Morton. M. ps. are uncorrected. The nitro-cyanides were prepared by the methods described in Parts XIII and XIV of this series.

Reduction of 3-*Nitro*-3-*methyl*-n-*butyl Cyanide.*—(a) *With iron and hydrochloric acid.* Iron filings (30—60 mesh) (70 g.), water (150 c.c.), and hydrochloric acid (20 c.c. of 35%) were stirred together until the solution was no longer acid to Congo-red. The mixture was then heated to 100° and a solution of 3-nitro-3-methyl-*n*-butyl cyanide (47·5 g.) in alcohol (100 c.c.) was run in during 1 hour. The mixture was stirred and refluxed for 18 hours, cooled, and the filtered solution acidified to Congo-red with hydrochloric acid. The alcohol was distilled under reduced pressure, the residue diluted with sufficient water to dissolve the salts, and washed with ether. The aqueous solution was made strongly alkaline with potassium hydroxide and extracted repeatedly with ether (see later). The aqueous alkaline solution was then treated with solid potassium hydroxide and the precipitate collected and dissolved in a little water. Dilute hydrochloric acid was added until the solution was no longer alkaline to Clayton-yellow, and, after evaporation under reduced pressure, the product was isolated by extraction with absolute alcohol, evaporation of the extract and treatment with acetone giving 5-*amino*-2 : 2-*dimethylpyrroline* N-*oxide* (II) (8·0 g.) as a crystalline solid, which separated from alcohol–acetone in colourless plates, m. p. 238° (Found : C, 56·35; H, 9·45; N, 22·15. $C_6H_{12}ON_2$ requires C, 56·25; H, 9·4; N, 21·9%). The product was very soluble in water, chloroform, and alcohol, insoluble in ether, acetone, ethyl acetate, dioxan, and hydrocarbons. The *hydrochloride* had m. p. 173° (Found : Cl, 21·75. $C_6H_{12}ON_2$,HCl requires Cl, 21·6%). The *picrate*, m. p. 160°, formed yellow needles from alcohol (Found : N, 20·0. $C_6H_{12}ON_2$,$C_6H_3O_7N_3$ requires N, 19·6%).

The ethereal extract was dried (KOH) and distilled, giving 5-*imino*-2 : 2-*dimethylpyrrolidine* (III) as colourless crystals (14·4 g.), b. p. 108—110°/15 mm., m. p. 73—74° [Found : *M* (by titration with 0·1N-hydrochloric acid to bromophenol-blue), 113·2. $C_6H_{12}N_2$ requires *M*, 112]. The *picrate*, m. p. 203—204°, formed yellow needles from alcohol (Found : N, 20·4. $C_6H_{12}N_2$,$C_6H_3O_7N_3$ requires N, 20·55%).

A solution of benzoyl chloride (0·6 g.) in dry ether (5 c.c.) was cautiously added to a solution of 5-imino-2 : 2-dimethylpyrrolidine (1 g.) in dry ether (5 c.c.). A vigorous reaction occurred, and after evaporation of the solvent the product was extracted with dilute aqueous ammonia and crystallised from 50% aqueous alcohol, giving the *monobenzoyl* derivative (0·6 g.) as colourless prisms, m. p. 98°, soluble in dilute hydrochloric acid and reprecipitated unchanged by addition of ammonia (Found : C, 72·0; H, 7·15; N, 12·65. $C_{13}H_{16}ON_2$ requires C, 72·2; H, 7·4; N, 12·95%).

Benzoyl chloride (6 g.) was added dropwise to a stirred and ice-cooled mixture of 5-imino-2 : 2-dimethylpyrrolidine (2 g.), sodium hydroxide (3·2 g.), and water (25 c.c.) at 10—15°. The mixture was stirred at 10—20° until the excess of benzoyl chloride had decomposed, and the precipitate was then collected, washed with water, and extracted with cold N-hydrochloric acid (50 c.c.). Treatment of the extract with aqueous ammonia precipitated a monobenzoyl derivative, identical with that described above. The acid-insoluble portion (3·2 g.) was repeatedly crystallised from acetone, giving colourless needles (0·3 g.), m. p. 179° (Found : C, 69·75; H, 5·65; N, 9·05%). This material was not further investigated. The acetone mother liquors were evaporated and the residue crystallised from alcohol, giving colourless needles of 5-*benzimido*-1-*benzoyl*-2 : 2-*dimethylpyrrolidine*, m. p. 133° (Found : C, 74·65; H, 6·6; N, 8·7. $C_{20}H_{20}O_2N_2$ requires C, 75·0; H, 6·25; N, 8·75%).

(b) *With zinc dust and ammonium chloride.* Zinc dust (25 g.) was added during 2½ hours to a vigorously stirred mixture of 3-nitro-3-methyl-*n*-butyl cyanide (20 g.), ammonium chloride (6 g.), and water (80 c.c.) at 10—15°. When reaction was complete the solution was filtered, neutralised with hydrochloric acid, evaporated under reduced pressure, and the residue extracted with absolute alcohol; the extract on dilution with dry ether gave the hydrochloride, m. p. 173°, of 5-amino-2 : 2-dimethylpyrroline *N*-oxide, from which the base, m. p. 238°, was obtained by basification.

(c) *Catalytically.* 3-Nitro-3-methyl-*n*-butyl cyanide (150 g.), dissolved in methyl alcohol (1500 c.c.), was shaken with Raney nickel and hydrogen at 20°/1 atm. until absorption of hydrogen ceased. The filtered solution was concentrated, finally by heating at 100°/20 mm., and the residue treated with acetone, giving 5-amino-2 : 2-dimethylpyrroline *N*-oxide. A second crop was obtained by concentrating the mother liquor and again treating the residue with acetone. The total yield was 101 g. (75%).

Reduction of 5-*Amino*-2 : 2-*dimethylpyrroline* N-*Oxide.*—(a) *Catalytically.* A solution of 5-amino-2 : 2-dimethylpyrroline *N*-oxide (10 g.) in anhydrous methanol (100 c.c.) was stirred with hydrogen and water and Raney nickel (1 g.) in an autoclave at 100°/100 atms. until absorption was complete, cooled, filtered from catalyst, and steam-distilled until free from volatile bases. The distillate was acidified with hydrochloric acid and evaporated to dryness. The hydrochloride was treated with a large excess of 40% aqueous potassium hydroxide, the base extracted with ether, the extract dried (KOH), and fractionated, giving 2 : 2-*dimethylpyrrolidine* (IV) (4·9 g.) as a colourless liquid, b. p. 105—106 (Found : *M* (by titration with 0·1N-hydrochloric acid to bromophenol-blue), 100·2. $C_6H_{13}N$ requires *M*, 99). The *picrate*, m. p. 190—191°, formed yellow needles from water (Found : N, 17·5. $C_6H_{13}N$,$C_6H_3O_7N_3$ requires N, 17·1%). The 2 : 4-*dinitrophenylcarbamyl* derivative (cf. McVeigh and Rose, *J.*, 1945, 621), m. p. 131°, formed long yellow needles from alcohol (Found : C, 50·65; H, 5·25; N, 18·2. $C_{13}H_{16}O_5N_4$ requires C, 50·65; H, 5·2; N, 18·2%).

(b) *With sodium and alcohol.* 5-Amino-2 : 2-dimethylpyrroline *N*-oxide (75 g.) was dissolved in absolute alcohol (2 l.) and treated rapidly at the boil with sodium (170 g.). When the sodium was completely dissolved, the solution was cooled and cautiously acidified to Congo-red with concentrated hydrochloric acid, filtered from salt and steam-distilled. The residual solution was diluted with an equal volume of 32% aqueous sodium hydroxide and extracted with ether. The extract, after drying

and distillation, yielded 5-imino-2 : 2-dimethylpyrrolidine (14·2 g.). The steam-distillate was acidified with hydrochloric acid and evaporated to dryness, leaving a hydrochloride, which, after basification and distillation, yielded 2 : 2-dimethylpyrrolidine (7·2 g.).

(c) *By distillation with zinc dust.* 5-Amino-2 : 2-dimethylpyrroline *N*-oxide (30 g.) was mixed thoroughly with zinc dust (30 g.) and heated, 20 g. at a time, in a distillation apparatus under 20 mm. The bath was heated to 280° and the temperature was then slowly raised to 320° and held at this until distillation ceased. The distillate was extracted with ether and the extract dried (KOH) and fractionated giving 5-imino-2 : 2-dimethylpyrrolidine (7 g.), b. p. 106°/15 mm.

(d) *With iron and hydrochloric acid.* 5-Amino-2 : 2-dimethylpyrroline *N*-oxide (20 g.) was reduced for 48 hours at 95—100° with iron (35 g.) and hydrochloric acid as described above for the reduction of the nitro-cyanide. Isolation as before gave 5-imino-2 : 2-dimethylpyrrolidine (7·9 g.), together with much unchanged starting materials.

Reduction of 5-Imino-2 : 2-dimethylpyrrolidine.—(a) *Catalytically.* The base (5 g.) was hydrogenated at 100°/100 atms. under anhydrous conditions as described above for 5-amino-2 : 2-dimethylpyrroline *N*-oxide. The resulting solution was filtered and fractionated, giving 2 : 2-dimethylpyrrolidine (IV) (3·8 g.); picrate, m. p. 190—191°.

(b) *With sodium and alcohol.* 5-Imino-2 : 2-dimethylpyrrolidine (7 g.) was reduced with sodium (50 g.) and absolute alcohol (600 c.c.) as described above for the pyrroline oxide. The product was worked up as before to give a small amount of 2 : 2-dimethylpyrrolidine, together with unchanged 5-imino-2 : 2-dimethylpyrrolidine (3·2 g.).

2 : 2-*Dimethyl-5-pyrrolidone* (V).—(*a*) A solution of 5-imino-2 : 2-dimethylpyrrolidine (3 g.) in water (30 c.c.) was stirred and refluxed for 3 hours with Raney nickel (0·1 g.); ammonia was evolved. The filtered solution was distilled, giving 2 : 2-*dimethyl-5-pyrrolidone* (2·1 g.) as colourless, hygroscopic crystals, m. p. 42°, b. p. 140°/20 mm. (Found : C, 63·4; H, 9·7; N, 12·15. $C_6H_{11}ON$ requires C, 63·7; H, 9·75; N, 12·4%). The *hydrochloride* had m. p. 150—152° (Found : Cl, 23·4. $C_6H_{11}ON,HCl$ requires Cl, 23·75%).

(*b*) 5-Amino-2 : 2-dimethylpyrroline *N*-oxide (5 g.), dissolved in methyl alcohol (100 c.c.), was stirred with Raney nickel and hydrogen at 100°/100 atms. until absorption of hydrogen ceased. Distillation of the product gave 2 : 2-dimethyl-5-pyrrolidone (3·2 g.).

Methylation of 5-Imino-2 : 2-dimethylpyrrolidine.—Methyl sulphate (40 g.) was added dropwise to a stirred and cooled mixture of 5-imino-2 : 2-dimethylpyrrolidine (10 g.) and aqueous sodium hydroxide (80 c.c. of 16%) at 10—15°. The mixture was stirred at 10—20° until the excess of methyl sulphate had decomposed, and was then treated with an equal volume of 32% sodium hydroxide solution and extracted with ether. The extract was dried (KOH) and distilled, giving 5-*methylimino*-1 : 2 : 2-*trimethylpyrrolidine* (VI) (11 g.) as a colourless oil, b. p. 97—98°/18 mm. The *picrate*, m. p. 125°, formed yellow needles from water (Found : C, 46·2; H, 5·1; N, 19·25. $C_8H_{16}N_2,C_6H_3O_7N_3$ requires C, 45·55; H, 5·15; N, 19·0%).

1 : 2 : 2-*Trimethyl-5-pyrrolidone* (VII).—The base (above) (6·8 g.) in water (70 c.c.) was boiled with Raney nickel for 3 hours. An aqueous solution of the evolved gases was shown to be free from ammonia (no precipitate with Nessler's reagent), but, on boiling with *N*-nitro-*N'*-2 : 4-dinitrophenylurea, gave *N*-2 : 4-dinitrophenyl-*N'*-methylurea, m. p. and mixed m. p. with an authentic specimen, 204° (cf. McVeigh and Rose, *loc. cit.*). The aqueous residue was filtered from catalyst and distilled, giving 1 : 2 : 2-*trimethyl-5-pyrrolidone* (VII) (4·9 g.), as a colourless oil, b. p. 130°/60 mm. (Found : C, 66·2; H, 10·2; N, 10·95. $C_7H_{13}ON$ requires C, 66·1; H, 10·25; N, 11·05%).

5-*Amino*-2-*methylpyrroline N-Oxide* (VIII).—3-Nitro-*n*-butyl cyanide (32 g.) in methyl alcohol (400 c.c.) was hydrogenated in the presence of Raney nickel at 20°/1 atm. The filtered solution was concentrated and the residue was stirred with acetone and the solid collected (5 g.). Crystallisation from chloroform–acetone gave colourless, hygroscopic needles, m. p. 206° (Found : C, 52·65; H, 8·4; N, 24·3. $C_5H_{20}ON_2$ requires C, 52·65; H, 8·75; N, 24·55%).

5-*Amino*-2 : 2-*pentamethylenepyrroline* N-*Oxide* (IX).—1-Nitro-1-(2-cyanoethyl)*cyclo*hexane (21 g.) was hydrogenated and the product (8 g.) isolated as described above. Crystallisation from acetone–alcohol gave the *base* as colourless leaflets, m. p. 206° (Found : N, 16·4. $C_9H_{16}ON_2$ requires N, 16·65%). The *hydrochloride* had m. p. 200° (Found : Cl, 17·45. $C_9H_{16}ON_2,HCl$ requires Cl, 17·3%).

2-*Amino*-3-*phenyl*-4 : 4-*dimethylpyrroline* N-*Oxide* (X).—3-Nitro-1-phenyl-2 : 2-dimethyl-*n*-propyl cyanide (5 g.), dissolved in methyl alcohol (50 c.c.), was shaken with hydrogen and 5% palladised calcium carbonate (1 g.) until absorption of hydrogen was complete. After filtration from catalyst, the solution was evaporated on the steam-bath and the residue was treated with acetone and collected (3 g.); crystallisation from acetone–alcohol gave colourless granules, m. p. 189—190° (Found : N, 13·7. $C_{12}H_{16}ON_2$ requires N, 13·7%).

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