139. *Search for New Analgesics. Part III. Homologues of Amidone, isoAmidone, and Some Related Compounds.*

By E. Walton, P. Ofner, and R. H. Thorp.

In view of the established value of "Amidone" (III; R = COEt) as an analgesic, four series of related *ketones* (types III, IV, V, and VI, where R = COAlk or COAr) have been prepared by condensing diphenylmethyl cyanide with a chloro-base, and treating the resulting basic *cyanides* with Grignard reagents. In addition, the cyanide (III; R = CN) was resolved by means of tartaric acid, and from the optically active isomers (+)- and (−)-amidone were obtained. *Amides*, *acids*, *esters*, and *alkanes* of types (III and VI; R = $CO{\cdot}NH_2$, CO_2H, CO_2Alk, and H, respectively) have also been prepared.

These compounds have been tested for analgesic and respiratory depression activities. These two properties generally remain associated but not always in the same ratio, maximal activity being attained in the ethyl ketones in all four series described.

Amidone (III; R = COEt) was synthesised by I.G. workers during the last war (Report No. P.B. 981, Office of the Publication Board, Washington, D.C., p. 84) and is now established as an analgesic with an activity similar to that of morphine. Some 27 related compounds were mentioned in the same report (p. 87), many of which also showed considerable activity. Thus it is clear that the discovery of amidone opens up a new field in the search for synthetic analgesics. Such a search should not only be of theoretical interest, but may be of great practical value in producing a drug free from the side-effects still found in amidone.

The present communication describes the preparation and testing of several series of amidone-type compounds, some of which have already been referred to in preliminary communications (*Nature*, 1947, **159**, 679; **160**, 605). Condensation of diphenymethyl cyanide with the chlorodimethylaminopropane from either 2-dimethylaminopropan-1-ol (I; X = OH), or 1-dimethylaminopropan-2-ol (II; X = OH), gave a mixture of cyanides (III; R = CN) and (IV; R = CN) by a reaction that has already been discussed by Schultz *et al.* (*J. Amer. Chem. Soc.*, 1947, **69**, 188, 2454) and by Brode and Hill (*ibid.*, p. 724).

$CH_3{\cdot}CH(NMe_2){\cdot}CH_2X$ (I.) $CH_3{\cdot}CHX{\cdot}CH_2{\cdot}NMe_2$ (II.) $R{\cdot}CPh_2{\cdot}CH_2{\cdot}CHMe{\cdot}NMe_2$ (III.) $R{\cdot}CPh_2{\cdot}CHMe{\cdot}CH_2{\cdot}NMe_2$ (IV.)

In accordance with the results of Schultz *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 48), the hydrochlorides of the chlorodimethylaminopropanes (I and II; X = Cl) were found to have different physical properties. On the other hand, the hydrochloride of (I) could be readily converted into that of (II) by heat treatment, but there was no evidence that this reaction was reversible.

Reaction of the cyanide (III; R = CN) with the appropriate Grignard reagent yielded the corresponding *methyl*, ethyl, n-*propyl*, iso*propyl*, *butyl*, *phenyl*, and *benzyl* ketones (III; R = COMe, COEt, $COPr^n$, $COPr^i$, COBu, COPh, $CO{\cdot}CH_2Ph$, respectively). The corresponding ketimines were not encountered as intermediates during the preparation of these ketones, except in the case of the *iso*propyl and the phenyl ketone. In the latter case the ketimine was isolated as a stable crystalline *monohydrochloride* (III; R = $CPh{:}NH$). [The ketimine (III; R = $CEt{:}NH$) corresponding to amidone has also been isolated as picrate by Easton, Gardner, Evanick, and Stevens (*J. Amer. Chem. Soc.*, 1948, **70**, 76), but only by using specially mild conditions for the decomposition of the reaction product.]

Similarly, the cyanide (IV; R = CN) reacted with Grignard reagents to give the *methyl*, ethyl, *propyl*, and iso*propyl* ketones (IV; R = COMe, $COPr^n$, and $COPr^i$, respectively). In this series there was clear evidence of the formation of stable intermediate ketimines (isolated as methiodides * in the case of IV; R = CMe:NH and CEt:NH), probably owing to the steric hindrance effect of the 2-methyl group. The Grignard reaction products were therefore in all cases decomposed by acid hydrolysis. In this way *iso*amidone was obtained without difficulty in the form of hydrochloride, *hydrobromide*, *hydriodide*, *nitrate*, and methiodide (cf. Easton *et al.*, *loc. cit.*).

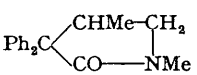
In view of its importance as an analgesic, the resolution of amidone was attempted by means of a variety of optically active acids, but without marked success. With D-tartaric acid it formed a diastereo-compound, (±)-amidone hydrogen D-tartrate (Thorp, Walton, and Ofner, *Nature*, 1947, **160**, 605; cf. Brode and Hill, *J. Org. Chem.*, 1948, **13**, 191). The penultimate cyanide (III; R = CN), on the other hand, was readily resolved by means of D-tartaric acid, and from the resolved *cyanides* (+)- and (−)-amidone were prepared without difficulty. The *salts* of the optically active cyanides have anomalous rotations in water, but otherwise the cyanide and amidone bases, and their salts, all show normal rotations (Thorp, Walton, and Ofner, *loc. cit.*).

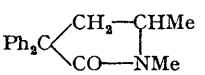
In addition to the compounds of types (III) and (IV), two further series of *ketones* (V; R = COMe, COEt, COPr, $COPr^i$) and (VI; R = COMe, COEt, COPr, COPh) have been prepared from the corresponding cyanides in a similar way. A few of these ketones have already been

(V.) $R{\cdot}CPh_2{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$ $R{\cdot}CPh_2{\cdot}CH_2{\cdot}CH_2{\cdot}NC_5H_{10}$ (VI.)

referred to elsewhere (*e.g.*, B.I.O.S. Final Report No. 116, Item No. 24, pp. 51, 65; Report No. P.B. 981, *loc. cit.*), but they were prepared again in view of the importance of comparing a complete series by a standardised pharmacological procedure.

In the course of this work the cyanides (III, IV, and VI; R = CN) were selected for hydrolysis, etc.; (III and VI; R = CN) were readily converted by means of sulphuric acid through the *amides* into the corresponding *carboxylic acids*, which were then treated with either diazomethane or diazoethane to give *esters*, but prolonged treatment of the nitrile (IV; R = CN) with 50% v/v sulphuric acid failed to give the corresponding amide or acid. With hydrobromic acid under pressure, however, this cyanide yielded the *pyrrolidone* (VII), while the isomeric *pyrrolidone* (VIII) was obtained on treatment of the acid (III; R = CO_2H) with thionyl chloride. Compounds (VII) and (VIII) had similar properties and identical melting points, but their mixture showed a marked depression.

(VII.) 

 (VIII.)

The resistance of the cyanide (IV), compared with that of (III), to sodamide and hydrolytic agents, and the stability of the ketimines obtainable from it by reaction with Grignard reagents may be taken as evidence that in this case the *C*-methyl group causes appreciable steric hindrance.

The carboxylic acids (III and VI; R = CO_2H) readily lost carbon dioxide at moderate temperatures to give the corresponding substituted *butane* and propane (R = H), both of which show antihistaminic activity (Report No. P.B. 981, *idem*, p. 38). The same two alkanes were obtained by direct elimination of the cyano-group from the corresponding nitriles with sodamide, but attempts to obtain the *iso*butane from the cyanide (IV; R = CN) by a similar reaction were unsuccessful.

Preliminary attempts to condense 1 : 1-diphenylbutan-2-one (prepared from diphenylacetonitrile and ethylmagnesium bromide) with 2-chloro-1-dimethylaminopropane, with a view to obtaining amidone, were likewise unsuccessful.

Pharmacological Results.—The compounds described have been tested pharmacologically in a preliminary manner by the methods already published (Thorp, *Brit. J. Pharmacol.*, 1946, **1**, 113) and the results are shown in the table. It will be seen that :

1. Respiratory depression and analgesic action always occur together.

2. Analgesic activity in each of the series examined shows sharp maxima with the ethyl ketone compounds, but is much less in the higher and lower analogues. It is surprising to note that, whereas the propyl ketone corresponding to amidone is depressant and poorly analgesic, the *iso*propyl analogue is a convulsant drug and shows no analgesic properties. In the

* That these derivatives are methiodides of the ketimines and not hydriodides of (IV; R = CMe:NMe and CEt:NMe, respectively) follows from their stability in dilute alkali.

*iso*amidone series of analogues both the propyl and the *iso*propyl ketones are powerful convulsant drugs. It is also noteworthy that *iso*amidone is less depressant than amidone.

3. In the piperidinoethyl and amidone series, such esters as have been examined show analgesic activity of the same order as the corresponding ketones.

4. In no case has significant analgesic activity been shown with the penultimate cyanides.

Pharmacological results.

	Salt.	Analgesic activity (morphine = 1 at a dose of 3 mg./kg.).	Resp. depress. activity (morphine = 1).	Approx. L.D. 50, I.V., mice, mg./kg.	Toxic concn. on isolated rabbit heart.
Compound (III) : R =					
COMe	HCl	0·05	Nil	35	—
COEt	HCl	1·3	1·4—2·0	24·2(21—28) *	1 : 100,000
COEt	MeI	Nil	Nil	10	—
(+)-COEt	HCl	Nil	<0·1	29·9(27—33) *	1 : 100,000
(−)-COEt	HCl	2·2	2·7—3·3	26·0(23—30) *	1 : 100,000
COPr	HBr	0·1	0·1—0·2	25	1 : 50,000
COPr^{i}	HNO_3	Nil	Stimulant	45	—
COBu	HCl	0·05	Nil	20	1 : 100,000
CPh:NH	HCl	Nil	Nil	30	—
COPh	HBr	Nil	Nil	40	—
CO·CH_2Ph	HCl	<0·1	Nil	7	1 : 500,000
CN	HCl	Nil	Nil	45	1 : 200,000
CO·NH_2	HCl	Nil	Nil	55	—
CO_2H	H_2SO_4	Nil	Nil	250	1 : 10,000
CO_2Me	HBr	0·2—0·25	0·5	26	1 : 100,000
CO_2Et	HBr	0·2	0·2	40	—
H	HBr	0·1—0·3	0·1—0·2	20	1 : 100,000
Pyrrolidone (VIII) ‡	—	0·3—0·4	—	15	—
Compound (IV) : R =					
COMe	HBr	0·1—0·2	0·2—0·2	60	1 : 100,000
COEt	HNO_3	1·0—1·2	0·5—0·7	40	—
COPr	HCl	Nil	Stimulant	12	1 : 200,000
COPr^{i}	HBr	Nil	Stimulant	30	1 : 200,000
CN	HBr	Nil	—	60	1 : 100,000
Pyrrolidone (VII) ‡	—	Nil	—	16	—
Compound (V) : R =					
COMe	HCl	0·1—0·2	0·2	70	—
COEt	HCl	0·5	0·5—0·7	45	—
COPr	HI	Nil	<0·1	50	—
COPr^{i}	HBr	Nil	<0·1	65	—
Compound (VI) : R =					
COMe	HBr	Nil	0·2	12	1 : 200,000
COEt	HBr	0·3—0·4	0·5	20	—
COPr	HBr	0·15—0·2	0·2	18	1 : 200,000
COPh	HBr	0·1—0·15	—	16	1 : 200,000
CN	HCl	0·05—0·1	Nil	50	—
CO·NH_2	Base	0·1	—	30	1 : 40,000 †
CO_2H	H_2SO_4	—	—	175	1 : 2,500
CO_2Me	HBr	0·5	1·0	20	—
CO_2Et	HBr	0·5	0·5—0·7	15	1 : 100,000
H	HCl	Nil	Slightly stimulant	25	1 : 200,000

* More accurate estimate of L.D.50 together with limits (P = 0·95) in parentheses.
† Produced marked coronary constriction at concentrations between 1 : 100,000 and 1 : 40,000.
‡ The discrepancy between the activities of these two pyrrolidones is being further examined.

Experimental.

1-Chloro-2-dimethylaminopropane (I; X = Cl).—The corresponding propanol (I; X = OH) (b. p. 145—148°; 32 g.), prepared by reduction of ethyl α-dimethylaminopropionate (Karrer, *Helv. Chim. Acta*, 1922, **5**, 477), was run into thionyl chloride (46 ml.) and chloroform (120 ml.), and the mixture subsequently warmed for 3 hours to remove the gases formed. The chloroform was removed under reduced pressure and the residual semi-solid hydrochloride of (I; X = Cl) washed out with acetone–ether. It crystallised from acetone in broad deliquescent needles, m. p. 101—102° (Found : N, 8·98; Cl, 44·8. Calc. for $C_5H_{12}NCl,HCl$: N, 8·85; Cl, 44·9%).

2-Chloro-1-dimethylaminopropane (II; X = Cl).—(*a*) The corresponding propanol (II; X = OH),

b. p. 122—124°, prepared from propylene oxide and dimethylamine (cf. Goldfarb, *J. Amer. Chem. Soc.*, 1941, **63**, 2280) and treated as described above for the isomeric alcohol, gave the hydrochloride of (II; X = Cl), which crystallised from a comparatively large volume of acetone in long silky needles, m. p. 190—191° (Found: N, 8·95; Cl, 44·9. Calc. for $C_5H_{12}NCl,HCl$: N, 8·85; Cl, 44·9%).

(*b*) 1-Chloro-2-dimethylaminopropane hydrochloride (m. p. 100—101°; 5 g.) was stirred in a test-tube immersed in an oil-bath at 140—160°. After 3 minutes the resulting solid was washed out with acetone and crystallised from the same solvent to give a hydrochloride (2·7 g.), m. p. 189—190°, identical with that obtained by process (*a*). This higher-melting hydrochloride (2 g.) was heated at 190—200° until molten. Lixiviation with acetone led to the recovery of unchanged material (1·1 g.), but no lower-melting isomer could be recovered from the mother-liquors.

Diphenylmethyl Cyanide.—This was prepared in good yield by dehydration of diphenylacetamide (Neure, *Annalen*, 1889, **250**, 141).

1 : 1-*Diphenylbutan-2-one.*—Diphenylacetonitrile (75 g.) in xylene (75 ml.) was added to the Grignard reagent (3 mols.) from magnesium (28 g.), ethyl bromide (127 g.) and dry ether (300 ml.), and the mixture heated on the steam-bath, the ether being removed at the same time by distillation. After 1 hour the reaction mixture, which now contained a solid adduct, was decomposed with dilute hydrochloric acid and extracted with ether. The ethereal extract on distillation gave a fraction (60·4 g.), b. p. 163—167°/4 mm., which contained 1·7% of nitrogen, indicating the presence of unchanged nitrile. It was therefore refluxed with 50% v/v sulphuric acid (100 ml.) for ½ hour, made alkaline with sodium hydroxide, and extracted with ether. The extract now gave a nitrogen-free fraction, b. p. 155—158°/4 mm., consisting of 1 : 1-diphenylbutan-2-one (Found: C, 85·7; H, 7·0. Calc. for $C_{16}H_{16}O$: C, 85·7; H, 7·1%), which yielded an oxime, crystallising from ethyl alcohol in cubes, m. p. 119° (Found: N, 6·00. Calc. for $C_{16}H_{17}ON$: N, 5·86%) (Maxim, *Ann. Chim.*, 1928, **9**, 55, gives m. p. 110°), and a semicarbazone from the same solvent as elongated prisms, m. p. 195—196° (cf. Orékhoff, *Bull. Soc. chim.*, 1919, **25**, 182).

Derivatives of 3-*Dimethylamino*-1 : 1-*diphenyl*-n-*butyl Cyanide* (III; R = CN).—The mixture of isomeric cyanides (III and IV; R = CN) (26 g.) obtained by the German process (Report No. P.B. 981, p. 97) was crystallised from light petroleum (b. p. 60—80°) to give the cyanide (III; R = CN) (13·5 g.) as needles, m. p. 90—91°. It formed: (a) a *hydrochloride*, crystallising from alcohol–ether in slender prisms, m. p. 181—183° (Found: N, 9·10; Cl, 11·3. $C_{19}H_{22}N_2,HCl$ requires N, 8·90; Cl, 11·3%); (b) a *hydrobromide*, crystallising from either water or alcohol–ether in needles, m. p. 175° (Found: Br, 22·2. $C_{19}H_{22}N_2,HBr$ requires Br, 22·3%); (c) a *hydriodide*, cream-coloured tablets, m. p. 203—204°, from either water or alcohol (Found: I, 32·0. $C_{19}H_{22}N_2,HI$ requires I, 31·3%); (d) a *nitrate*, rhombs, m. p. 168—170° (decomp.), from alcohol (Found: N, 12·2. $C_{19}H_{22}N_2,HNO_3$ requires N, 12·3%); (e) a *methiodide*, needles, m. p. 238—246°, from water (Found: N, 6·65. $C_{20}H_{25}N_2I$ requires N, 6·66%).

3-*Dimethylamino*-1 : 1-*diphenyl*-2-*methyl*-n-*propyl Cyanide* (IV; R = CN).—The petrol mother-liquors, obtained after separation of the above cyanide (III; R = CN), were evaporated, and the residual basic oil treated with 40% hydrobromic acid. The resulting lower layer, consisting of hydrobromide, was separated and warmed with half its volume of methyl ethyl ketone. The semi-solid mass obtained on cooling was filtered, and the resulting *hydrobromide* (17·5 g.) recrystallised from alcohol–ether in hexagonal leaflets (14 g.), m. p. 223—224° (Found: N, 7·64; Br, 22·1. $C_{19}H_{22}N_2,HBr$ requires N, 7·80: Br, 22·3%). The base from this hydrobromide formed silky needles, m. p. 68—69° (cf. Schultz, Robb, and Sprague, *J. Amer. Chem. Soc.*, 1947, **69**, 188). The *hydrochloride* crystallised from alcohol–ether in brilliant prisms, m. p. 224—225°, very soluble in water (Found: N, 8·84; Cl, 11·3. $C_{19}H_{22}N_2,HCl$ requires N, 8·90; Cl, 11·3%). The *hydriodide* crystallised from water in leaflets, and from alcohol in needles, m. p. 212—213° (Found: N, 7·0; I, 30·5. $C_{19}H_{22}N_2,HI$ requires N, 6·90; I, 31·3%); the *nitrate* from alcohol–ether in hexagonal leaflets, m. p. 178° (decomp.) (Found: N, 12·3. $C_{19}H_{22}N_2,HNO_3$ requires N, 12·3%); the *hydrogen* D-*tartrate* (unresolved diastereo-compound) from acetone in rectangular prisms, m. p. 88—98°, very soluble in water (Found: N, 6·48. $C_{19}H_{22}N_2,C_4H_6O_6$ requires N, 6·54%), and the *methiodide* from alcohol in needles, m. p. 235—245° (Found: N, 6·68; I, 29·8. $C_{20}H_{25}N_2I$ requires N, 6·7; I, 30·2%).

5-*Dimethylamino*-3 : 3-*diphenylhexan*-2-*one* (III; R = COMe).—The cyanide (III; R = CN) (5 g.) dissolved in dry xylene (20 ml.) was added to the Grignard reagent from magnesium (1·3 g.), methyl iodide (7·7 g.), and ether (15 ml.). The mixture was heated first on the steam-bath for 2 hours (the ether being allowed to evaporate) and then on a sand-bath for the same period. Considerable precipitation occurred. The product was decomposed with dilute hydrochloric acid, and the aqueous layer (which contained oily hydriodides) extracted with ether. The aqueous layer (plus unextractable oil) was now made alkaline with sodium hydroxide solution, and the oil extracted with ether from the magnesia gel. The ether was removed, the residue dissolved in dilute hydrochloric acid, and the filtered solution evaporated to dryness and treated with alcohol–ether. A solid *hydrochloride*, crystallising from alcohol–ether in minute rhombs, m. p. 185—187°, and very soluble in water, was eventually obtained (Found: N, 4·68; Cl, 10·7. $C_{20}H_{25}ON,HCl$ required N, 4·22; Cl, 10·7%). The oily base from a similar preparation gave a *hydrobromide*, which crystallised from water in rhombs and from alcohol–ether in hexagonal needles, m. p. 193—195° (Found: Br, 20·7. $C_{20}H_{25}ON,HBr$ requires Br, 21·3%). The *hydriodide* crystallised from water or alcohol–ether in hexagonal leaflets, m. p. 180—182° (Found: I, 29·8. $C_{20}H_{25}ON,HI$ requires I, 30·2%). The free *base*, obtained from the hydrobromide, crystallised from alcohol–water in hexagonal needles, m. p. 72—73°, soluble in cold light petroleum (Found: N, 5·12. $C_{20}H_{25}ON$ requires N, 4·74%).

Derivatives of 6-*Dimethylamino*-4 : 4-*diphenylheptan*-3-*one* ("*Amidone*") (III; R = COEt).—The base, prepared by a similar method to that described in Report P.B. 981, p. 97, crystallised from light petroleum (b. p. 60—80°) in hexagonal needles, m. p. 80—82°. In addition to the hydrochloride and hydrobromide, it gave a *hydriodide* as tablets, m. p. 198—199°, from water (Found: N, 3·20; I, 29·1. $C_{21}H_{27}ON,HI$ requires N, 3·20: I, 29·1%); a *nitrate* as prisms, m. p. 108—110° (decomp.), from water (Found: N, 8·18. $C_{21}H_{27}ON,HNO_3$ requires N, 7·53%), and a *methiodide* as rhombs, m. p. 168—170°, from alcohol–ether (Found: N, 3·27; I, 28·1. $C_{22}H_{30}ONI$ requires N, 3·10; I, 28·2%).

7-*Dimethylamino*-5 : 5-*diphenyloctan*-4-*one* (III; R = COPr).—The cyanide (III; R = CN) (5 g.) in

xylene (20 ml.) was caused to react with the Grignard reagent from magnesium (1·3 g.), *n*-propyl iodide (9·2 g.), and ether (15 ml.), as described above for the methyl ketone (III; R = COMe). The product was decomposed with 10% sodium hydroxide, and the xylene removed in a vacuum. The oil was extracted from the gelatinous mixture with ether and worked up in two ways: (*a*) A portion was dissolved in dilute hydrochloric acid, and the aqueous solution evaporated to dryness. Treatment of the residue with alcohol–ether gave the hydrochloride as a deliquescent solid, which was readily converted directly into the *nitrate*, which crystallised from alcohol–ether in hexagonal prisms, m. p. 95—97° (Found: N, 7·43. $C_{22}H_{29}ON,HNO_3$ requires N, 7·25%). This salt showed maximal solubility in tepid rather than boiling water. (*b*) A portion, treated with dilute colourless hydriodic acid, gave the *hydriodide* as a sticky solid, which crystallised from alcohol–ether in leaflets, m. p. 155—157° (Found: N, 3·44; I, 28·2. $C_{22}H_{29}ON,HI$ requires N, 3·10; I, 28·2%). It separated from water as an oil. The *hydrobromide*, from the regenerated base, crystallised from alcohol–ether in rhombs, m. p. 87—89°, very soluble in alcohol alone (Found: Br, 19·3. $C_{22}H_{29}ON,HBr$ requires Br, 19·8%).

6-*Dimethylamino*-4 : 4-*diphenyl*-2-*methylheptan*-3-*one* (III; R = $COPr^i$).—The cyanide (III; R = CN) (15 g.) in xylene (15 ml.) was added to *iso*propylmagnesium bromide (4 mols.) in ether (60 ml.), and the mixture warmed at 100° for 4 hours, the ether being allowed to evaporate. [Early experiments had indicated that prolonged reflux at the b. p. of xylene led to formation of the butane (VII; R = H), see below.] The product was decomposed with water, made strongly alkaline with sodium hydroxide solution, evaporated to dryness at 50—70° in a vacuum, and extracted with ether. Evaporation of the ethereal extract gave a basic oil which, on account of its high solubility in hydrobromic acid, appeared to be the intermediate ketimine. After being refluxed with 20% hydrobromic acid for 2 hours, it formed a less soluble oily hydrobromide, from which the base was isolated and distilled to give the impure *iso*propyl ketone (III; R = $COPr^i$) (10·1 g.), b. p. 176—186°/4 mm. The *nitrate* crystallised from alcohol–ether in slender prisms, m. p. 116—118° (Found: N, 7·29. $C_{22}H_{29}ON,HNO_3$ requires N, 7·25%).

2-*Dimethylamino*-4 : 4-*diphenylnonan*-5-*one* (III; R = COBu).—The cyanide (III; R = CN) (5 g.) was condensed with the Grignard reagent from *n*-butyl iodide (10 g.), as described for the hexanone, and the mixture refluxed until the formation of grey adduct was complete (about 5 hours). Decomposition with dilute hydrochloric acid gave the crude *hydriodide* as an oil, which on being washed with ether yielded a yellow solid. The latter, after several crystallisations from alcohol–ether, gave plates, m. p. 140—143° (Found: I, 27·8. $C_{23}H_{31}ON,HI$ requires I, 27·3%). The base isolated from the crude hydriodide gave (all from alcohol–ether): a *hydrochloride*, minute plates, m. p. 83—86°, very soluble in water (Found: N, 4·00; Cl, 9·32. $C_{23}H_{31}ON,HCl$ requires N, 3·75; Cl, 9·50%); a *hydrobromide*, plates, m. p. 103—105° (Found: N, 3·55; Br, 18·9. $C_{23}H_{31}ON,HBr$ requires N, 3·35; Br, 19·1%); and a *nitrate*, prisms, m. p. 77—78° (Found: N, 7·3. $C_{23}H_{31}ON,HNO_3$ requires N, 7·0%).

Phenyl 3-*Dimethylamino*-1 : 1-*diphenyl*-n-*butyl Ketone* (III; R = COPh).—The cyanide (III; R = CN) (15 g.) was combined with phenylmagnesium bromide (3 mols.) in ether (40 ml.), and the product worked up as described for the *iso*propyl ketone. The basic oil (12 g.), purified through hydrochloric acid solution, gave the *ketimine* (III; R = CPh:NH) *hydrochloride*, which crystallised from methyl ethyl ketone in needles, m. p. 136—137° (Found: N, 6·5; Cl, 9·0. $C_{25}H_{28}N_2,HCl$ requires N, 7·1; Cl, 9·1%). A solution of the crude ketimine base in excess of 20% hydrobromic acid after 2 hours' refluxing gave the *ketone* (III; R = COPh) *hydrobromide* as an oil, which crystallised from alcohol–ether in plates, m. p. 181—183° (Found: N, 3·3; Br, 18·2. $C_{25}H_{27}ON,HBr$ requires N, 3·2; Br, 18·2%). The *hydrochloride* crystallised from methyl ethyl ketone in cubes, m. p. 197—198° (Found: N, 3·46; Cl, 9·0. $C_{25}H_{27}ON,HCl$ requires N, 3·55; Cl, 9·0%).

5-*Dimethylamino*-1 : 3 : 3-*triphenylhexan*-2-*one* (III; R = $CO{\cdot}CH_2Ph$).—The crude basic oil from the cyanide (III; R = CN) (15 g.) and benzylmagnesium chloride (3 mols.) was isolated as described for the *iso*propyl ketone. This oil was apparently the ketone (and not the ketimine), because with 3N-hydrochloric acid it gave a *ketone hydrochloride*, which crystallised from alcohol–ether in needles, m. p. 236—237° (Found: N, 3·50; Cl, 8·94. $C_{26}H_{29}ON,HCl$ requires N, 3·43; Cl, 8·94%). The *hydrobromide* crystallised from alcohol in needles, m. p. 243—244° (Found: N, 3·14; Br, 17·6. $C_{26}H_{29}ON,HBr$ requires N, 3·10; Br, 17·7%).

Resolution of 3-*Dimethylamino*-1 : 1-*diphenyl*-n-*butyl Cyanide* (III; R = CN).—The corresponding inactive cyanide (40 g.) and D-tartaric acid (21·6 g.) were together dissolved in acetone (430 ml.), and to the filtered solution water (10 ml.) was added. Crystalline (−)-*cyanide hydrogen* D-*tartrate* rapidly separated. After 24 hours at 0°, the tartrate was collected; it recrystallised from acetone (400 ml.) plus water (5 ml.) in needles (28 g.), m. p. 109—112°, $[\alpha]_D^{20°}$ +16° (in water) (Found: N, 6·7. $C_{19}H_{22}N_2,C_4H_6O_6$ requires N, 6·5%). The (−)-*cyanide* base from this tartrate crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 99—101°, $[\alpha]_D^{21°}$ −51° (in alcohol) (Found: N, 10·3. $C_{19}H_{22}N_2$ requires N, 10·1%).

The acetone mother-liquors plus a little ether after 4 days at 0° deposited a crystalline solid, which was collected and crystallised from a mixture of acetone (60 ml.), ether (40 ml.), and water (5 ml.) to give the (+)-*cyanide hydrogen* D-*tartrate* (14 g.), which formed granules, m. p. 66—70°, $[\alpha]_D^{20°}$ +5° in water (Found: N, 6·5. $C_{19}H_{22}N_2,C_4H_6O_6$ requires N, 6·5%). The (+)-*cyanide* had m. p. 101° and $[\alpha]_D^{22°}$ +49° (in alcohol) (Found: N, 9·86. $C_{19}H_{22}N_2$ requires N, 10·1%). Its *hydrobromide* crystallised from alcohol–ether in needles, m. p. 216—218°, $[\alpha]_D^{22°}$ +5° (in alcohol) and −4° (in water) (Found: N, 7·8; Br, 22·4. $C_{19}H_{22}N_2,HBr$ requires N, 7·8; Br, 22·3%); and its *nitrate* crystallised from water in needles, m. p. 169—171° (decomp.), $[\alpha]_D^{20°}$ +5° and −6° (in alcohol and water, respectively) (Found: N, 12·4. $C_{19}H_{22}N_2,HNO_3$ requires N, 12·3%).

(−)-6-Dimethylamino-4 : 4-diphenylheptan-3-one [(−)-amidone] (III; R = COEt), prepared from the (−)-cyanide and ethylmagnesium bromide, was isolated as *hydrobromide*, which crystallised from water in leaflets and from alcohol–ether in hexagonal tablets, m. p. 234—235°, $[\alpha]_D^{22°}$ −134° (in alcohol) (Found: N, 3·4; Br, 20·4. $C_{21}H_{27}ON,HBr$ requires N, 3·6; Br, 20·5%). The *base* from this salt, after purification by solution in light petroleum (b. p. 60—80°) in which it is relatively soluble, crystallised from alcohol–water in tablets, m. p. 99—101°, $[\alpha]_D^{22°}$ −32° (in alcohol) (Found: N, 4·5. $C_{21}H_{27}ON$ requires N, 4·5%). The *hydrochloride* crystallised from both

alcohol–ether and very dilute hydrochloric acid in tablets, m. p. 241—242° (slight decomp.), $[\alpha]_D^{21°}$ −130° (in water) (Found: N, 4·55; Cl, 10·3. $C_{21}H_{27}ON,HCl$ requires N, 4·05; Cl, 10·3%).

(+)-6-Dimethylamino-4 : 4-diphenylheptan-3-one [(+)-amidone], from the (+)-cyanide, had m. p. 98—100°, $[\alpha]_D^{20°}$ +28° (in alcohol). Its *hydriodide* crystallised from alcohol–ether in rectangular tablets, m. p. 175—177° (decomp.) (Found: N, 3·1; I, 28·9. $C_{21}H_{27}ON,HI$ requires N, 3·2; I, 29·1%), and its *nitrate* separated from the same solvent in silky needles, m. p. 148° (decomp.), $[\alpha]_D^{19°}$ +137° (in alcohol) (Found: N, 7·8. $C_{21}H_{27}ON,HNO_3$ requires N, 7·5%).

γ-Dimethylamino-αα-diphenylvaleric Acid (III; R = CO_2H) *and its Amide* (III; R = $CO{\cdot}NH_2$).—The cyanide (III; R = CN) (2 g.), concentrated sulphuric acid (4 ml.), and water (4 ml.) were heated under reflux for 20 minutes, diluted with an equal volume of water, and cooled to 0°. The *hydrogen sulphate* (2·3 g.) of the carboxylic acid (III; R = CO_2H), which separated, was collected and recrystallised from water acidified with sulphuric acid in rhombic leaflets, m. p. 222—223° (Found: S, 8·06. $C_{19}H_{23}O_2N,H_2SO_4$ requires S, 8·10%). The free *acid* (III; R = CO_2H), obtained from this salt by neutralisation to pH 6·8, crystallised from water in rectangular tablets, m. p. 198—199° (decomp.) (Found: N, 4·4. $C_{19}H_{23}O_2N$ requires N, 4·7%). Its *hydrochloride* crystallised from water in minute leaflets, m. p. 213—216° (Found: N, 4·3; Cl, 10·7. $C_{19}H_{23}O_2N,HCl$ requires N, 4·2; Cl, 10·6%).

The mother-liquors from the above hydrogen sulphate, made alkaline to indigo-carmine, yielded the *amide* (III; R = $CO{\cdot}NH_2$) (0·9 g.), which crystallised from dilute alcohol in long prisms, m. p. 175—176°, practically insoluble in water (Found: N, 9·1. $C_{19}H_{24}ON_2$ requires N, 9·45%). Its hydrochloride crystallised from alcohol–ether in leaflets, m. p. 190—191° (slightly deliquescent).

Methyl and ethyl esters (III; R = CO_2Me and CO_2Et respectively). (*a*) A mixture of the carboxylic acid (III; R = CO_2H) (1 g.) and an excess of an ethereal solution of diazomethane was left for 4 days, then filtered, and the ether and diazomethane removed. The residue was made alkaline, extracted with ether, and the extract dried. Removal of the solvent yielded the *methyl* ester, which crystallised from light petroleum (b. p. 60—80°) in rhombic leaflets, m. p. 60—65° (Found: N, 4·6; OMe, 9·7. $C_{20}H_{25}O_2N$ requires N, 4·5; OMe, 10·0%). The *hydrochloride* crystallised from 2N-hydrochloric acid in needles, m. p. 166—168° (decomp.), readily soluble in water (Found: Cl, 10·2; OMe, 8·5. $C_{20}H_{25}O_2N,HCl$ requires Cl, 10·2; OMe, 8·9%). The *hydrobromide* crystallised from alcohol–ether in prisms, m. p. 182° (decomp.), soluble in water (Found: Br, 20·9; OMe, 8·1. $C_{20}H_{25}O_2N,HBr$ requires Br, 20·4; OMe, 7·9%). (*b*) The ethyl ester, prepared in the same way but from diazoethane, remained as an oil, the hydrochloride of which was deliquescent. On the other hand, its *hydrobromide* crystallised from alcohol–ether in rectangular leaflets, m. p. 167—168° (Found: Br, 20·4; OEt, 11·3. $C_{21}H_{27}O_2N,HBr$ requires Br, 19·7; OEt, 11·1%).

Refluxing the acid (III; R = CO_2H) with ethyl alcohol and sulphuric acid for 2 hours yielded only traces of the ethyl ester.

3-*Dimethylamino*-1 : 1-*diphenylbutane* (III; R = H).—(*a*) A mixture of the cyanide (III; R = CN) (5 g.), sodamide (0·7 g.), and toluene (10 ml.) was refluxed for 6—7 hours, decomposed with water, and extracted with dilute hydrochloric acid. The aqueous layer was made alkaline and extracted with ether. The ethereal residue on solution in light petroleum (b. p. 60—80°) yielded unchanged cyanide (2·5 g.) and an oily fraction from which the butane *hydrobromide* was obtained as tablets, m. p. 159—160° (from alcohol–ether) (Found: N, 4·2; Br, 23·9. $C_{18}H_{23}N,HBr$ requires N, 4·2; Br, 23·9%). (*b*) The carboxylic acid (III; R = CO_2H) heated at 200° for 15 minutes gave an oil, which in turn yielded a hydrobromide identical with the above. The *methiodide* crystallised from alcohol in needles, m. p. 195—196° (Found: N, 3·5; I, 32·1. $C_{19}H_{26}NI$ requires N, 3·5; I, 32·1%); it was also isolated from among the products of an early attempt to prepare the ketone (III; R = $COPr^t$) (see above).

3 : 3-*Diphenyl*-1 : 5-*dimethylpyrrolid*-2-*one* (VIII).—The carboxylic acid (III; R = CO_2H) (0·8 g.), dissolved in dry chloroform (10 ml.), was added slowly to thionyl chloride (0·5 ml.) in chloroform (5 ml.), and the mixture warmed for 4 hours on the steam-bath. A solid slowly separated. The chloroform and thionyl chloride were removed by evaporation, and the residue treated with a little ethyl alcohol. The *pyrrolidone* separated as a solid, and crystallised from aqueous alcohol in rectangular prisms, m. p. 122—123°, insoluble in dilute acids and alkalis (Found: C, 81·1; H, 7·0; N, 5·4. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·2; N, 5·3%).

5-*Dimethylamino*-3 : 3-*diphenyl*-4-*methylpentan*-2-*one* (IV; R = COMe).—The cyanide (IV; R = CN) (4·2 g.) in xylene (20 ml.) was added to the Grignard reagent from methyl iodide (6·4 g.) and magnesium (1·1 g.) in ether. The mixture was heated on the steam-bath for 1 hour and then refluxed for a similar period on a sand-bath, the ether being allowed to evaporate. The product was decomposed with ice, made strongly alkaline, evaporated to dryness in a vacuum and extracted with ether. The ethereal residue, purified through cold dilute hydrochloric acid, yielded the ketimine (IV; R = CMe:NH) as a basic oil, the *methiodide* of which crystallised from alcohol–ether in needles, decomposing at 176—230° (Found: N, 6·4; I, 29·0. $C_{21}H_{29}N_2I$ requires N, 6·4; I, 29·1%). The ketimine, refluxed with excess of 20% hydrobromic acid for 2 hours, gave on cooling the *hydrobromide* of the pentanone (IV; R = COMe) as a solid, which crystallised from alcohol–ether in long hair-like needles, m. p. 194—196° (Found: N, 3·6; Br, 21·5. $C_{20}H_{25}ON,HBr$ requires N, 3·7; Br, 21·3%). The *pentanone* base from the hydrobromide crystallised, on evaporation of its solution in light petroleum, in stout prisms, m. p. 61—65° (Found: N, 4·96. $C_{20}H_{25}ON$ requires N, 4·75%).

6-*Dimethylamino*-4 : 4-*diphenyl*-5-*methylhexan*-3-*one* (IV; R = COEt) (iso*Amidone*).—The cyanide (IV; R = CN) (16·6 g.) was treated with the Grignard reagent from ethyl bromide (19·6 g.) and magnesium (4·3 g.), and the product worked up as described for the pentanone (IV; R = COMe). The oily *ketimine* boiled at 94°/1 mm. (Found: N, 9·7. $C_{21}H_{28}N_2$ requires N, 9·1%) and formed a *methiodide*, which crystallised from water in hexagonal leaflets, partly decomposing at 158—160° but melting at 240° (Found: N, 6·2; I, 28·1. $C_{22}H_{31}N_2I$ requires N, 6·2; I, 28·2%). Refluxed for 2½ hours with 20% hydrobromic acid, the ketimine yielded iso*amidone hydrobromide* (10·3 g.) as a solid, which crystallised from water in prisms, m. p. 139—144°, soluble in hot benzene (Found: N, 3·6; Br, 20·8. $C_{21}H_{27}ON,HBr$ requires N, 3·6; Br, 20·5%). The oily *iso*amidone base from this hydrobromide yielded a hydrochloride,

crystallising from dilute hydrochloric acid in hexagonal tablets, m. p. 152—153° (metastable form, m. p. 114—116°, obtained on one occasion) (Found: N, 4·3; Cl, 10·5. Calc. for $C_{21}H_{27}ON,HCl$: N, 4·05; Cl, 10·3%); a *hydriodide* from water in feathery needles, m. p. 206—208° (Found: N, 3·3; I, 28·9. $C_{21}H_{27}ON,HI$ requires N, 3·2; I, 29·1%); a *nitrate* from alcohol–ether in cubes, m. p. 182—183° (decomp.) (Found: N, 7·8. $C_{21}H_{27}ON,HNO_3$ requires N, 7·5%), and a methiodide from water in needles, m. p. 235—245° (decomp.) (Found: N, 3·2; I, 28·4. Calc. for $C_{22}H_{30}ONI$: N, 3·1; I, 28·2%). Attempts to resolve *iso*amidone led to the formation of the unresolved *hydrogen* D-*tartrate*, which crystallised from acetone in needles, m. p. 150—154° (Found: N, 3·1. $C_{21}H_{27}ON,C_4H_6O_6$ requires N, 3·05%).

1-*Dimethylamino*-3 : 3-*diphenyl*-2-*methylheptan*-4-*one* (IV; R = COPr).—The cyanide (IV; R = CN) (16·6 g.) and the Grignard reagent from *n*-propyl bromide (22·2 g.) and magnesium (4·3 g.) were caused to react as described for the pentanone (IV; R = COMe). The product, after decomposition with water and evaporation to dryness in a vacuum, afforded an ethereal extract, which on extraction with dilute hydrochloric acid gave the *heptanone hydrochloride* (3·75 g.) as a crystalline solid, which separated from dilute hydrochloric acid in hexagonal leaflets, m. p. 80—100°, probably containing water of crystallisation (Found, for dried material: N, 4·1; Cl, 9·90. $C_{22}H_{29}ON,HCl$ requires N, 3·9; Cl, 9·9%). The free *base* crystallised from light petroleum (b. p. 60—80°) in parallelepipeds, m. p. 100—101° (Found: N, 4·44. $C_{22}H_{29}ON$ requires N, 4·33%).

6-*Dimethylamino*-4 : 4-*diphenyl*-2 : 5-*dimethylhexan*-3-*one* (IV; R = COPr^i).—To prepare this ketone it was necessary to treat the corresponding cyanide with 5 mols. of *iso*propylmagnesium bromide in the manner described above. The purified basic oil, refluxed with 20% hydrobromic acid for 3 hours, gave a semi-solid *hydrobromide*, which crystallised from water in hexagonal plates, m. p. 81—85° (Found: N, 3·4; Br, 20·1. $C_{22}H_{29}ON,HBr$ requires N, 3·5; Br, 19·8%).

3 : 3-*Diphenyl*-1 : 4-*dimethylpyrrolid*-2-*one* (VII).—The cyanide (IV) (2 g.) and excess of 48% hydrobromic acid were heated for 3½ hours at 180° in a sealed tube, and the acid then removed in a vacuum. The residual sticky solid was collected, washed, and crystallised from dilute alcohol to give the *pyrrolidone* in the form of rectangular prisms, m. p. 121—123° [104—106° when mixed with (VIII)] (Found: C, 81·5; H, 6·86; N, 5·4. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·16; N, 5·3%).

3-*Dimethylamino*-1 : 1-*diphenyl*-n-*propyl Cyanide* (V; R = CN).—Diphenylmethyl cyanide (67·2 g.), 2-dimethylaminoethyl chloride (22 g.), and sodamide (6·8 g.) in benzene (200 ml.), caused to react as for the cyanides (III and IV; R = CN), gave a basic oil (39 g.), which was purified by crystallisation of its *hydriodide* from methyl alcohol; rectangles, m. p. 221—223° (Found: N, 7·16; I, 32·8. $C_{18}H_{20}N_2,HI$ requires N, 7·14; I, 32·6%). The *hydrochloride* crystallised from methyl ethyl ketone in leaflets and from alcohol–ether in needles, m. p. 196—197° (Found: N, 9·36; Cl, 11·9. $C_{18}H_{20}N_2,HCl$ requires N, 9·32; Cl, 11·8%).

5-*Dimethylamino*-3 : 3-*diphenylpentan*-2-*one* (V; R = COMe).—The cyanide (V; R = CN) (14 g.) and methylmagnesium iodide (3 mols.), heated at 100° in xylene (14 ml.) for 4 hours and worked up through hydrochloric acid solution as described for (IV; R = COMe), gave a basic oil (9 g.), which formed a *hydrochloride*, crystallising from alcohol–ether in parallelepipeds, m. p. 152—153° (Found: N, 4·46; Cl, 11·3. $C_{19}H_{23}ON,HCl$ requires N, 4·4; Cl, 11·2%).

6-*Dimethylamino*-4 : 4-*diphenylhexan*-3-*one* (V; R = COEt). This was prepared in similar manner from ethylmagnesium bromide. Its hydrochloride crystallised from methyl ethyl ketone in hexagonal tablets, m. p. 171—172° (Found: N, 4·2; Cl, 10·8. Calc. for $C_{20}H_{25}ON,HCl$: N, 4·2; Cl, 10·7%).

1-*Dimethylamino*-3 : 3-*diphenylheptan*-4-*one* (V; R = COPr).—The cyanide (V; R = CN) and *n*-propylmagnesium iodide (3 mols.) gave a basic oil, which formed a *hydriodide*, crystallising from methyl ethyl ketone in rectangular tablets, m. p. 156—157° (Found: N, 3·2; I, 28·9. $C_{21}H_{27}ON,HI$ requires N, 3·2; I, 29·1%).

6-*Dimethylamino*-4 : 4-*diphenyl*-2-*methylhexan*-3-*one* (V; R = COPr^i).—The same cyanide and *iso*propylmagnesium bromide (4 mols.) yielded a ketimine base, which on refluxing with 20% hydrobromic acid gave a basic oil. The fraction, b. p. 177—190°/5 mm., gave a *hydrobromide*, which crystallised from methyl ethyl ketone–ether in plates, m. p. 104—106° (Found: N, 3·65; Br, 20·3. $C_{21}H_{27}ON,HBr$ requires N, 3·6; Br, 20·5%).

3-*Piperidino*-1 : 1-*diphenyl*-n-*propyl Cyanide* (VI; R = CN). This was prepared as described in D.R.-P. 710,227 (but before this patent was acquired). It crystallised from light petroleum in needles, m. p. 73—74° (Found: N, 9·2. Calc. for $C_{21}H_{24}N_2$: N, 9·2%). Its *hydrochloride* crystallised from alcohol–ether in leaflets, m. p. 196—197° (Found: C, 74·0; H, 7·3; N, 8·3; Cl, 10·4. $C_{21}H_{24}N_2,HCl$ requires C, 74·1; H, 7·3; N, 8·2; Cl, 10·4%); its *hydrobromide* crystallised from water in cubes, m. p. 185—186° (Found: N, 7·3; Br, 21·1. $C_{21}H_{24}N_2,HBr$ requires N, 7·3; Br, 20·8%); its *hydriodide* formed prisms, m. p. 152—153° from water (Found: N, 6·5; I, 29·4. $C_{21}H_{24}N_2,HI$ requires N, 6·5; I, 29·4%), and its *nitrate*, plates m. p. 155° (decomp.) (Found: N, 11·4. $C_{21}H_{24}N_2,HNO_3$ requires N, 11·5%).

5-*Piperidino*-3 : 3-*diphenylpentan*-2-*one* (VI; R = COMe).—The cyanide (VI; R = CN) and methylmagnesium iodide (3 mols.), refluxed in xylene in the usual way and decomposed with dilute hydriodic acid, afforded a solid *hydriodide*, which crystallised from water in rectangular tablets, m. p. 158—159° (Found: N, 3·2; I, 28·4. $C_{22}H_{27}ON,HI$ requires N, 3·1; I, 28·3%). The *hydrobromide* crystallised from alcohol–ether in parallelepipeds, m. p. 162—163° (Found: N, 3·5; Br, 20·2. $C_{22}H_{27}ON$ requires N, 3·5; Br, 19·9%).

6-*Piperidino*-4 : 4-*diphenylhexan*-3-*one* (VI; R = COEt).—The reaction product of the cyanide (VI; R = CN) and ethylmagnesium bromide (3 mols.), after decomposition with dilute hydrobromic acid and removal of xylene, gave a solid *hydrobromide*, which crystallised from alcohol–ether in rectangular tablets, m. p. 192—193° (Found: C, 66·4; H, 7·4; N, 3·4; Br, 19·3. $C_{23}H_{29}ON,HBr$ requires C, 66·4; H, 7·2; N, 3·4; Br, 19·2%).

1-Piperidino-3 : 3-diphenylheptan-4-one (VI; R = COPr) was isolated as hydriodide from the cyanide (VI; R = CN) and propylmagnesium iodide as described for the pentanone (VI; R = COMe). After crystallisation from alcohol–ether it melted at 217—220°, but it was not analysed. The *hydro-*

bromide crystallised from acetone–ether in hexagonal leaflets, m. p. 158—160° (Found : N, 3·25; Br, 18·4. $C_{24}H_{31}ON,HBr$ requires N, 3·25; Br, 18·6%).

Phenyl 3-*Piperidino*-1 : 1-*diphenyl*-n-*propyl Ketone* (VI; R = COPh).—The adduct from the cyanide (VI; R = CN) and phenylmagnesium bromide (4 mols.), obtained in the usual way and decomposed with dilute hydrobromic acid, gave the *hydrobromide*, which crystallised from alcohol–ether in parallelepipeds, m. p. 191—193°, sparingly soluble in cold water (Found : N, 3·1; Br, 17·3. $C_{27}H_{29}ON,HBr$ requires N, 3·0; Br, 17·2%). The base boiled at 248—253°/5 mm.

γ-Piperidino-αα-diphenylbutyric Acid and Amide (VI; R = CO_2H and $CO{\cdot}NH_2$).—The cyanide (1·9 g.) was refluxed for 30 minutes with sulphuric acid (3·6 ml.) and water (3·6 ml.) and the solution made alkaline. The *amide* separated, and crystallised from alcohol in leaflets (0·6 g.), m. p. 178—179° (Found : C, 77·9; H, 8·7; N, 8·79. $C_{21}H_{26}ON_2$ requires C, 78·3; H, 8·1; N, 8·7%). The amide hydrochloride, isolated by evaporation, was a deliquescent solid.

When the alkaline filtrate from the amide was neutralised and partly evaporated, the *acid* separated as a white solid (0·5 g.), m. p. 230—235° (decomp.), insoluble in cold water and alcohol separately, but soluble in a mixture of these solvents (Found : N, 4·7. $C_{21}H_{25}O_2N$ requires N, 4·3%). The *hydrochloride* crystallised from water or from alcohol–ether in rectangular tablets, m. p. 236° (decomp.) (Found : Cl, 10·0. $C_{21}H_{25}O_2N,HCl$ requires Cl, 9·9%). In another preparation of the acid, the *hydrogen sulphate* separated on dilution of the reaction mixture, and was crystallised from water; m. p. 105—114° (Found : N, 3·3; S, 7·8. $C_{21}H_{25}O_2N,H_2SO_4$ requires N, 3·3; S, 7·6%).

The methyl ester (VI; R = CO_2Me), prepared from the acid and diazomethane as described for the ester (III; R = CO_2Me), was isolated as an oil, but its *hydrobromide* crystallised from water in feathery needles, m. p. 78—82°, containing water of crystallisation (Found : H_2O, 7·85. $C_{22}H_{27}O_2N,HBr,2H_2O$ requires H_2O, 7·94%. Found, for anhydrous material : MeO, 7·5. $C_{23}H_{27}O_2N,HBr$ requires MeO, 7·4%). The *ethyl ester hydrobromide*, prepared in the same way but from diazoethane, crystallised from both water and alcohol–ether in tablets, m. p. 194—196° (Found : EtO, 10·9; Br, 19·1. $C_{23}H_{29}O_2N,HBr$ requires EtO, 10·4; Br, 18·5%).

3-*Piperidino*-1 : 1-*diphenylpropane* (VI; R = H).—A mixture of the cyanide (VI; R = CN) (2·3 g.), sodamide (0·9 g.), and benzene (25 ml.), refluxed for 3 hours and worked up as described for the butane (III; R = H), gave an oily base, which formed a *hydrochloride* crystallising from alcohol–ether in leaflets, m. p. 208—210° (Found : N, 4·45; Cl, 11·2. $C_{20}H_{25}N,HCl$ requires N, 4·44; Cl, 11·2%). The same base was obtained by heating the carboxylic acid (VI; R = CO_2H) at 230° for 5 minutes.

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Wellcome Research Laboratories, Langley Court, Beckenham, Kent.
Wellcome Chemical Works, Dartford, Kent.
Chelsea Polytechnic, London, S.W. 3.
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