113. *Analgesics. Part I. Esters and Ketones derived from α-Amino-ω-cyano-ωω-diarylalkanes.*

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A number of basic cyanides (V) have been prepared either (*a*) by reaction of a diarylmethyl cyanide with a chloro-amine $R_2N\cdot[CH_2]_n\cdot Cl$, or (*b*) by treatment of a diarylmethyl cyanide with an αω-dihalogeno-paraffin, and reaction of the resulting halogeno-cyanide with a secondary amine. The amino-cyanides were converted into amino-ketones by treatment with Grignard reagents, and into amino-esters by direct esterification with alcoholic sulphuric acid.

The acids $R_2N\cdot CH_2\cdot CH_2\cdot CPh_2\cdot CO_2H$ (R = Me or Et) on treatment with thionyl chloride gave the 3 : 3-diphenyl-1-alkylpyrrolid-2-one; the homologous acid, $Et_2N\cdot CH_2\cdot CH_2\cdot CH_2\cdot CPh_2\cdot CO_2H$, on similar treatment, gave an acid chloride which showed no tendency to cyclise.

The analgesic activities of the amino-esters and amino-ketones are given.

Although morphine has been widely used as an analgesic for a very long time, it is known to have many disadvantages; in particular, its depressant effect on the respiratory centre and its pronounced tendency to cause addiction are serious drawbacks in clinical practice. Much work has been done, particularly in America, on the preparation of derivatives of morphine that might retain analgesic activity while lacking the undesirable effects of the parent compound (Small, Eddy, Mosettig, and Himmelsbach, Public Health Service, Supplement No. 138, U.S. Treasury Dept., Washington, 1938), and some success has now been achieved with the introduction of methyldihydromorphinone (metopon) (Lee, *J. Pharm. Exp. Ther.*, 1942, **75**, 161). Many attempts have also been made by these and other workers to prepare a synthetic substitute for morphine; the first useful compound to emerge from this work was pethidine, the hydrochloride of ethyl 4-phenyl-1-methylpiperidine-4-carboxylate (Eisleb, *Ber.*, 1941, **74**, 1433) which has about one-third of the analgesic activity of morphine, and has been widely used in the past few years. Although a great many compounds related to pethidine have been prepared and tested (Eisleb, *loc. cit.*; Schaumann, *Arch. exp. Path. Pharm.*, 1940, **196**, 109; Bergel *et al.*, *J.*, 1944, 261, 265, 267, 269; MacDonald, Woolfe, Bergel, Morrison, and Rinderknecht, *Brit. J. Pharmacol.*, 1946, **1**, 4), only one appears to be of any importance, namely, ethyl 3-phenyl-1-methylpiperidine-3-carboxylate (β-pethidine), which has been tested clinically (Glazebrook and Branwood, *Lancet*, 1945, ii, 528).

A new class of compounds with analgesic activity was described by Bockmühl and Ehrhart (U.S.P. 2,230,774); these are of the type represented by formula (I; R = H or alkyl,

(I.) $Alk_2N\cdot CHR\cdot CH_2\cdot CPh_2\cdot COR'$ $\qquad$ $R_2N\cdot[CH_2]_n\cdot CAr_2\cdot COR'$ (II.)

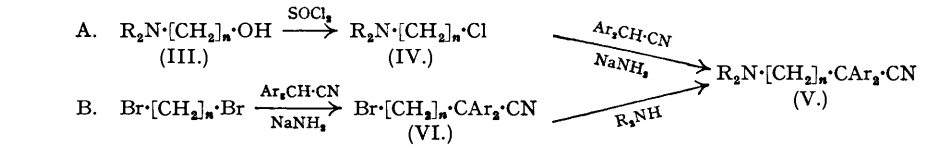
R′ = alkoxyl). Considerably more information about these compounds was obtained from Germany at the end of the war, the most complete report being that of Kleiderer, Rice, Conquest, and Williams (Report No. 981, Office of the Publication Board, Department of Commerce, Washington, D.C.). In general, ketones of type I (R = H or alkyl, R′ = alkyl) were more effective than the corresponding esters, and the compounds that appeared to be most favoured were 6-dimethylamino-4 : 4-diphenylhexan-3-one (I; Alk = Me, R = H, R′ = Et) and 6-dimethylamino-4 : 4-diphenylheptan-3-one (I; Alk = Me, R = Me, R′ = Et), the latter being known as amidone. Amidone was said to have 5—10 times the activity of pethidine, and it has recently been investigated pharmacologically and clinically both in this country and in America (Scott and Chen, *J. Pharm. Exp. Ther.*, 1946, **87**, 63; *Science*, 1946, **104**, 587; Hewer and Keele, *Lancet*, 1947, ii, 281; Steel and Gunderson, *ibid.*, 1947, ii, 370; Isbell *et al.*, *J. Amer. Med. Assoc.*, 1947, **135**, 888).

We have prepared a number of compounds of the same general type, with a view to determining the effect on the analgesic activity of alterations in various parts of the molecule. We did not have access to the full report of the German work until the investigation was well advanced, and some duplication has resulted.

In this paper we describe the preparation of a number of esters (II; R′ = OEt) and ketones (II; R′ = alkyl or Ph) with terminal basic substituents. The synthesis of amidone and its analogues is dealt with in the following paper.

Both esters and ketones were prepared, as described below, from the appropriate cyanides

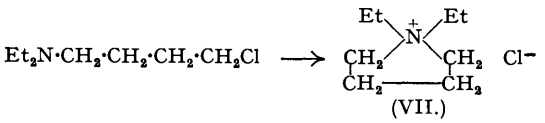
(V). Two methods were employed for the synthesis of unbranched cyanides with terminal basic substituents :



Method A.—The amino-alcohols (III; $n = 2$, 3, and 4) were, in most instances, prepared by standard methods. 2-Pyrrolidinoethanol was obtained by the reaction of 1 : 4-dibromobutane with ethanolamine in alcohol (cf. v. Braun, *Ber.*, 1911, **44**, 1252). 2-(2 : 6-*Dimethylmorpholino*)-*ethanol* was prepared similarly from di-(2-chloro*iso*propyl) ether and ethanolamine in the presence of potassium carbonate. The chloro-ether and the derivatives of 2 : 6-dimethylmorpholine prepared from it can exist in *meso*- and (±)-forms; the solid derivatives prepared in this series melted over ranges of several degrees, and were probably mixtures of the two forms.

The amino-alcohols were converted into the chloro-amine hydrochlorides by treatment with thionyl chloride in benzene (cf. Slotta and Behnisch, *Ber.*, 1935, **68**, 754) or in chloroform. The free bases (IV) were liberated from their hydrochlorides immediately before use.

Reaction of the chloro-amines (IV; $n = 2$ or 3) with diarylmethyl cyanides in the presence of sodamide in benzene (Bockmühl and Ehrhart, *loc. cit.*) gave satisfactory yields of the cyanides (V; $n = 2$ or 3). All attempts to prepare 5-diethylamino-1 : 1-diphenylamyl cyanide (V; R = Et, Ar = Ph, $n = 4$) by reaction of 1-chloro-4-diethylaminobutane with sodiodiphenylmethyl cyanide were unsuccessful; this failure is presumably due to the ready cyclisation of the free chloro-amine to *NN*-diethylpyrrolidinium chloride (VII), which was rapidly deposited from a cold ethereal solution of the base, and was characterised as the *picrate*. Even by working rapidly the cyclisation could not be prevented, and the use of method A for the preparation of this type of compound had to be abandoned.



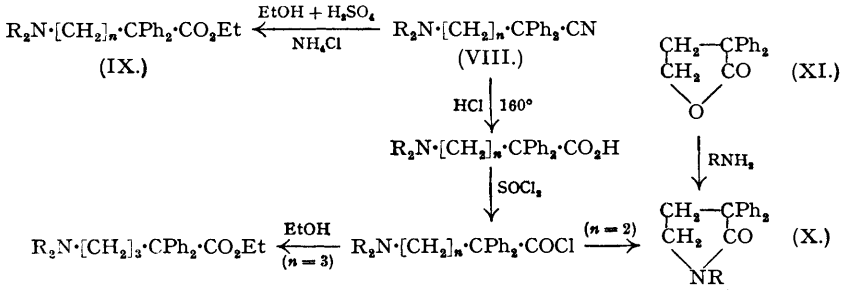
Method B.—The sodium derivative of diphenylmethyl cyanide, prepared by means of sodamide in boiling benzene, reacts readily with excess of ethylene dichloride or ethylene dibromide to give the 3-halogeno-1 : 1-diphenylpropyl cyanide accompanied by only a small quantity of 1 : 4-*dicyano*-1 : 1 : 4 : 4-*tetraphenylbutane* (cf. Murray and Cloke, *J. Amer. Chem. Soc.*, 1946, **68**, 126). 3-*Bromo*-1-*phenyl*-1-p-*tolylpropyl cyanide* was prepared similarly from phenyl-*p*-tolylmethyl cyanide and ethylene dibromide. In the same way, 1 : 3-dibromopropane and 1 : 4-dibromobutane react with sodiodiphenylmethyl cyanide to give the compounds (VI; Ar = Ph, $n = 3$) and (VI; Ar = Ph, $n = 4$), respectively; the latter compound could not be obtained pure, but the crude product, separated as far as possible from 1 : 6-*dicyano*-1 : 1 : 6 : 6-*tetraphenylhexane*, was used for the next stage.

Several attempts to cause ethylene dibromide to react with diphenylmethyl cyanide in the presence of sodium ethoxide in alcohol or benzene were unsuccessful (cf. B.P. 563,665).

Attempts to cause 3-chloro-1 : 1-diphenylpropyl cyanide to react with piperidine in benzene, toluene, or aqueous alcohol containing sodium hydrogen carbonate gave only traces of the required 1 : 1-*diphenyl*-3-*piperidinopropyl cyanide* (V; $R_2 = -[CH_2]_5-$, Ar = Ph, $n = 2$). The bromo-compounds (VI; $n = 2$), however, reacted readily with a number of secondary amines. The reaction conditions varied from one amine to another but generally the reaction was carried out without a solvent or in xylene, excess of base being used to neutralise the liberated hydrogen bromide. The cyanides (V; $n = 2$) were usually obtained in satisfactory yield. The *compounds* (VI; Ar = Ph, $n = 3$) and (VI; Ar = Ph, $n = 4$) both reacted readily with morpholine to give the *cyanides* (V; $R_2 = -CH_2 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_2-$, Ar = Ph, $n = 3$) and (V; $R_2 = -CH_2 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_2-$, Ar = Ph; $n = 4$).

The conversion of the cyanides (VIII) into the corresponding ethyl esters (IX) was achieved by Bockmühl and Ehrhart (*loc. cit.*) by preliminary sulphuric acid hydrolysis to the carboxylic acid, followed by esterification in the presence of sulphuric acid, water being removed as a water–alcohol azeotrope. This method proved to be unsatisfactory in our hands, but a direct

conversion into the ester was carried out by heating the cyanide with alcohol, concentrated sulphuric acid, and ammonium chloride in a sealed tube at 160° (cf. Bergel, Morrison, and Rinderknecht, *J.*, 1944, 265). While this method gave fair yields of the substituted butyric esters (IX; $n = 2$), the substituted *valeric ester* (IX; R = Et, $n = 3$) could not be obtained



pure when prepared thus. This compound was, however, prepared successfully by hydrolysis of 4-diethylamino-1 : 1-diphenylbutyl cyanide (VIII; R = Et, $n = 3$) with hydrochloric acid at 160°, conversion of the *carboxylic acid* into the acid chloride by means of thionyl chloride, and treatment of the acid chloride with alcohol.

TABLE I.

Analgesic Activities of Amino-ketones and Amino-esters.

Compound. R·CH₂·CH₂·CPh₂·COR′ R =	R′ =	Analgesic activity (pethidine = 1).
Me_2N	OEt	⅔—1
Et_2N	OEt	0—⅓ (*a*)
Piperidino	OEt	1 (*a*, *c*)
Morpholino	OEt	1 (*a*)
Me_2N	Me	0—⅓ (*a*)
Me_2N	Et	1 (*a*, *d*)
Me_2N	Pr^n	⅔ (*a*)
Me_2N	Ph	0 (*a*)
Et_2N	Et	⅔—1
Pr^n_2N	Et	0—⅓
Bu^n_2N	Et	0—⅓
(PhCH₂)NMe	Et	0
$(PhCH_2)_2N$	Et	(*e*)
Pyrrolidino	Et	4 (*f*)
Piperidino	Et	2—3 (*a*, *b*, *f*)
2-Methylpiperidino	Et	0
3-Methylpiperidino	Et	0—⅓
4-Methylpiperidino	Et	3 (*f*)
2 : 6-Dimethylpiperidino	Et	0—⅓
Morpholino	Me	½—1
Morpholino	Et	7 (*a*, *d*, *f*)
Morpholino	Pr^n	1
2-Methylmorpholino	Et	1½
2 : 6-Dimethylmorpholino	Et	1½
O<[CH₂]₄>N·CH₂·CH₂·CPh(*p*-Me·C₆H₄)·COEt		0
O<[CH₂]₄>N·CH₂·CH₂·C(*o*-Me·C₆H₄)₂·COEt		0
$Et_2N·CH_2·CH_2·CH_2·CPh_2·CO_2Et$		0
$Et_2N·CH_2·CH_2·CH_2·CPh_2·COEt$		0
O<[CH₂]₄>N·CH₂·CH₂·CH₂·CPh₂·COEt		0
O<[CH₂]₄>N·CH₂·CH₂·CH₂·CH₂·CPh₂·COEt		0

(*a*) These compounds are listed by Kleiderer *et al.* (*loc. cit.*).
(*b*) See Thorp, Walton, and Ofner (*Nature*, 1947, **159**, 679).
(*c*) See MacDonald, Wolfe, Bergel, Morrison, and Rinderknecht (*loc. cit.*).
(*d*) See Scott, Robbins, and Chen (*Science*, 1946, **104**, 587).
(*e*) The compound was too insoluble to be tested.
(*f*) The quoted activities of these compounds relative to pethidine are on a weight basis.

Attempts to prepare the esters (IX; R = Me, $n = 2$) and (IX; R = Et, $n = 2$) *via* the acid chloride gave rather surprising results. The corresponding cyanides were hydrolysed with concentrated hydrochloric acid at 150°. Treatment of the resulting acids with thionyl chloride

gave, not the expected acid chlorides, but neutral, water-insoluble compounds having the elementary composition of 3 : 3-*diphenyl*-1-*methyl*- (X; R = Me) and -1-*ethyl*-*pyrrolid*-2-*one* (X; R = Et), respectively. In view of the extreme ease of this reaction it is rather surprising that the higher acid chloride shows no tendency at all to cyclise to a piperidone.

The pyrrolidones (X; R = Me) and (X; R = Et) were also prepared by reaction of αα-diphenyl-γ-butyrolactone (XI; for preparation see Part II) with methylamine and ethylamine respectively, in aqueous alcohol; they were found to be identical with the corresponding compounds prepared from the cyanides (VIII).

The conversion of the cyanides (V) into ketones (XII) was accomplished readily in most instances by the use of excess of Grignard reagent. A fairly high temperature (> 80°) was necessary, and the reactions were carried out in toluene at water-bath temperature. With 1 : 1-*di*-o-*tolyl*-3-*morpholinopropyl cyanide* (V; R = $^-CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2^-$, Ar = *o*-tolyl, *n* = 2) the methyl groups appeared to hinder the reaction; our usual conditions gave a very low yield of the *ketone*, and much unchanged cyanide was recovered.

$$\text{(V.)}\quad R_2N{\cdot}[CH_2]_n{\cdot}CAr_2{\cdot}CN \xrightarrow{R'MgX} R_2N{\cdot}[CH_2]_n{\cdot}CAr_2{\cdot}COR' \quad \text{(XII.)}$$

For testing, the compounds were converted, where possible, into hydrochlorides. Very often crystalline hydrochlorides could not be obtained; the compound was then dissolved in an equivalent quantity of hydrochloric acid. Analgesic activity was measured in rats against that of pethidine, two methods being used : (*a*) the thermal radiation method of D'Amour and Smith (*J. Pharm. Exp. Ther.*, 1941, **72**, 74), using the apparatus of Hardy, Wolff, and Goodell (*J. Clin. Invest.*, 1940, **19**, 659) as modified by Thorp (*Brit. J. Pharmacol.*, 1946, **1**, 113); (*b*) the electric grid method of Dodds, Lawson, Simpson, and Williams (*J. Physiol.*, 1945, **104**, 47). Except with the most active compounds, the comparison was made at one fifth the L.D. 50 of both pethidine and the compound under examination.

The relative activities are given in Table I. A complete account of the pharmacological investigation of the compounds described in this and the following paper will be published elsewhere.

Experimental.

(M. p.s are corrected.)

Preparation of Straight-chain ω-Amino-cyanides—Method A.

Preparation of Amino-alcohols.—2-*Dibenzylaminoethanol.* Benzylation of ethanolamine by the method of Rumpf and Kwass (*Bull. Soc. chim.*, 1943, **10**, 347) gave only a 47% yield; the use of solid potassium carbonate in place of sodium hydroxide solution to remove acid formed raised the yield to 61%. The compound boiled at 204—206°/15 mm. and melted at 46—47° (Gabel, *ibid.*, 1934, **1**, 1006, gives b. p. 220—225°/23 mm. and m.p. 45·5—47°).

2-*Pyrrolidinoethanol.* A solution of 1 : 4-dibromobutane (86·4 g.) in ethanol (100 c.c.) was warmed on the steam-bath, and ethanolamine (73·2 g.) was added gradually at such a rate that the mixture boiled gently. When the addition was complete, the mixture was boiled under reflux for 3 hours. Most of the ethanol was distilled off, and ether was added to the residue. The precipitated oil solidified on being left in the refrigerator, and was filtered off and washed thoroughly with ether. The filtrate and washings were dried (K_2CO_3), the ether was removed, and the residue was distilled. The amino-alcohol boiled at 73—75°/11 mm. (Found : Equiv., 115·9. Calc. for $C_6H_{13}ON$: Equiv., 115·2). Yield 30·8 g.; 67%.

The picrate melted at 86—87° after crystallisation from alcohol (Found : C, 42·3; H, 4·7; N, 16·2. Calc. for $C_6H_{13}ON,C_6H_3O_7N_3$: C, 41·9; H, 4·7; N, 16·3%) (v. Braun, Braunsdorf, and Räth, *Ber.*, 1922, **55**, 1666, give b. p. 187—189° for the base and m. p. 96° for the picrate).

2-*Morpholinoethanol.* (*a*) The method of Gilman and Woods (*J. Amer. Chem. Soc.*, 1945, **67**, 1843), using ethylene chlorohydrin and morpholine, gave a 91% yield when the period of heating under reflux was extended to 4 hours. (*b*) Ethylene oxide (104 g.) was passed into a boiling mixture of morpholine (180 g.) and anhydrous methanol (35 c.c.) during about 2½ hours. The mixture was boiled for a further 45 minutes and distilled under reduced pressure. 2-Morpholinoethanol boiled at 111—115°/17 mm. (Gilman and Woods, *loc. cit.*, give b. p. 116—119°/21—23 mm.). Yield 230 g.; 85%.

2-(2 : 6-*Dimethylmorpholino*)*ethanol.* Di-(2-chloro*iso*propyl) ether (160 g.), ethanolamine (80 g.), and anhydrous potassium carbonate (150 g.) were heated together at 150° for 6 hours. The mixture was extracted with 4 portions (each 100 c.c.) of boiling benzene and the extract dried (K_2CO_3). Removal of the benzene and distillation of the residue, gave the *amino-alcohol* as a colourless liquid, b. p. 109°/10 mm. (Found : N, 8·95. $C_8H_{17}O_2N$ requires N, 8·8%). Yield 117 g.; 79%.

4-*Diethylaminobutanol.* The method of Smorgonskiĭ and Gol'dfarb (*J. Gen. Chem. Russia*, 1940, **10**, 1113) gave rather poor yields, apparently owing to hydrolysis of the acetyl group during reaction of 4-bromobutyl acetate with diethylamine. The following method was found more satisfactory : a solution of 4-bromobutyl acetate (19·5 g.) and diethylamine (14·6 g.) in dry toluene (25 c.c.) was boiled under reflux for 3 hours. After cooling, diethylamine hydrobromide was filtered off, and washed with toluene. The filtrate and washings were combined, and the toluene was removed under reduced pressure. A solution of sodium hydroxide (20 g.) in alcohol (200 c.c.) was added to the residue, and the mixture was

boiled under reflux for 3 hours. Most of the alcohol was removed, a small amount of water was added, and the solution was extracted thoroughly with ether. The extract was dried (K_2CO_3), the ether was removed, and the residue distilled. 4-Diethylaminobutanol boiled at 103—106°/15 mm. (Smorgonskiĭ and Gol'dfarb, *loc. cit.*, give b. p. 87—90°/8 mm.). Yield 8·5 g.; 59%.

Preparation of Chloro-amines.—Except where otherwise stated the following method was used (cf. Slotta and Behnisch, *Ber.*, 1935, **68**, 754); the amino-alcohol was dissolved in 10 volumes of benzene, and thionyl chloride in about 100% excess was added gradually with occasional shaking to the ice-cooled solution. When the addition was complete, the mixture was boiled under reflux for 2 hours and allowed to cool. In most cases the chloro-amine hydrochloride could be filtered off directly; otherwise the benzene and excess of thionyl chloride were removed, and ether was added to the residue; crystallisation then resulted.

The hydrochlorides were converted into the bases by dissolving in a little water, adding an excess of a solution of sodium hydroxide or potassium carbonate, extracting thoroughly with ether, drying the extract (K_2CO_3), and distilling. In some cases the bases were not isolated; benzene was used in the extraction, and the dried benzene solution was used for the next stage. The bases were always liberated from their hydrochlorides immediately before use.

2-*Di*-n-*butylaminoethyl chloride.* 2-Di-*n*-butylaminoethanol (Burnett, Jenkins, Peet, Dreger, and Adams, *J. Amer. Chem. Soc.*, 1937, **59**, 2248), treated with thionyl chloride as above, gave the crude chloro-amine hydrochloride, m. p. 78—82°, in 92% yield. The base, obtained in 87% yield, boiled at 106—110°/18 mm. (Blicke and Maxwell, *ibid.*, 1942, **64**, 428, give b.p. 114—115°/23 mm.).

2-*Dibenzylaminoethyl chloride.* The *hydrochloride* (98% yield) melted at 191—192° after crystallisation from alcohol–ether (Found: N, 4·5; Cl, 23·3. $C_{16}H_{18}NCl,HCl$ requires N, 4·7; Cl, 23·9%). (Eisleb, U.S.P. 1,949,247, gives m. p. 192° but quotes no analysis.) The *base*, obtained in 80% yield, boiled at 194—195°/12 mm. (Found: N, 5·7; Cl, 14·2. $C_{16}H_{18}NCl$ requires N, 5·4; Cl 13·65%).

2-*Pyrrolidinoethyl chloride.* The hydrochloride (yield 87%) melted at 168—170° after crystallisation from acetone. The base, obtained in 82% yield, boiled at 55—56°/11 mm. The compound was characterised as its *picrate*, which melted with decomposition at 316° after crystallisation from acetone (Found: N, 15·7. $C_6H_{12}NCl,C_6H_3O_7N_3$ requires N, 15·5%).

2-*Piperidinoethyl chloride.* The crude hydrochloride, obtained in 97% yield from 2-piperidinoethanol (Vassiliades, *Bull. Soc. chim.*, 1937, **4**, 1131), melted at 228—230° (Blicke and Maxwell, *loc. cit.*, give m. p. 229—231°). The base (yield 53%) boiled at 79—80°/13 mm. (Gilman and Woods, *loc. cit.*, give b. p. 36—38°/0·5 mm.).

2-(2 : 6-*Dimethylmorpholino*)*ethyl chloride.* The *hydrochloride* (89% yield) melted at 240—244° (decomp.) after crystallisation from alcohol (Found: N, 7·1; Cl, 32·9. $C_8H_{16}ONCl,HCl$ requires N, 6·5; Cl, 33·1%). The *base*, obtained in 72% yield, boiled at 94°/12 mm. (Found: C, 54·1; H, 9·3; N, 8·5. $C_8H_{16}ONCl$ requires C, 54·1; H, 9·1; N, 7·9%).

4-*Diethylaminobutyl chloride.* A solid hydrochloride could not be isolated; when an aqueous solution of the crude hydrochloride was treated with alkali and extracted with ether, the extract rapidly deposited an oil which solidified when kept. This compound was hygroscopic but it was converted into NN-*diethylpyrrolidinium picrate* which melted at 273—273·5° (decomp.) (Found: N, 15·6. $C_8H_{17}N,C_6H_3O_7N_3$ requires N, 15·7%).

An attempt to use a dry benzene extract of the base in the next stage was unsuccessful, even though the extract was left for a very short time only.

Preparation of Amino-cyanides.—The majority of the compounds were prepared by the following general method; variations from this method are described under the individual compounds.

Diphenylmethyl cyanide (Hoch, *Compt. rend.*, 1933, **197**, 770) (0·1 g.-mol.) was dissolved in dry benzene (150 c.c.), sodamide (0·103 g.-mol.) was added, and the mixture was stirred at room temperature till no further darkening occurred. A solution of the appropriate chloro-amine (0·1 g. mol.) in dry benzene (150 c.c.) was added, and the mixture was stirred overnight at room temperature. The solution was extracted with successive portions of 2N-hydrochloric acid (about 0·3 g.-mol. in all), and the combined aqueous layers, together with the sparingly soluble hydrochloride which usually separated as a third, lowest layer, were made strongly alkaline. The resulting oil was extracted with ether or benzene, the extract dried (K_2CO_3), the solvent removed, and the residue purified by distillation or crystallisation.

3-*Dimethylamino*-1 : 1-*diphenylpropyl cyanide.* Prepared in 70% yield from 2-dimethylaminoethyl chloride (Slotta and Behnisch, *loc. cit.*), the cyanide distilled at 150—152°/0·8 mm. as a colourless oil. It was characterised as the *hydrochloride*, which separated from ethanol–ether as colourless crystals, m. p. 200—201° (Found: C, 71·7; H, 7·0; N, 9·6; Cl, 12·1. $C_{18}H_{20}N_2,HCl$ requires C, 71·9; H, 7·0; N, 9·3; Cl, 11·8%).

3-*Diethylamino*-1 : 1-*diphenylpropyl cyanide.* Prepared in 70—78% yield from 2-diethylaminoethyl chloride hydrochloride (Slotta and Behnisch, *loc. cit.*), without isolation of the base, the *cyanide* distilled as a colourless viscous oil at 165°/1 mm. (Found: C, 81·6; H, 8·3; N, 9·8. $C_{20}H_{24}N_2$ requires C, 82·15; H, 8·3; N, 9·6%).

3-*Di*-n-*butylamino*-1 : 1-*diphenylpropyl cyanide.* The reaction of 2-di-*n*-butylaminoethyl chloride with diphenylmethyl cyanide was carried out by the general method but the method of isolation had to be modified. After being stirred overnight the benzene solution was extracted with hydrochloric acid, the amino-cyanide in this case remaining in the benzene layer. The benzene solution was dried (K_2CO_3), the solvent removed, and the residue distilled. 3-*Di*-n-*butylamino*-1 : 1-*diphenylpropyl cyanide* boiled at 170—172°/0·25 mm. (Found: C, 83·0; H, 9·8; N, 8·0. $C_{24}H_{32}N_2$ requires C, 82·7; H, 9·3; N, 8·0%). Yield 66%.

3-*Dibenzylamino*-1 : 1-*diphenylpropyl cyanide.* A solution of diphenylmethyl cyanide (52 g.) in dry benzene (400 c.c.) was treated with sodamide (11 g.), and the mixture was boiled under reflux with stirring till no further solid separated. A solution of 2-dibenzylaminoethyl chloride (liberated from 76 g. of the hydrochloride) in benzene (400 c.c.) was added, and the mixture was boiled under reflux with stirring for 16 hours. After cooling, the mixture was washed with water, and dried over potassium carbonate. Dry hydrogen chloride was passed into the warm solution, and excess of the gas was

eliminated by boiling. Addition of petroleum (b. p. 60—80°) and cooling caused the separation of 3-*dibenzylamino*-1 : 1-*diphenylpropyl cyanide hydrochloride*, which melted at 169—171·5° after recrystallisation from benzene (Found : N, 6·3; Cl, 7·6. $C_{30}H_{28}N_2$,HCl requires N, 6·2; Cl, 7·8%). Yield 61 g., 53%, based on the chloro-amine hydrochloride.

The *base*, prepared from the hydrochloride in 92% yield, melted at 60·5—61·5° after crystallisation from petroleum (Found : C, 86·2; H, 6·7; N, 6·85. $C_{30}H_{28}N_2$ requires C, 86·5; H, 6·8; N, 6·7%).

1 : 1-*Diphenyl*-3-*pyrrolidinopropyl cyanide*. Diphenylmethyl cyanide (17·4 g.) was converted into the sodio-derivative by boiling under reflux with sodamide (3·6 g.) in dry benzene (150 c.c.) with stirring until the separation of solid was complete. 2-Pyrrolidinoethyl chloride (11·7 g.) in benzene (20 c.c.) was added gradually, and the mixture was stirred overnight at room temperature. The *product* melted at 71·5—72·5° after crystallisation from petroleum (b. p. 60—80°) (Found : C, 83·0; H, 7·3; N, 9·6. $C_{20}H_{22}N_2$ requires C, 82·7; H, 7·6; N, 9·7%). Yield, 84% based on chloro-amine.

1 : 1-*Diphenyl*-3-*piperidinopropyl cyanide*. Prepared by the general method in 57% yield, the *cyanide* melted at 70—71° after crystallisation from petroleum (b. p. 60—80°) (Found : C, 82·8; H, 8·2; N, 9·2. $C_{21}H_{24}N_2$ requires C, 82·8; H, 7·95; N, 9·2%). (Thorp, Walton, and Ofner, *Nature*, 1947, **159**, 679, give m. p. 73° but do not quote analytical figures.)

1 : 1-*Diphenyl*-3-*morpholinopropyl cyanide*. 2-Morpholinoethyl chloride (Mason and Block, *J. Amer. Chem. Soc.*, 1940, **62**, 1443) on reaction with diphenylmethyl cyanide gave 1 :1-*diphenyl*-3-*morpholinopropyl cyanide* in 56% yield. After crystallisation from petroleum (b. p. 40—60°) the cyanide melted at 82—82·5° (Found : C, 78·7; H, 7·2; N, 9·1. $C_{20}H_{22}ON_2$ requires C, 78·4; H, 7·2; N, 9·1%).

1 : 1-*Diphenyl*-3-(2 : 6-*dimethylmorpholino*)*propyl cyanide*. The *cyanide* (yield 48%) crystallised from petroleum (b. p. 60—80°) in colourless plates, m. p. 67—72° (Found : C, 78·7; H, 7·8; N, 8·2. $C_{22}H_{26}ON_2$ requires C, 79·0; H, 7·8; N, 8·4%). The *hydrochloride* melted at 190—194° (decomp.) after crystallisation from acetone–ether (Found : N, 7·7. $C_{22}H_{26}ON_2$,HCl requires N, 7·6%).

4-*Diethylamino*-1 : 1-*diphenylbutyl cyanide*. Reaction of 3-diethylaminopropyl chloride (Slotta and Behnisch, *loc. cit.*) with diphenylmethyl cyanide by the general method gave only a 50% yield of the desired compound, much of the starting materials being recovered unchanged. By preparing sodiodiphenylmethyl cyanide in boiling benzene, and heating under reflux for 3 hours after the addition of the chloro-amine, the yield was raised to 75%. 4-Diethylamino-1 : 1-diphenylbutyl cyanide boiled at 160—163°/0·3 mm. The *hydrochloride* melted at 158—160° (Found : C, 73·5; H, 7·8; N, 8·6; Cl, 10·9. $C_{21}H_{26}N_2$,HCl requires C, 73·55; H, 7·9; N, 8·2; Cl, 10·3%).

1 : 1-*Di*-o-*tolyl*-3-*morpholinopropyl cyanide*. A solution of di-*o*-tolylmethyl cyanide (Fuson and Rachlin, *J. Amer. Chem. Soc.*, 1942, **64**, 1567) (5·27 g.) in benzene (40 c.c.) was treated with sodamide (1 g.), and the mixture was boiled under reflux with stirring until the separation of solid was complete (about 1¾ hrs.). To the cooled suspension was added gradually a solution of 2-morpholinoethyl chloride (3·8 g.) in dry benzene (10 c.c.), and the mixture was boiled under reflux with stirring for 3 hours. The *product* melted at 138—139° after crystallisation from petroleum (b. p. 60—80°) (Found : C, 78·7; H, 7·95; N, 8·6. $C_{22}H_{26}ON_2$ requires C, 79·0; H, 7·8; N, 8·4%). Yield 5·5 g., 70%.

Preparation of Straight-chain ω-Amino-cyanides. Method B.

3-*Chloro*-1 : 1-*diphenylpropyl cyanide*. A solution of diphenylmethyl cyanide (19·3 g.) in dry benzene (140 c.c.) was treated with sodamide (4 g.), and the mixture was boiled under reflux with stirring until the separation of solid was complete (about 1 hour). The mixture was cooled to room temperature, and ethylene dichloride (17·2 g.) was added. The mixture was stirred, heated under reflux for 4 hours, and, after cooling, was washed with water and dried. Removal of the benzene left an oil which boiled between 130° and 140°/0·4 mm., and solidified on standing (18 g.; 70% yield). Crystallisation from petroleum (b. p. 40—60°) gave the *cyanide* in large colourless crystals, m. p. 51·5—53° (Found : C, 75·7; H, 5·5; N, 5·6; Cl, 14·3. $C_{16}H_{14}NCl$ requires C, 75·1; H, 5·5; N, 5·5; Cl, 13·9%). The residue in the distillation flask was crystallised from benzene, giving 1 : 4-*dicyano*-1 : 1 : 4 : 4-*tetraphenylbutane*, m. p. 200—204° (Found : C, 87·3; H, 6·0; N, 6·7. $C_{30}H_{24}N_2$ requires C, 87·4; H, 5·9; N, 6·8%).

Prolonged treatment of the chloro-cyanide with piperidine in benzene, toluene, or aqueous ethanol containing sodium hydrogen carbonate gave only traces of 1 : 1-diphenyl-3-piperidinopropyl cyanide, the starting materials being largely recovered.

3-*Bromo*-1 : 1-*diphenylpropyl cyanide*. Diphenylmethyl cyanide (96·5 g.) was treated with sodamide (20 g.) in boiling benzene (750 c.c.) as above, and, after cooling, ethylene dibromide (75 c.c.) was added. The mixture was boiled under reflux with stirring for 3½ hours, cooled, and washed with water. The benzene solution was dried, the solvent removed, and the residue heated on the water-bath under reduced pressure to remove excess of ethylene dibromide. On trituration with petroleum, the oily residue solidified, and was filtered off and dried. Yield 111—120 g., 74—80%. The *solid*, m. p. 60—63°, was pure enough for use in the next stage, but it could be crystallised from petroleum with some difficulty, and then melted at 68·5—70° (Found : C, 64·0; H, 4·8; N, 4·8; Br, 26·5. $C_{16}H_{14}NBr$ requires C, 64·0; H, 4·7; N, 4·7; Br, 26·6%).

3-*Di*-n-*propylamino*-1 : 1-*diphenylpropyl cyanide*. A mixture of 3-bromo-1 : 1-diphenylpropyl cyanide (30 g.) and dipropylamine (20 g.) was boiled under reflux for 16 hours. After cooling, ether was added, and dipropylamine hydrobromide was filtered off. The filtrate was evaporated to dryness, and the residue was dissolved in hot benzene, and treated with hydrogen chloride. The excess of hydrogen chloride was boiled off and the solution allowed to cool; 3-di-*n*-propylamino-1 : 1-diphenylpropyl cyanide hydrochloride then separated, and had m. p. 84—85° after crystallisation from benzene–petroleum (b. p. 60—80°). Yield 24 g., 67%. The *base* (79% yield) boiled at 179—180°/1·2 mm. (Found : C, 82·4; H, 8·5; N, 8·6. $C_{22}H_{28}N_2$ requires C, 82·4; H, 8·8; N, 8·7%).

3-*Benzylmethylamino*-1 : 1-*diphenylpropyl cyanide*. 3-Bromo-1 : 1-diphenylpropyl cyanide (15 g.) and benzylmethylamine (12 g.) were heated together on the water-bath overnight. Ether was added,

the precipitate of benzylmethylamine hydrobromide filtered off, and the filtrate extracted with an excess of 2N-hydrochloric acid. The acid extract was made strongly alkaline, and the oil extracted with ether. The ether solution was dried, the ether removed, and the residue distilled, giving the amino-cyanide, b. p. 190—196°/0·3—0·4 mm. Yield 11·4 g., 67%. The *hydrochloride*, prepared in benzene and crystallised from acetone–ether, melted at 147·5—150° (Found: C, 76·3; H, 6·6; N, 7·2; Cl, 9·1. $C_{24}H_{24}N_2$,HCl requires C, 76·5; H, 6·7; N, 7·4; Cl, 9·4%).

1 : 1-*Diphenyl*-3-*piperidinopropyl cyanide*. 3-Bromo-1 : 1-diphenylpropyl cyanide (3 g.), piperidine (2 c.c.), and toluene (20 c.c.) were boiled under reflux for 20 hours. Piperidine hydrobromide was filtered off, and the filtrate was extracted with an excess of 2N-hydrochloric acid. The acid extract was made strongly alkaline, and extracted with ether. Removal of the ether left an oil which solidified, and melted at 70—71° after crystallisation from petroleum. Yield 1·9 g., 63%.

The replacement of toluene by xylene in the above experiment gave a yield of 70%. When the reaction was carried out with only 1 mol. of piperidine, with sodium hydrogen carbonate to neutralise acid formed, and aqueous alcohol as solvent, a yield of 60% of the amino-cyanide resulted.

1 : 1-*Diphenyl*-3-(2-*methylpiperidino*)*propyl cyanide*. A mixture of 3-bromo-1 : 1-diphenylpropyl cyanide (22·3 g.), 2-methylpiperidine (14·9 g.), and xylene (150 c.c.) was boiled under reflux for 24 hours. The product (61% yield) was not distilled but was converted into the *hydrochloride* which melted at 188—189° after crystallisation from ethyl acetate (Found: N, 7·4. $C_{22}H_{26}N_2$,HCl requires N, 7·9%).

1 : 1-*Diphenyl*-3-(3-*methylpiperidino*)*propyl cyanide*. Prepared as above, the *base* boiled at 178—180°/0·1 mm. (Found: C, 83·3; H, 8·1; N, 8·4. $C_{22}H_{26}N_2$ requires C, 83·0; H, 8·2; N, 8·8%). Yield 57%.

1 : 1-*Diphenyl*-3-(4-*methylpiperidino*)*propyl cyanide*. The *cyanide*, prepared in 59% yield by the method used for the isomeric compounds, boiled at 184—185°/0·025 mm., and had m. p. 61—62° after crystallisation from aqueous ethanol (Found: N, 8·4%). The *hydrochloride* melted at 189·5—191° after crystallisation from acetone–ether (Found: N, 7·6%).

1 : 1-*Diphenyl*-3-(2 : 6-*dimethylpiperidino*)*propyl cyanide*. 2 : 6-Dimethylpiperidine was prepared by reduction of 2 : 6-dimethylpyridine with sodium and alcohol; the two forms were separated by treatment of the hydrochlorides with acetone (Marcuse and Wolffenstein, *Ber.*, 1899, **32**, 2525). The major portion of the salt was the high-melting form to which these workers assigned the *meso*-structure. The base obtained from this hydrochloride was used in the reaction with 3-bromo-1 : 1-diphenylpropyl cyanide.

3-Bromo-1 : 1-diphenylpropyl cyanide (23·8 g.) and 2 : 6-dimethylpiperidine (18 g.) were heated in an oil-bath at 180—200° for 22 hours. After cooling, ether was added, and the precipitate of dimethylpiperidine hydrobromide was filtered off. The ether was removed, and the residue heated for a further 6 hours. The product boiled at 170—172°/0·04 mm. The *hydrochloride* melted at 239—243° after crystallisation from ethyl acetate (Found: N, 8·0; Cl, 9·4. $C_{23}H_{28}N_2$,HCl requires N, 7·6; Cl, 9·6%). Yield 11·5 g., 44%.

1 : 1-*Diphenyl*-3-*morpholinopropyl cyanide*. 3-Bromo-1 : 1-diphenylpropyl cyanide (75 g.) and morpholine (45 g.) were heated on the water-bath for 16 hours. Ether was added, morpholine hydrobromide was filtered off, and the filtrate was worked up. The amino-cyanide (59 g., 77% yield) melted at 82° after crystallisation from petroleum.

1 : 1-*Diphenyl*-3-(2-*methylmorpholino*)*propyl cyanide*. 3-Bromo-1 : 1-diphenylpropyl cyanide (15 g.) and 2-methylmorpholine (Cottle, Jeltsch, Stoudt, and Walters, *J. Org. Chem.*, 1946, **11**, 286) (10 g.) were heated on the water-bath for 16 hours; the *product* boiled at 160°/0·025 mm. (Found: N, 8·7. $C_{21}H_{24}ON_2$ requires N, 8·75%). Yield 11 g., 69%. The hydrochloride melted at 132—135° after crystallisation from ethyl acetate–ether (Found: N, 8·0; Cl, 9·8. $C_{21}H_{24}ON_2$,HCl requires N, 7·85; Cl, 9·9%).

3-*Bromo*-1-*phenyl*-1-p-*tolylpropyl cyanide*. Phenyl-*p*-tolylmethyl cyanide (Hoch, *loc. cit.*) (10·35 g.) was dissolved in benzene (80 c.c.), sodamide (2 g.) was added, and the mixture was boiled under reflux with stirring till the separation of solid was complete. The suspension was cooled to room temperature, ethylene dibromide (16·45 g.) was added gradually, and the mixture was boiled under reflux with stirring for 3 hours. After cooling, the solution was washed with water, dried, and evaporated. Distillation of the residue gave 3-*bromo*-1-*phenyl*-1-p-*tolylpropyl cyanide* (10·6 g., 68% yield), b. p. 126—136°/0·02 mm. (Found: Br, 25·75. $C_{17}H_{16}NBr$ requires Br, 25·4%).

1-*Phenyl*-1-p-*tolyl*-3-*morpholinopropyl cyanide*. 3-Bromo-1-phenyl-1-*p*-tolylpropyl cyanide (6·7 g.) and morpholine (3·7 g.) were heated on the water-bath for 16 hours. The *product* distilled at 170°/0·02 mm. (Found: N, 8·8. $C_{21}H_{24}ON_2$ requires N, 8·75%). Yield 5·2 g., 76%. The *hydrochloride* melted at 220—224° after crystallisation from acetone–ether (Found: C, 70·4; H, 7·2; N, 8·0; Cl, 9·8. $C_{21}H_{24}ON_2$,HCl requires C, 70·7; H, 7·1; N, 7·85; Cl, 9·9%).

1 : 1-*Diphenyl*-4-*morpholinobutyl cyanide*. Diphenylmethyl cyanide (19·3 g.) was converted into its sodio-derivative by treatment with sodamide (4 g.) and boiling benzene (50 c.c.); the cold suspension was treated with 1 : 3-dibromopropane (35·3 g.), and the mixture was heated under reflux with stirring for 4 hours. After cooling, the mixture was washed with water and dried. The benzene was removed, and excess of dibromopropane distilled off at *ca.* 115°/15 mm. The residual oil was used for the next stage without purification. The 4-*bromo*-1 : 1-*diphenylbutyl cyanide* could be distilled, and then crystallised from petroleum (b. p. 40—60°); it melted at 77—78° (Found: C, 64·9; H, 5·7; Br, 26·2. $C_{17}H_{16}NBr$ requires C, 65·0; H, 5·1; Br, 25·4%).

The crude bromo-compound from the above experiment was heated overnight on the steam-bath with morpholine (20 g.); after cooling, ether was added, morpholine hydrobromide filtered off, and the ether filtrate extracted with an excess of 2N-hydrochloric acid. The oily hydrochloride, which separated, solidified and was filtered off; yield 11 g., 31% based on diphenylmethyl cyanide. On crystallisation from alcohol the 1 : 1-*diphenyl*-4-*morpholinobutyl cyanide hydrochloride* melted at 245—247° (Found: C, 70·4; H, 6·9; N, 7·75; Cl, 10·5. $C_{21}H_{24}ON_2$,HCl requires C, 70·7; H, 7·1; N, 7·85; Cl, 9·9%). The *base* melted at 65—66° after crystallisation from petroleum (b. p. 40—60°) (Found: C, 78·4; H, 7·4; N, 9·0. $C_{21}H_{24}ON_2$ requires C, 78·7; H, 7·55; N, 8·75%).

1 : 1-*Diphenyl*-5-*morpholinoamyl cyanide*. Diphenylmethyl cyanide (19·3 g.) was converted into

its sodio-derivative by means of sodamide (4 g.) in boiling benzene (150 c.c.). After cooling, the suspension was treated with 1 : 4-dibromobutane (37·5 g.). The mixture was boiled under reflux for 4 hours, washed with water, and dried. Benzene was removed and the residue heated at 150° under reduced pressure to remove excess of dibromobutane. The residue (19 g.) was treated with morpholine (17·4 g.) in boiling xylene (50 c.c.) for 2 hours, and the product was worked up in the usual way. 1 : 1-*Diphenyl-5-morpholinoamyl cyanide* (10 g., 30% based on diphenylmethyl cyanide) melted at 97—98° after crystallisation from petroleum (b. p. 60—80°) (Found : C, 78·7; H, 7·9; N, 8·2. $C_{22}H_{26}ON_2$ requires C, 79·0; H, 7·8; N, 8·4%).

In one run on the same scale an attempt was made to purify the intermediate bromo-compound. Addition of petroleum to the crude oily material gave a solid (6·5 g.) which melted at 224—228° after crystallisation from benzene–petroleum, and was found by analysis to be 1 : 6-*dicyano*-1 : 1 : 6 : 6-*tetraphenylhexane* (Found : C, 87·4; H, 6·6; N, 6·1. $C_{32}H_{28}N_2$ requires C, 87·2; H, 6·4; N, 6·4%). It was not possible to obtain the pure bromo-compound from the petrol-soluble material.

Preparation of Amino-acids and -esters and Pyrrolidones.

Ethyl 3-*dimethylamino*-1 : 1-*diphenylpropane*-1-*carboxylate.* 3-Dimethylamino-1 : 1-diphenylpropyl cyanide (10 g.), anhydrous ethanol (25 c.c.), concentrated sulphuric acid (8 c.c.), water (0·1 c.c.), and ammonium chloride (1·8 g.) were heated in a sealed tube at 150° for 16 hours. The contents of the tube were diluted with water, made alkaline with 40% sodium hydroxide solution with cooling, and extracted with ether; an intermediate oily layer was run off with the aqueous layer. The extract was dried (K_2CO_3), the ether removed, and the residue distilled. The *ester* (5 g.; 42%) boiled at 150—153°/0·6 mm. (Found : C, 77·2; H, 8·05; N, 4·4; OEt, 14·2. $C_{20}H_{25}O_2N$ requires C, 77·1; H, 8·1; N, 4·5; OEt, 14·5%). The *hydrochloride* melted at 192—194° after crystallisation from acetone–ether (Found : C, 69·4; H, 7·8; N, 4·1; Cl, 10·75. $C_{20}H_{25}O_2N$,HCl requires C, 69·1; H, 7·5; N, 4·0; Cl, 10·2%).

Ethyl 3-*diethylamino*-1 : 1-*diphenylpropane*-1-*carboxylate.* The preparation was similar to that described for the dimethylamino-analogue. The *ester*, obtained in 43% yield, distilled at 165°/0·4 mm. (Found : C, 77·85; H, 9·0; N, 4·4; OEt, 14·0. $C_{22}H_{29}O_2N$ requires C, 77·8; H, 8·6; N, 4·1; OEt, 13·3%) (Bockmühl and Ehrhart, *loc. cit.*, give b. p. 200—202°/5 mm. but quote no analytical figures).

Ethyl 1 : 1-*diphenyl*-3-*piperidinopropane*-1-*carboxylate.* Prepared in 51% yield by the method described above, the *ester* distilled at 170—178°/0·4 mm. and solidified on standing. After crystallisation from petroleum (b. p. 40—60°) it melted at 69—70·5° (Found : C, 78·3; H, 8·0; H, 4·45. $C_{23}H_{29}O_2N$ requires C, 78·6; H, 8·3; N, 4·0%) (Bockmühl and Ehrhart, *loc. cit.*, give b. p. 208—212°/3 mm. but quote no analytical figures).

Ethyl 1 : 1-*diphenyl*-3-*morpholinopropane*-1-*carboxylate.* Prepared as above in 46% yield the *ester* boiled at 175—180°/0·5 mm. and melted at 68·5—70° after crystallisation from petroleum (b. p. 40—60°) (Found : C, 74·7; H, 7·9; N, 4·3. $C_{22}H_{27}O_3N$ requires C, 74·75; H, 7·7; N, 4·0%). The *hydrochloride* melted at 167·5—168·5° after crystallisation from acetone–ether (Found : N, 3·65; Cl, 8·2. $C_{22}H_{27}O_3N$,HCl requires N, 3·6; Cl, 9·1%) (Bockmühl and Ehrhart, *loc. cit.*, give b. p. 218—222°/4 mm. for the base and m. p. 166—167° for the hydrochloride but quote no analytical figures for either).

4-*Diethylamino*-1 : 1-*diphenylbutane*-1-*carboxylic acid.* 4-Diethylamino-1 : 1-diphenylbutyl cyanide (10 g.) and concentrated hydrochloric acid (50 c.c.) were heated at 155—160° in a sealed tube for 16 hours. The contents of the tube were evaporated to dryness under reduced pressure, and the residue was dissolved in the minimum quantity of hot water. The solution was made slightly alkaline with 2N-sodium carbonate solution. On being left in the refrigerator, a solid separated, which was filtered off and crystallised from acetone–ether. The *acid* melted at 141—142° (Found : C, 77·0; H, 8·2; N, 4·4. $C_{21}H_{27}O_2N$ requires C, 77·5; H, 8·4; N, 4·3%). Yield 5·6 g., 53%.

Ethyl 4-*diethylamino*-1 : 1-*diphenylbutane*-1-*carboxylate.* The acid (8·5 g.) was warmed cautiously with thionyl chloride (34 c.c.), and when the reaction became less vigorous the mixture was boiled under reflux for 30 minutes. The excess of thionyl chloride was removed, dry ethanol (45 c.c.) was added, and the mixture was boiled under reflux on the water-bath for 30 minutes. Most of the ethanol was removed, the residue was diluted with water, and an excess of sodium hydroxide solution was added with cooling. The oil was extracted with ether, the extract dried, the ether removed, and the residue distilled. The *ester* (6·8 g., 74%) boiled at 169—174°/0·5 mm. (Found : N, 3·9; OEt, 11·8. $C_{23}H_{31}O_2N$ requires N, 4·0; OEt, 12·75%).

3-*Dimethylamino*-1 : 1-*diphenylpropane*-1-*carboxylic acid.* 3-Dimethylamino-1 : 1-diphenylpropyl cyanide (5 g.) and concentrated hydrochloric acid (25 c.c.) were heated in a sealed tube at 150° for 16 hours. The solution was evaporated to dryness under reduced pressure; the residue was dissolved in a small volume of water, and made slightly alkaline with 2N-sodium carbonate. On cooling in the refrigerator, a solid separated which was filtered off and dried (4·9 g., 91%). On crystallisation from water the *acid* melted at 197—198° (decomp.) (Found : C, 76·3; H, 7·4; N, 4·6. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·5; N, 4·9%).

3 : 3-*Diphenyl*-1-*methylpyrrolid*-2-*one.* (*a*) 3-Dimethylamino-1 : 1-diphenylpropane-1-carboxylic acid (1 g.) and thionyl chloride (4 c.c.) were boiled under reflux for 30 minutes. The excess of thionyl chloride was removed, water was added to the residue, and the solid was filtered off. Crystallisation from aqueous alcohol gave white needles, m. p. 146·5—147°, of the *pyrrolidone*. The melting point was not depressed on admixture with a specimen of the compound prepared as described below (Found : C, 80·85; H, 6·8; N, 5·75. $C_{17}H_{17}ON$ requires C, 81·2; H, 6·8; N, 5·6%). Yield 0·85 g., 96%.

(*b*) $\alpha\alpha$-Diphenyl-γ-butyrolactone (for preparation see following paper) (2 g.), aqueous methylamine (25%, 5 c.c.), and ethanol (20 c.c.) were heated in a sealed tube at 160° for 16 hours. The contents of the tube deposited a crystalline solid, m. p. 146—147°, when left. A further quantity was obtained by concentration of the mother-liquors. On crystallisation from aqueous alcohol the material melted at 146·5—147° (Found : C, 80·8; H, 6·95; N, 5·2%). Yield 1·8 g., 85%.

3-*Diethylamino*-1 : 1-*diphenylpropane*-1-*carboxylic acid.* 3-Diethylamino-1 : 1-diphenylpropyl cyanide (5 g.) and concentrated hydrochloric acid (25 c.c.) were heated overnight in a sealed tube at 140—150°.

TABLE II.

Amino-ketones.

Compound.	Yield, %.	Deriv.	B. p.	Crystaln. solvent.	M. p.	Analysis. Found, %. C.	H.	N.	Cl.	Required, %. C.	H.	N.	Cl.	Notes.
$NMe_2{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COMe$	83	HCl	—	Acetone–ether	186—187·5°	71·6	7·9	4·6	11·3	71·8	7·6	4·4	11·2	
$NMe_2{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COEt$	78	—	154—156°/ 0·8 mm.	—	—	81·6	8·6	4·7	—	81·3	8·5	4·7	—	1
	—	HCl	—	Acetone–ether	173·5—175	72·1	8·0	4·2	10·9	72·4	7·9	4·2	10·7	
$NMe_2{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COPr$	84	—	161—167/ 1 mm.	—	—	82·0	8·6	4·5	—	81·6	8·8	4·5	—	
$NMe_2{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COPh$	89	—	178—184/ 0·3 mm.	—	—	—	—	—	—	—	—	—	—	
	—	HCl	—	Acetone–ether	227—228	76·1	6·9	3·9	9·3	75·9	6·9	3·7	9·3	
$NEt_2{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COEt$	77	—	160—165/ 0·5 mm.	—	—	—	—	4·2	—	—	—	4·3	—	
	—	HCl	—	Acetone–ether	141—143	73·5	8·0	3·9	9·3	73·4	8·4	3·9	9·85	
$NPr_2{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COEt$	65	—	180/0·9 mm.	—	—	82·15	9·4	4·0	—	82·0	9·5	4·0	—	
$NBu_2{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COEt$	70	—	173—180/ 0·5 mm.	—	—	—	—	4·0	—	—	—	3·7	—	2
$N(CH_2Ph)Me{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COEt$	60	—	180—185/ 0·04 mm.	—	—	84·5	7·7	4·2	—	84·05	7·9	3·8	—	
$N(CH_2Ph)_2{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COEt$	54	—	—	Ethanol	86—87	85·3	6·9	3·4	—	85·8	7·4	3·1	—	2
	—	HCl	—	Acetone–ether	162—164 decomp.	79·1	7·0	2·8	7·15	79·4	7·1	2·9	7·3	
$CH_2(CH_2{\cdot}CH_2)N{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COEt$	68	—	Subl. 130/ 0·01 mm.	—	68—70	81·8	8·5	4·6	—	82·2	8·5	4·4	—	3
	—	HCl	—	Benzene	80·5—82·5	74·7	8·1	3·4	—	73·8	7·9	3·9	—	
$CH_2(CH_2{\cdot}CH_2)N{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COEt$	74	HI	—	Water	197—198	—	—	3·25	—	—	—	3·0	—	4
	—	HCl	—	Acetone–ether	175—176	74·0	8·1	4·15	—	74·3	8·1	3·8	—	
$CH_2(CH_2{\cdot}CHMe)N{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COEt$	60	—	169—172/ 0·2 mm.	—	—	82·9	8·8	3·95	—	82·5	8·95	4·0	—	
$CH_2(CHMe{\cdot}CH_2)N{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COEt$	60	—	186—188/ 0·5 mm.	—	—	82·9	9·0	3·8	—	82·5	8·95	4·0	—	
$CHMe(CH_2{\cdot}CH_2)N{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COEt$	53	—	180—184/ 0·1 mm.	—	—	82·2	8·6	4·3	—	82·5	8·95	4·0	—	
$CH_2(CH_2{\cdot}CHMe)N{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COEt$	69	—	166—168/ 0·02 mm.	—	—	82·8	9·05	3·9	—	82·6	9·15	3·9	—	2, 5
$O(CH_2{\cdot}CH_2)N{\cdot}CH_2{\cdot}CH_2{\cdot}CPh_2{\cdot}COMe$	66	—	—	Petrol. (b. p. 40—60°)	100—101	78·4	8·0	4·5	—	78·0	7·8	4·3	—	6
	—	HCl	—	Ethyl acetate	185·5—186·5	70·0	7·5	4·2	9·2	70·1	7·3	3·9	9·9	

O<CH$_2$—CH$_2$ / CH$_2$—CH$_2$>N·CH$_2$·CH$_2$·CPh$_2$·COEt	84		—	Ethanol	114—115·5	78·3	8·0	4·3	—	78·3	8·1	4·15	—	7
	—	HCl	—	Ethanol–ether	234·5—237	—	—	3·6	10·1	—	—	3·75	9·5	
O<CH$_2$—CH$_2$ / CH$_2$—CH$_2$>N·CH$_2$·CH$_2$·CPh$_2$·COPr	50	HCl	—	Ethyl acetate	179·5—181·5	70·7	7·8	3·7	9·4	71·2	7·8	3·6	9·1	
O<CH$_2$—CH$_2$ / CHMe—CH$_2$>N·CH$_2$·CH$_2$·CPh$_2$·COEt	65	—	—	Petrol. (b. p. 40—60°)	95—96	78·0	8·5	4·0	—	78·6	8·3	4·0	—	
	—	HCl	—	Acetone–ether	187—189	70·8	7·5	3·6	9·5	71·2	7·8	3·6	9·1	
O<CHMe—CH$_2$ / CHMe—CH$_2$>N·CH$_2$·CH$_2$·CPh$_2$·COEt	32	—	—	Petrol. (b. p. 40—60°)	77—81	79·3	8·6	3·95	—	78·9	8·55	3·8	—	8
	—	HCl	—	Acetone–ether	170—174	—	—	3·5	—	—	—	3·5	—	
O<CH$_2$–CH$_2$ / CH$_2$–CH$_2$>N·CH$_2$·CH$_2$·CPh(*p*-Me·C$_6$H$_4$)·COEt	61	—	—	Petrol. (b. p. 60—80°)	89—91	78·25	8·2	3·9	—	78·6	8·3	4·0	—	
	—	HCl	—	Acetone–ether	175—177	—	—	3·65	9·2	—	—	3·6	9·1	
O<CH$_2$—CH$_2$ / CH$_2$—CH$_2$>N·CH$_2$·CH$_2$·C[*o*-Me·C$_6$H$_4$)$_2$·COEt	—	HCl	—	Ethyl acetate	218—221	—	—	3·7	8·55	—	—	3·5	8·8	9
NEt$_2$·CH$_2$·CH$_2$·CH$_2$·CPh$_2$·COEt	82	—	165—170/ 0·3 mm.	—	—	81·35	9·2	4·3	—	81·8	9·3	4·15	—	
O<CH$_2$—CH$_2$ / CH$_2$—CH$_2$>N·[CH$_2$]$_3$·CPh$_2$·COEt	74	—	—	Acetone–water	98—99	78·85	8·05	4·1	—	78·6	8·3	4·0	—	
	—	HCl	—	Acetone–ether	189—190·5	—	—	3·85	9·2	—	—	3·6	9·1	
O<CH$_2$—CH$_2$ / CH$_2$—CH$_2$>N·[CH$_2$]$_4$·CPh$_2$·COEt	79	—	169—173/ 0·01 mm.	—	—	79·1	8·35	3·6	—	78·9	8·55	3·8	—	

NOTES.

1. In the report of Kleiderer *et al.* (*loc. cit.*) the b. p. of the base is quoted as 186—187°/2·5 mm. and the m. p. of the hydrochloride as 173—175°, but no analytical figures are quoted for either.

2. Owing to the toluene solubility of the salts of these ketones, the entire mixture was made alkaline after decomposition of the Grignard complex and the ketone was extracted with ether.

3. After decomposition of the Grignard complex, the mixture was cooled and the aqueous and toluene layers were decanted from the lowest, gummy layer, which was then treated with alkali and extracted with ether.

The hydrochloride did not give a satisfactory analysis even after repeated crystallisation.

4. The hydriodide crystallised after decomposition of the Grignard complex and cooling.

5. The ketone is believed to have the *meso*-configuration (see above, under the corresponding cyanide).

6. The Grignard reagent was prepared from methyl bromide.

7. The method of isolation was similar to that described in Note 2, but in this instance the free base solidified on basification of the gummy hydriodide and the extraction was omitted.

8. After decomposition of the Grignard complex, the toluene layer was separated and treated with water and ether; the heavy oil was separated and basified with sodium hydroxide. The base was extracted with ether, the dried extract evaporated, and the residue triturated with light petroleum (b. p. 40—60°), when the solid ketone was obtained. The product is presumably a mixture of the (±)- and *meso*-forms.

9. After isolation by the general method, the product was a gum which deposited some unchanged cyanide on trituration with petrol. The filtrate was evaporated and the residue converted into hydrochloride, which was purified by crystallisation from ethyl acetate.

On dilution of the contents of the tube with a little water, a solid separated which was filtered off and dried. The *hydrochloride* was crystallised by dissolving in acetone containing a little ethanol and adding ether, and had m. p. 206—208° (decomp.) (Found: C, 68·8; H, 7·6; N, 4·1; Cl, 9·85. $C_{20}H_{25}O_2N$,HCl requires C, 69·1; H, 7·5; N, 4·0; Cl, 10·2%). The *3-diethylamino-1 : 1-diphenylpropane-1-carboxylic acid* was liberated from an aqueous solution of the hydrochloride by means of sodium carbonate; after crystallisation from ethanol–ether it melted at 183—184° (decomp.) (Found: N, 4·7. $C_{20}H_{25}O_2N$ requires N, 4·5%). Yield 4·6 g., 86%.

3 : 3-Diphenyl-1-ethylpyrrolid-2-one. (*a*) 3-Diethylamino-1 : 1-diphenylpropane-1-carboxylic acid (5 g.) was boiled under reflux for 30 minutes with thionyl chloride (20 c.c.), and the excess of thionyl chloride was removed. Water was added, and the solid was filtered off and crystallised from aqueous alcohol. The *product* (3·8 g.; 89%) melted at 111·5—113°, the m. p. being undepressed on admixture with a specimen prepared as described below (Found: C, 81·5; H, 7·4; N, 5·1. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·2; N, 5·3%).

(*b*) αα-Diphenyl-γ-butyrolactone (2 g.), aqueous ethylamine (33%., 5 c.c.), and ethanol (20 c.c.) were heated in a sealed tube at 180° for 16 hours. After most of the ethanol had been removed 3 : 3-diphenyl-1-ethylpyrrolid-2-one (2·1 g.; 94%) crystallised as colourless needles which melted at 111·5—112·5° after further crystallisation from aqueous alcohol (Found: C, 81·1; H, 7·0; N, 5·4%).

Conversion of the Amino-cyanides into Amino-ketones.

A Grignard reagent was prepared from magnesium (0·1 g.-mol.) and an alkyl halide (0·1 g.-mol.) in ether (unless otherwise stated the halide used was methyl iodide, ethyl iodide, propyl bromide, or bromobenzene). A solution of the amino-cyanide (0·05 g.-mol.) in dry toluene (*ca.* 35 c.c.) was added, and the ether was removed by distillation until the internal temperature was 95—97°. The residue was heated overnight on the water-bath, and, after cooling, was cautiously decomposed with 2N-hydrochloric acid (200 c.c.). The mixture was heated on the water-bath for 30 minutes to ensure the complete hydrolysis of the intermediate imine. The toluene layer was separated and washed with a little 2N-hydrochloric acid. The combined acid layers, together with a gummy lowest layer which was usually present, were made alkaline with sodium hydroxide, and extracted with ether or, in some cases, benzene. (An alternative method, which avoids the troublesome precipitate of magnesium hydroxide, involves the addition of *ca.* 20 g. of ammonium chloride to each 100 c.c. of the acid solution and basification with ammonia.) The extract was dried (K_2CO_3) and evaporated to dryness, and the residue purified by distillation or crystallisation. The base was converted into the hydrochloride whenever this could be obtained crystalline.

The compounds prepared, together with their physical constants and analytical figures, are listed in Table II. Any departures from the above general method will be found in the notes to the Table.

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