98. *Experiments in the Piperidine Series. Part I.*

By A. H. Cook and K. J. Reed.

Addition of methylamine to acrylonitrile gave mono- and bis-β-cyanoethylmethylamine, of which the latter was converted into derivatives of 4-piperidone and thence into more complex heterocyclic systems. Attempts to prepare piperidone homologues by similar routes were unsuccessful, but β-cyanoethyl(carbethoxymethyl)-methylamine was prepared and cyclised to pyrrolidone derivatives.

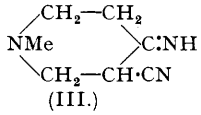
These experiments arose from the need for 4-piperidone derivatives for conversion into compounds of possible analgesic activity. Prill and McElvain (*J. Amer. Chem. Soc.*, **1933**, **55**, 1236) obtained ethyl 1-methyl-4-piperidone-3-carboxylate by Dieckmann ring closure of bis-(β-carbethoxyethyl)methylamine and described its hydrolysis to 1-methyl-4-piperidone. During the present work *methyl 1-methyl-4-piperidone-3-carboxylate* and its *hydrochloride* were prepared by similar methods. The methyl resembled the ethyl ester in the free state in readily undergoing an irreversible change to a water-soluble solid, although the nature of the change was not elucidated. In view of this sensitivity, a similar series of reactions involving the corresponding nitriles was investigated. Methylamine and acrylonitrile easily afforded *β-cyanoethylmethylamine* (I) or *bis-*

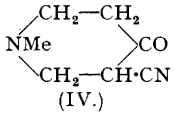
(β-*cyanoethyl*)*methylamine* (II) according to the proportions of reactants and conditions. The former was characterised as its hydrochloride, *picrate*, and α-*naphthylurea*, and (II) as its *picrate*. B.P. 404,744 describes

(I.) $NHMe{\cdot}CH_2{\cdot}CH_2{\cdot}CN$ $NMe(CH_2{\cdot}CH_2{\cdot}CN)_2$ (II.)

reactions of this type, although none of the examples describes the use of methylamine. The nature of these cyanoethyl compounds was confirmed by alcoholysis to known products obtained by addition of methylamine to methyl and ethyl acrylates, which were identified as their *picrates*. (II) was smoothly cyclised by sodium to 4-*imino*-3-*cyano*-1-*methylpiperidine* (III), characterised as its *picrate*, which was hydrolysed to the *hydrochloride* of 3-*cyano*-1-*methylpiperidone* (IV); the free base was, however, at least as sensitive as the corresponding esters and attempts to obtain it pure failed. An attempt to perform the cyclisation with potassium in liquid ammonia led to an altered product, and although cryoscopic determinations of molecular weights were untrustworthy, analysis indicated that it was a *hydrochloride* of a base isomeric with the starting material. It was regarded as probably a linear iminonitrile dimeride.

These β-keto-acid derivatives underwent several typical condensations. For instance, methyl 1-methyl-4-piperidone-3-carboxylate condensed with benzamidine with surprising facility; from analytical evidence and the fact that the product was identical with that from the corresponding ethyl ester it must be formulated as the *hydroxy-pyrimidine* (V). When benzamidine was replaced by guanidine, condensation was equally


(III.)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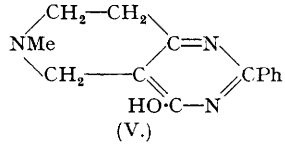
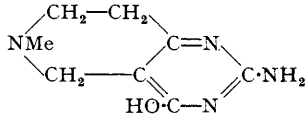
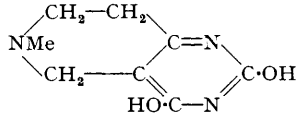
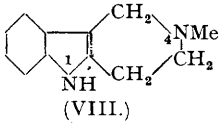

(V.)

easy and again, as both esters afforded the same product, it is to be expressed as the *aminohydroxypyrimidine* (VI). On the other hand, reaction with urea to give the *dihydroxypyrimidine* (VII) required more drastic conditions and a similar condensation with *S*-methyl*iso*thiourea has not so far been observed.

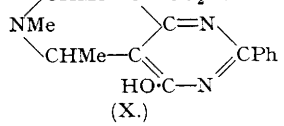
(VI.) 


(VII.)

Although methyl and ethyl 1-methyl-4-piperidone-3-carboxylate were readily converted into 1-methyl-4-piperidone, characterised as its *picrate*, by hot 20% hydrochloric acid (cf. Thayer and McElvain, *J. Amer. Chem. Soc.*, **1927**, **41**, 2862), similar hydrolysis of the cyanopiperidone was less successful. Attempts to prepare 1-*methyl*-4-*piperidonephenylhydrazone* led to a colourless compound which analysis showed to be the required derivative, $C_{12}H_{17}N_3$. This was, however, unstable, and even on crystallisation under ordinary conditions it absorbed oxygen and afforded a coloured *compound*, $C_{12}H_{17}O_2N_3$. Catalytic hydrogenation of this derivative resulted in absorption of 2·2 g.-mols. of hydrogen, but the original phenylhydrazone was not regenerated and the nature of the oxygenated product remains obscure. In other ways the phenylhydrazone appeared to be normal, and it was cleanly converted into 4-*methyl*-2 : 3 : 4 : 5-*tetrahydro*-4-*carboline* (VIII).


(VIII.)

NHMe·CH₂·CHMe·CN
(IX.)


(X.)

The facility with which many of the above reactions took place led to attempts to obtain further substituted piperidine derivatives by similar methods.

Equimolecular amounts of methylamine and methacrylonitrile gave a good yield of β-*cyano*-n-*propylmethylamine* (IX), characterised as its *picrate* and α-*naphthylurea*, but under no conditions was there any evidence of the formation of the desired bis-(β-cyanopropyl)methylamine. Extensive efforts were also made to obtain appropriate cyano-esters by (*a*) addition of β-cyanoethylmethylamine to ethyl crotonate, (*b*) addition of acrylonitrile to ethyl β-methylaminobutyrate, (*c*) reaction of β-chloropropionitrile with ethyl β-methylaminobutyrate, or (*d*) reaction of β-cyanoethylmethylamine with ethyl β-chlorobutyrate. In (*a*) and (*b*) only complex mixtures were recovered; (*c*) likewise afforded mixtures of (presumably) condensation products and deamination of the methylaminobutyric ester to ethyl crotonate was the only reaction identified, whilst in (*d*) the main reaction was removal of hydrogen chloride from the chloro-ester. (*a*) and (*b*), and the addition of methylamine to methacrylonitrile provide examples of the expected decrease in reactivity of acrylic derivatives consequent upon the introduction of a methyl group into the α- or β-position. Although the desired reaction (*d*) was not realised, β-cyanoethylmethylamine and ethyl chloroacetate gave an excellent yield of β-*cyanoethyl*(*carbethoxymethyl*)*methylamine*, which was cyclised by sodium. The results of Prill and McElvain (*loc. cit.*) suggest that, of the alternative modes of cyclisation, the formation of 3-cyano-1-methyl-4-pyrrolidone

will prevail and the isolation of 3-*cyano*-1-*methyl*-4-*pyrrolidone* and 1-*methyl*-4-*pyrrolidone*-3-*carboxyamide* confirmed this expectation. The preparation of simple methylated analogues of the piperidine derivatives described above was not accomplished, and this part of the project was abandoned.

Experimental.

Acrylonitrile (30 g.) was slowly added with stirring and cooling to methylamine (21 g.) in methanol (73 g.), and the solution kept for 24 hours. Removal of solvent, and distillation gave *β-cyanoethylmethylamine* (37 g., 78%), b. p. 74°/16 mm., $n_D^{15°}$ 1·4342 (Found: C, 57·3; H, 9·5. $C_4H_8N_2$ requires C, 57·1; H, 9·6%). A small amount of bis(cyanoethyl)methylamine (below) was obtained from the higher-boiling fractions. β-Cyanoethylmethylamine was very soluble in water and most organic liquids. The hydrochloride separated from ethanol–ether as deliquescent needles, m. p. 83—85°, subliming at 60° in a high vacuum; the *picrate* crystallised from ethanol in rhombic plates, m. p. 131—132° (Found: N, 22·05. $C_{10}H_{11}O_7N_5$ requires N, 22·35%); reaction with α-naphthyl *iso*cyanate in benzene gave the *α-naphthylurea* derivative, which separated from benzene as large needles, m. p. 105—107° (Found: N, 16·55. $C_{15}H_{15}ON_3$ requires N, 16·6%).

Acrylonitrile (17 g.) was heated (sealed tube) with methylamine (11 g.) at 80° for 16 hours. Distillation gave *bis-(β-cyanoethyl)methylamine* as a viscous liquid, b. p. 195—198°/20 mm. or 138°/5 mm., $n_D^{18°}$ 1·4633 (Found: C, 60·95; H, 8·25. $C_7H_{11}N_3$ requires C, 61·2; H, 8·0%). The amine was miscible with water, ethanol, or chloroform but sparingly soluble in light petroleum; its *picrate* separated from ethanol as needles, m. p. 172° (Found: N, 23·1. $C_{13}H_{14}O_7N_6$ requires N, 22·95%). β-Cyanoethylmethylamine (42 g.), concentrated sulphuric acid (100 g.), and ethanol (125 g.) were heated under reflux for 5 hours, the solution diluted with water (300 c.c.), and potassium carbonate added. Liberated β-carbethoxyethylmethylamine was taken up in chloroform and distilled. It had b. p. 65°/15 mm., $n_D^{18°}$ 1·4451 (yield, 24 g.); the *picrate* crystallised from ethanol–light petroleum in needles, m. p. 92—93° (Found: N, 15·8. $C_{12}H_{16}O_9N_4$ requires N, 15·55%). Alcoholysis of bis-(β-cyanoethyl)methylamine was carried out similarly for 20 hours to yield bis-(β-carbomethoxyethyl)methylamine (yield 46%), b. p. 137—140°/14 mm., $n_D^{17°}$ 1·4462; the *picrate* separated from ethanol in rhombic prisms, m. p. 113° (Found: N, 12·5. $C_{15}H_{20}O_{11}N_4$ requires N, 13·0%), identical with a picrate prepared from Morsch's product (*Monatsh.*, 1933, **63**, 229).

Bis-(β-cyanoethyl)methylamine (13·7 g.) in liquid ammonia (400 c.c.) was treated with potassium (7·8 g.) with stirring during 3 hours. After a further 2 hours, ammonium chloride (20 g.) and ether (150 c.c.) were added, and ammonia removed; extraction of the residue with cold ethanol (200 c.c.) and treatment of the extract with hydrogen chloride gave the *dimeride*(?) *hydrochloride*, which separated from acetic acid in small prisms, m. p. 210—220° (decomp.), varying with the rate of heating [Found: C, 48·2; H, 7·0. $(C_7H_{12}N_3Cl)_x$ requires C, 48·4; H, 6·95%].

A suspension of " molecular " sodium (1·5 g.) in toluene (20 c.c.) containing bis-(β-cyanoethyl)methylamine (10 g.) was warmed to 60°, and the vigorous exothermic reaction completed by refluxing for 15 mins. The cold product was decomposed with ice-water, and the aqueous solution acidified (Congo-red) and saturated with potassium carbonate at <10°. 4-*Imino*-3-*cyano*-1-*methylpiperidine* was precipitated, and more obtained by extracting the mother-liquors with chloroform. It separated from acetone or benzene in large prismatic needles, m. p. 122—123° (Found: C, 60·9; H, 8·4; *M*, cryoscopic in camphor, 141. $C_7H_{11}N_3$ requires C, 61·2; H, 8·0%; *M*, 137); its *picrate* separated from acetone–ethanol in orange rosettes, m. p. 160—162° (Found: N, 23·0. $C_{13}H_{14}O_7N_6$ requires N, 22·95%). The finely powdered imino-nitrile (2 g.) was added to 25% hydrochloric acid (3·5 c.c.), and solution completed by warming for 15 mins. (steam-bath). Evaporation to dryness in a vacuum, extraction with ethanol (50 c.c.), and addition of ether precipitated 3-*cyano*-1-*methyl*-4-*piperidone hydrochloride*, which separated from ethanol–ether (1 : 1) in small prisms, m. p. 167° (decomp.) (Found: N, 16·05. $C_7H_{11}ON_2Cl$ requires N, 16·05%).

Bis-(β-carbomethoxyethyl)methylamine was cyclised by the method described by Prill and McElvain (*loc. cit.*) for the diethyl ester. *Methyl* 1-*methyl*-4-*piperidone*-3-*carboxylate hydrochloride* crystallised from ethanol–ether in prisms, m. p. 165° (decomp.) (Found: N, 6·8. $C_8H_{14}O_3NCl$ requires N, 6·75%). Treatment of the latter with potassium carbonate liberated *methyl* 1-*methyl*-4-*piperidone*-3-*carboxylate* as an oil, b. p. 87—88°/4·5 mm. (Found: C, 56·3; H, 7·6. $C_8H_{13}O_3N$ requires C, 56·15; H, 7·65%).

Ethyl 1-methyl-4-piperidone-3-carboxylate hydrochloride (4·4 g.) and benzamidine hydrochloride (3·2 g.) in the minimum of water were added to potassium carbonate (6 g.) in water (30 c.c.). After 12 hours' standing, 4-*hydroxy*-2-*phenyl*-5 : 6-(1′ : 2′ : 3′ : 6′-*tetrahydro*-1′-*methyl*-5′ : 4′-*pyrido*)*pyrimidine* (3·6 g.) was filtered off; it was amphoteric, and crystallised from ethanol in long, pale yellow needles, m. p. 225—227° (Found: C, 69·9; H, 6·2. $C_{14}H_{15}ON_3$ requires C, 69·7; H, 6·25%). The compound was obtained similarly from the methyl ester. Ethyl 1-methyl-4-piperidone-3-carboxylate hydrochloride (3·2 g.) and guanidine nitrate (1·8 g.), each in the minimum of water, were added to potassium carbonate (4 g.) in cold water (30 c.c.). After 8 hours 2-*amino*-4-*hydroxy*-5 : 6-(1′ : 2′ : 3′ : 6′-*tetrahydro*-1′-*methyl*-5′ : 4′-*pyrido*)*pyrimidine* (1·9 g.) was filtered off and recrystallised from water, separating in glistening leaflets, m. p. 284° (decomp.) (Found: C, 52·9; H, 7·1. $C_8H_{12}ON_4$ requires C, 53·3; H, 6·7%); it was amphoteric, and sparingly soluble in the common organic solvents.

A solution of urea (1·05 g.) and methyl 1-methyl-4-piperidone-3-carboxylate (3 g.) in ethanol (25 c.c.) containing sodium (0·4 g.) was heated for 8 hours at 100° (autoclave), and the cold suspension treated with dry hydrogen chloride. The precipitate was sublimed at 200° in a high vacuum and gave pale yellow prisms of 2 : 4-*dihydroxy*-5 : 6-(1′ : 2′ : 3′ : 6′-*tetrahydro*-1′-*methyl*-5′ : 4′-*pyrido*)*pyrimidine hydrochloride*, m. p. 285° (decomp.) (Found: C, 44·0; H, 5·3. $C_8H_{12}O_2N_3Cl$ requires C, 44·15; H, 5·55%); it was soluble in water, but sparingly soluble in organic solvents. 3 : 5-Dicarbethoxy-1 : 2 : 6-trimethyl-4-piperidone (Mannich, *Arch. Pharm.*, 1934, **272**, 323) (5·7 g.) in ethanol (20 c.c.) was added to benzamidine hydrochloride (3·2 g.) in water (25 c.c.) containing potassium carbonate (3 g.). After 7 days the brown solid was collected and recrystallised from ethanol; the 4-*hydroxy*-2-*phenyl*-5 : 6-(1′ : 2′ : 3′ : 6′-*tetrahydro*-1′ : 2′ : 6′-*trimethyl*-3′-*carbethoxy*-5′ : 4′-*pyrido*)*pyrimidine* separated in micro-needles, m. p. 215° (yield of pure product, 0·4 g.) (Found: C, 63·4; H, 6·95; N, 11·7. $C_{19}H_{23}O_3N_3,H_2O$ requires C, 63·5; H, 7·0; N, 11·7%). It sublimed unchanged in a high vacuum.

1-Methyl-4-piperidone (1·1 g.) was added to phenylhydrazine hydrochloride (1·4 g.) in water (3 c.c.). After 24 hours, excess of potassium carbonate was added, and the precipitated oil soon solidified (1·3 g.). 1-*Methyl*-4-*piperidonephenylhydrazone* could not be recrystallised without undergoing secondary change; after drying at room temperature in a high vacuum it had m. p. 100—102° (decomp.) (Found: C, 71·2; H, 8·35. $C_{12}H_{17}N_3$ requires C, 70·9; H, 8·45%). The colourless phenylhydrazone dissolved easily in common organic solvents, but on standing the solutions became yellow, that in light petroleum depositing yellow, feathery needles, m. p. 151° (decomp.). Recrystallisation from acetone containing a small amount of ethanol gave the *compound* in yellow needles, m. p. 156° (decomp.) (Found: C, 60·5; H, 7·3; N, 17·9. $C_{12}H_{17}O_2N_3$ requires C, 61·2; H, 7·3; N, 17·9%). On hydrogenation at room temperature and pressure over Adams's catalyst in ethanol, 2·2 g.-mols. of hydrogen were absorbed, the yellow colour disappearing. Filtration, concentration of the filtrate in a vacuum, and addition of acetone gave deliquescent prisms characterised as

the *picrate*, which separated from ethanol in shining yellow leaflets, m. p. 172—176° (Found: C, 40·1; H, 4·45; N, 14·0%).

1-Methyl-4-piperidonephenylhydrazone (3·5 g.) was heated on the steam-bath for 1 hour with concentrated sulphuric acid (35 c.c.) in water (100 c.c.). A crude product was precipitated by adding sodium hydroxide, and purified by sublimation at 80—90° in a high vacuum and crystallisation from dilute ethanol; *4-methyl-2 : 3 : 4 : 5-tetrahydro-4-carboline* (2·0 g.) separated as plates, m. p. 171—172° (Found: N, 15·2. $C_{12}H_{14}N_2$ requires N, 15·0%).

Ethyl chloroacetate (61·3 g.) was added with stirring to β-cyanoethylmethylamine (84 g.), and the mixture kept for 15 hours. The semi-solid product was diluted with ether (250 c.c.), and the filtrate distilled, eventually in a vacuum. *β-Cyanoethyl(carbethoxymethyl)methylamine* was collected as an oil, b. p. 99°/5 mm., $n_D^{17°}$ 1·4478 (76 g.) (Found: C, 56·55; H, 8·35. $C_8H_{14}O_2N_2$ requires C, 56·45; H, 8·3%); its *picrate* separated from ethanol in yellow needles, m. p. 111—112° (Found: C, 42·1; H, 4·3. $C_{14}H_{17}O_8N_5$ requires C, 42·3; H, 4·2%).

A cold solution prepared by adding ethanol (24·5 c.c.) to " molecular " sodium (9·5 g.) in toluene (40 c.c.) was treated dropwise with β-cyanoethyl(carbethoxymethyl)methylamine (70·5 g.), and the exothermic reaction finally completed on the steam-bath for 10 mins. The sodio-compound was filtered off, decomposed by cautious addition to liquid ammonia (500 c.c.), and the solution treated with ammonium chloride (40 g.). Removal of ammonia, extraction of the residue with cold ethanol (300 c.c.), concentration of the extract at 20° in a vacuum, and addition of ether precipitated crude *3-cyano-1-methyl-4-pyrrolidone*. It was purified by chromatography on alumina from ethanol and recovered by addition of ether to the concentrated alcoholic eluate; crystallisation from acetone–light petroleum gave needles, m. p. 175° (decomp.) (Found: N, 22·9. $C_6H_8ON_2$ requires N, 22·6%). The pyrrolidone was labile, and other methods of decomposing the sodio-compound were unsatisfactory. In one attempt it was decomposed in the ordinary manner with dilute hydrochloric acid, the acid solution evaporated to dryness in a vacuum, and the residue extracted with cold ethanol. Addition of ether to the extract and rejection of the first precipitate gave *1-methyl-4-pyrrolidone-3-carboxyamide*, which crystallised from ethanol–ether in prisms, m. p. 130—131° (Found: C, 50·65; H, 6·95. $C_6H_{10}O_2N_2$ requires C, 50·65; H, 7·1%); it was easily soluble in water and moderately soluble in common organic solvents. When the crude product, obtained, *e.g.*, by decomposing the sodio-compound with acetic acid, was boiled with 10 vols. of 20% hydrochloric acid for 2 hours, hydrolysis and decarboxylation occurred. Evaporation to dryness in a vacuum, addition of sodium hydroxide, and extraction with ether gave crude 1-methyl-3-pyrrolidone, characterised as its *picrate*, which crystallised from acetone–light petroleum in small brown prisms, m. p. 168° (decomp.) (Found: N, 16·9. $C_{11}H_{12}O_8N_4$ requires N, 17·05%).

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