444. *Search for New Analgesics. Part IV. Variations in the Basic Side-chain of Amidone.*

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With a Note on Some Pharmacological Results. By A. F. Green and A. C. White.

Ketones of types (I), (II), (XI), (XII), (XIII), and (XIV) (R being Alk·CO) have been prepared and, where necessary, their structures determined by established methods. Compounds bearing propionyl and 2-dialkylaminopropyl side-chains show maximal analgesic activity. The dibasic compounds (XVI and XVII; R = H) were obtained by reduction of the corresponding cyanides, but neither they nor their acetyl derivatives showed appreciable analgesic acitvity.

In Part III (*J.*, 1949, 648) several series of amidone analogues having considerable variations in the ketonic side-chain were described; those carrying a propionyl group showed maximal analgesic activity. In the work now described the emphasis has therefore been on varying the basic rather than the ketonic side-chain.

(*a*) 2-*Piperidinopropyl Series.*—A mixture of cyanides (I*a*) and (II*a*) was prepared by sodamide alkylation of diphenylmethyl cyanide with 2-chloro-1-piperidinopropane. At first only one of these cyanides (I*a*) was obtained but more recently both have been isolated (*Nature*,

(I.) $R{\cdot}CPh_2{\cdot}CHMe{\cdot}CH_2{\cdot}N{<}C_5H_{10}$

(*a*) R = CN (*b*) R = COMe (*c*) R = CEt:NH (*d*) R = COEt (*e*) R = CPr:NH (*f*) R = COPr

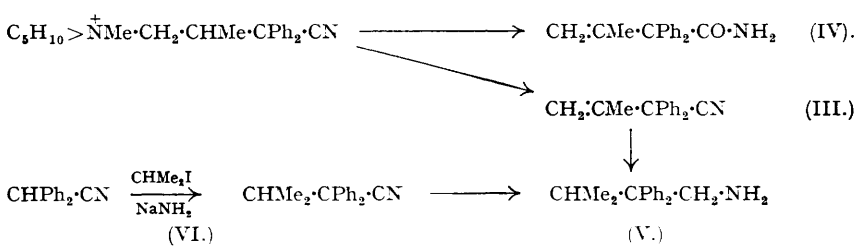
(II). $R{\cdot}CPh_2{\cdot}CH_2{\cdot}CHMe{\cdot}N{<}C_5H_{10}$

(*a*) R = CN (*b*) R = COMe (*c*) R = COEt (*d*) R = COPr (*e*) R = $CO{\cdot}NH_2$ (*f*) R = H

1949, **163**, 479) by methods described in the Experimental section. Each gave a series of ketones (I*b*, *d*, and *f*; II*b*, *c*, and *d*) with the corresponding Grignard reagents. As in the *iso*amidone series (Part III, *loc. cit.*), intermediate ketimines were encountered in the preparation of the three ketones (I*b*, *d*, and *f*), but only the ketimines (*Ic* and *e*) were isolated. There is thus evidence of increasing stability of the intermediate ketimines with increasing length of the associated side-chain.

The structures of compounds (I) and (II) have been determined by several methods.

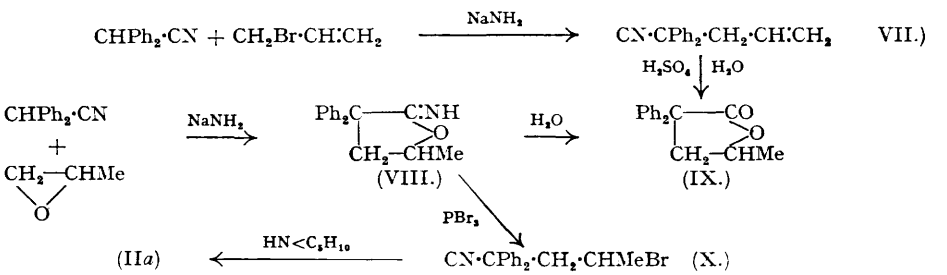
(i) Exhaustive methylation of the cyanide (I*a*) gave 1-methylpiperidine and 1 : 1-diphenyl-2-methylallyl cyanide (III), together with some 1 : 1-diphenyl-2-methylallylformamide (IV). The cyanide (III) was reduced to the primary amine (V) which was found to be identical with that



obtained by reduction of 1 : 1-diphenyl*iso*butyl cyanide (VI) (cf. *Nature*, 1949, **163**, 479; Schultz, Robb, and Sprague, *J. Amer. Chem. Soc.*, 1947, **69**, 2454).

(ii) The structure of the isomeric series (II) was confirmed by sodamide degradation of the cyanide (II*a*) and by hydrolysis of the ketone (II*c*) to give in both cases 3-piperidino-1 : 1-diphenylbutane (II*f*), which was identical with a specimen obtained by Dr. D. W. Adamson by an unambiguous method (cf. *J.*, 1949, S144). Attempts to prepare the butane (II*f*) by hydrolysis of the cyanide (II*a*) yielded only the corresponding amide (II*e*), which could not be further hydrolysed.

(iii) In addition the cyanide (II*a*) was synthesised from diphenylmethyl cyanide and propylene oxide by the unambiguous route described by Easton, Gardner, and Stevens (*J. Amer. Chem. Soc.*, 1947, **69**, 2941) :



In this synthesis, proof of the structure of (II*a*) was afforded by hydrolysis of the imino-tetrahydrofuran (VIII) to the lactone (IX), which was in turn obtained by condensation of diphenylmethyl cyanide and allyl bromide as shown in the scheme.

Structural proofs (i), (ii), and (iii) thus determined the positions of the branch methyl groups in the compounds of types (I) and (II).

In contrast with the results of Easton *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 76) who claimed to have obtained a third isomer of amidone, no such isomer was found during the working up of any other tertiary aminopropyl series. 4-Piperidino-1 : 1-diphenylbutyl cyanide (XI*a*) in particular might have been produced during the formation of the mixture of cyanides (I*a* and II*a*) by way of 3-piperidinopropylene, which in turn could have been formed by elimination of hydrogen chloride from 2-chloro-1-piperidinopropane. This possibility was, however, considered ruled out by the work described below.

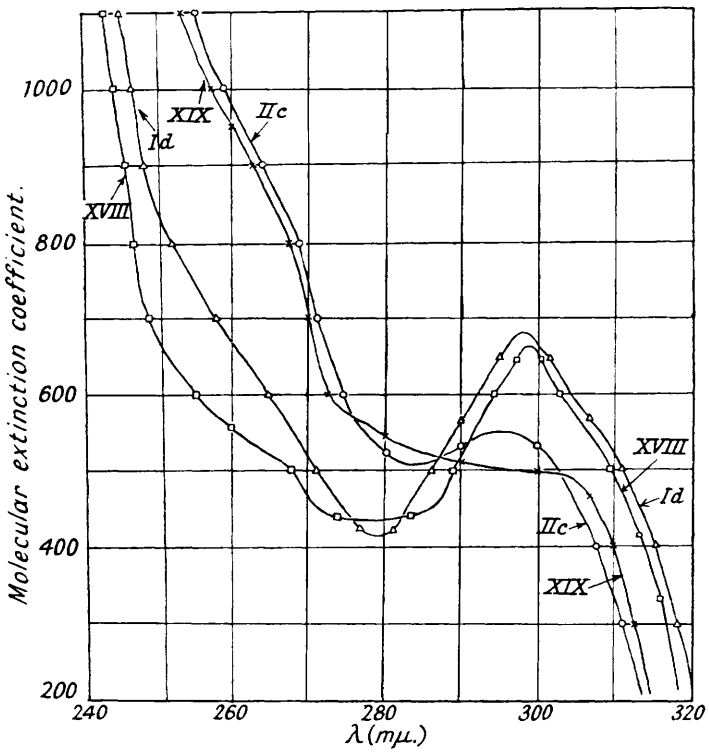
(*b*) 3-*Piperidinopropyl Series*.—The cyanide (XI*a*) was obtained from diphenylmethyl cyanide and 1-chloro-3-piperidinopropane [itself prepared from 3-piperidinopropan-1-ol (Hromatka, *Ber.*, 1942, **75***B*, 131)]; its hydrochloride was a well-defined crystalline compound different from those of cyanides (I*a*) and (II*a*). From it the corresponding acetyl, propionyl,

and *n*-butyryl derivatives (XI*b*, *c*, and *d*) were readily obtained without the production of stable ketimines (cf. however, Easton *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 76).

(XI.) $R{\cdot}CPh_2{\cdot}CH_2{\cdot}CH_2{\cdot}N{<}C_5H_{10}$
(*a*) R = CN (*c*) R = COEt
(*b*) R = COMe (*d*) R = COPr

(XII.) $R{\cdot}CPh_2{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2$
(*a*) R = CN (*d*) R = CO_2H
(*b*) R = COEt (*e*) R = CO_2Et
(*c*) R = $CO{\cdot}NH_2$ (*f*) R = H

(*c*) *2-Diethylaminoethyl Series.*—Earlier in this investigation several members of a 2-diethylaminoethyl series (XII*a*, *b*, *c*, *d*, *e*, and *f*) were prepared (cf. Part III, *loc. cit.*, and Dupré *et al.*, *J.*, 1949, 500), but further work on other 2-dialkylaminoethyl series * was abandoned when it



(XVIII) 6-*Dimethylamino*-4 : 4-*diphenyl*-5-*methylhexan*-3-*one* (iso*Amidone*). (I*d*) 6-*Piperidino*-4 : 4-*diphenyl*-5-*methylhexan*-3-*one*. (XIX) 6-*Dimethylamino*-4 : 4-*diphenylheptan*-3-*one* (*Amidone*). (II*c*) 6-*Piperidino*-4 : 4-*diphenylheptan*-3-*one*.

became apparent that the 2-dialkylaminopropyl side-chain was more effective in the development of analgesic activity.

$R{\cdot}CPh_2{\cdot}CHMe{\cdot}CH_2{\cdot}NEt_2$ (XIII.)
(*a*) R = CN
(*b*) R = CEt:NH
(*c*) R = COEt

$R{\cdot}CPh_2{\cdot}CH_2{\cdot}CHMe{\cdot}NEt_2$ (XIV.)
(*a*) R = CN
(*b*) R = COEt

$CH_2{:}CH{\cdot}CH_2{\cdot}CPh_2{\cdot}CO{\cdot}NH_2$ (XV.)

(*d*) *2-Diethylaminopropyl Series.*—The isomeric cyanides (XIII*a* and XIV*a*) were prepared from 2-chloro-1-diethylaminopropane and diphenylmethyl cyanide, and were separated from each other by taking advantage of the differing solubilities of their hydrochlorides in alcohol. Their structures were determined by exhaustive methylation. The methiodide of (XIII*a*) yielded the cyanide (III), whilst the methiodide of (XIV*a*) gave αα-diphenyl-β-vinylpropionamide (XV) and the lactone (IX) as degradation products (Schultz, Robb, and Sprague, *loc. cit.*).

With ethylmagnesium bromide the cyanide (XIII*a*) formed the ketimine (XIII*b*), which by

* A few other intermediates of this type are described in the Experimental Section.

hydrolysis was converted into the ketone (XIII*c*). On the other hand, only the ketone (XIV*b*) was isolated on similar treatment of the cyanide (XIV*a*).

It is of interest to note that in both the 2-piperidino- and 2-diethylamino-propyl series, the halide salts of the *iso*-compounds (I*a*) and (XIII*a*), owing to their higher melting points and lower solubilities, were more readily isolated than the corresponding salts in the normal series (II*a*) and (XIV*a*), whereas the reverse was the case in the original amidone series.

(*e*) *Miscellaneous Amidone Derivatives.*—Reduction of the cyanide precursors of amidone and *iso*amidone (Part III, *loc. cit.*) gave 1-amino-4-dimethylamino-2 : 2-diphenylpentane (XVI; R = H) and 1-amino-4-dimethylamino-2 : 2-diphenyl-3-methylbutane (XVII; R = H), from which the 1-acetamido- (XVI and XVII; R = COMe) and 1-phenylureido- (XVI; R = CO·NHPh) derivatives were prepared. No further work of this type is planned, as a number of similar derivatives have recently been described (*e.g.*, May and Mosettig, *J. Org. Chem.*, 1948, **13**, 459; Cheney *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 53, 57).

$NHR{\cdot}CH_2{\cdot}CPh_2{\cdot}CH_2{\cdot}CHMe{\cdot}NMe_2$ (XVI.)

$NHR{\cdot}CH_2{\cdot}CPh_2{\cdot}CHMe{\cdot}CH_2{\cdot}NMe_2$ (XVII.)

The authors are indebted to Dr. T. S. G. Jones for the ultra-violet absorption curves (shown in the figure) of pairs of isomeric ketones in two different dialkylaminopropyl series. It will be seen that these curves bear out the isomeric structures assigned to these ketones on the chemical evidence.

Pharmacological Results.—Several of the compounds described above were tested for analgesic activity in the rat and the results are summarised in the following table.

Pharmacological results.

	Salt.	Approx. analgesic activity (morphine = 1).	Approx. L.D. 50, I.V., mice, mg./kg.
Compound (I).			
R = COMe	HNO_3	0·2	30
CEt:NH	2HCl	nil	20
COEt	HBr	1·0	25
CPr:NH	2HBr	nil	40
COPr	HBr	0·25	30
Compound (II).			
R = COMe	HCl	0·2	15
COEt	HCl	2·4	15
COPr	HNO_3	nil	30
Compound (XI).			
R = COMe	H_2SO_4	nil	45
COEt	HBr	nil	40
COPr	H_2SO_4	nil	40
Compound (XII).			
R = COEt	HBr	0·1	30
Compound (XIII).			
R = CEt:NH	2HCl	nil	12
COEt	HBr	0·6	25
Compound (XIV).			
R = COEt	HBr	1·0	25
Compound (XVI).			
R = H	Base	nil	50
COMe	HBr	nil	80
Compound (XVII).			
R = H	HBr	nil	100
COMe	HBr	nil	110

(Activities less than 0·05 are described as nil.)

From these results it will be seen that :

(*a*) methyl branching in the basic side-chain, particularly in the β-position to the quaternary carbon atom, is an important factor in the development of analgesic activity;

(*b*) small variations in the basic group itself have a relatively minor effect;

(*c*) propionyl derivatives show maximal activity;

(*d*) the ketimines are inactive and apparently do not readily hydrolyse *in vivo* to give the active ketones;

(*e*) the dibasic compounds (XVI and XVII) are virtually inactive.

It should be noted that the above analgesic ratios will not necessarily be the same in other species. In the dog, for example, the ethyl ketones of types (II) and (XIV) have about half the activity of morphine, and the ethyl ketones of (I) and (XIII) have only a fifth to a tenth of the activity of morphine.

Experimental.

(M. p.s are uncorrected.)

3-Piperidino-1 : 1-diphenyl-2-methyl-n-propyl Cyanide (I*a*) *and 3-Piperidino-1 : 1-diphenyl-n-butyl Cyanide* (II*a*).—These two compounds have recently been mentioned (*Nature*, 1949, **163**, 479; Bockmühl

and Ehrhart, *Annalen*, 1948, **561**, 70), but details of their isolation, etc., were not given. The 2-chloro-1-piperidinopropane used in the preparation described below was obtained from 1-piperidinopropan-2-ol (Wenker, *J. Amer. Chem. Soc.*, 1938, **60**, 158), which was characterised as its *picrate*, hexagonal prisms (from alcohol), m. p. 134—135° (Found : N, 15·0. $C_8H_{17}ON,C_6H_3O_7N_3$ requires N, 15·1%) (cf. the picrate, m. p. 114—115°, of 2-piperidinopropan-1-ol, prepared from ethyl α-piperidinopropionate by Adkins and Pavlic, *J. Amer. Chem. Soc.*, 1947, **69**, 3040).

2-Chloro-1-piperidinopropane (35 g.) was added dropwise during 1 hour to a well-stirred suspension of sodamide (8·5 g.) in diphenylmethyl cyanide (52 g.) and dry benzene (100 ml.) at 40—50°. After a further 30 minutes, the mixture was refluxed for 5 hours and then decomposed with water (100 ml.). The benzene layer (plus washings) was extracted with dilute sulphuric acid, and the basic material (58 g.) regenerated by addition of alkali to the washed acid extract.

The pure cyanides (I*a* and II*a*) were isolated from this basic material by making use of the fact that as bases the cyanide (II*a*) tended to crystallise before the cyanide (I*a*), whereas in the form of their halide salts the reverse was the case. For example :

Method (a). The basic mixture (24 g.) with light petroleum (b. p. 60—80°) (50 ml.) at 0° gave first crops which recrystallised from the same solvent to give pure *cyanide* (II*a*) as hexagonal leaflets, m. p. 84—85° (Found : N, 8·8. $C_{22}H_{26}N_2$ requires N, 8·8%). The *hydrochloride* crystallised from alcohol–ether in needles, m. p. 200—201° (Found : N, 7·85; Cl, 10·0. $C_{22}H_{26}N_2,HCl$ requires N, 7·9; Cl, 10·0%), and the *hydrobromide* crystallised from the same solvent in leaflets, m. p. 170—172° (Found : N, 7·1; Br, 20·2. $C_{22}H_{26}N_2,HBr$ requires N, 7·0; Br, 20·1%). The *methiodide* crystallised from alcohol–ether in minute, slender, rectangular prisms, m. p. 169—171° (Found : N, 6·1; I, 27·6. $C_{23}H_{29}N_2I$ requires N, 6·1; I, 27·6%).

Later crops and the residues with hydrobromic acid formed a mixture of salts, which on fractional crystallisation from alcohol and a little ether gave the *hydrobromide* of the cyanide (I*a*) as long needles, m. p. 239—241° (Found : N, 7·0; Br, 20·3. $C_{22}H_{26}N_2,HBr$ requires N, 7·0; Br, 20·1%). The free *base* separated from light petroleum (b. p. 60—80°) in minute needles, m. p. 105—106° (Found : N, 8·8. $C_{22}H_{26}N_2$ requires N, 8·8%), and the *hydrochloride* crystallised from alcohol–ether in well-defined rectangular prisms, m. p. 226—227° (Found : N, 7·95; Cl, 10·6. $C_{22}H_{26}N_2,HCl$ requires N, 7·9; Cl, 10·0%). The *methiodide* crystallised from alcohol in minute, pointed prisms, m. p. 228—229° (Found : N, 6·1; I, 27·5. $C_{23}H_{29}N_2I$ requires N, 6·1; I, 27·6%).

Method (b). The basic mixture (80 g.) from the sodamide reaction was distilled and the fraction (74 g.), b. p. 206—234°/5 mm., converted into a mixture of hydrobromides. Treatment of the anhydrous hydrobromides with acetone (230 ml.) gave the hydrobromide of cyanide (I*a*) (32 g.) in pure form. The mother liquors yielded basic material, which on crystallisation gave the cyanide (II*a*).

5-Piperidino-3 : 3-diphenyl-4-methylpentan-2-one (Ib).—The cyanide (I*a*) (10 g.) in xylene (10 ml.) was added to the Grignard reagent from methyl iodide (13·6 g.), magnesium (2·3 g.), and dry ether (25 ml.). After 4 hours at 100° the xylene was removed under reduced pressure, and the reaction product decomposed with concentrated sodium hydroxide solution and taken to dryness. The residue was extracted with ether, which was then shaken with dilute hydrochloric acid. After removal of some unchanged cyanide hydrochloride, which separated, the acid solution was evaporated to dryness. The residue was taken up in methyl ethyl ketone, and (after removal of a small amount of ammonium chloride) precipitated with ether. The resulting deliquescent hydrochloride was converted through the oily base into the *pentanone nitrate*, which crystallised from water in tablets and from alcohol in needles, m. p. 195° (decomp.) (Found : N, 6·9. $C_{23}H_{29}ON,HNO_3$ requires N, 7·0%).

6-Piperidino-4 : 4-diphenyl-5-methylhexan-3-one (I*d*).—The cyanide (I*a*) (32 g.) in xylene (30 ml.) was added to the Grignard reagent from magnesium (7·3 g.), ethyl bromide (32·7 g.), and ether (75 ml.), and the product extracted with ether, as described above. After purification of this extract through the acid solution, the resulting basic oil (26·5 g.) was dissolved in alcoholic hydrogen chloride, and the solution evaporated to dryness. The residue, refluxed with methyl ethyl ketone, yielded the insoluble *dihydrochloride* of the ketimine (I*c*) (18·2 g.), which crystallised from alcohol in needles, m. p. 193° (decomp.), very soluble in water (Found : N, 6·6; Cl, 16·7. $C_{24}H_{32}N_2,2HCl$ requires N, 6·7; Cl, 16·8%).

The ketimine dihydrochloride, refluxed for 2·5 hours with 20% hydrobromic acid (75 ml.), gave an oily hydrobromide layer, which was purified by conversion through the base into the *ketone hydrochloride* (as I*d*); this formed needles, m. p. 197—198°, from methyl ethyl ketone (Found : N, 3·75; Cl, 9·15. $C_{24}H_{31}ON,HCl$ requires N, 3·6; Cl, 9·2%). The *hydrobromide* crystallised in needles, m. p. 208—209° (Found : N, 3·3; Br, 18·7. $C_{24}H_{31}ON,HBr$ requires N, 3·3; Br, 18·6%), and the *hydrogen sulphate* as micro-crystals, m. p. 219—221° (Found : N, 3·15; S, 7·2. $C_{24}H_{31}ON,H_2SO_4$ requires N, 3·1; S, 7·15%), both from alcohol–ether.

1-Piperidino-3 : 3-diphenyl-2-methylheptan-4-one (I*f*).—The cyanide (I*a*) (10 g.) in xylene (10 ml.) was added to *n*-propylmagnesium bromide (18·5 g.) in ether (25 ml.), and the mixture heated at 100° for 5 hours. The basic oil, extracted as described above, was converted into the hydrobromide, which, after being washed with hot methyl ethyl ketone and crystallised from alcohol–ether, gave the *ketimine dihydrobromide* (I*e*) as granules, m. p. 215—216° (Found : N, 5·3; Br, 30·8. $C_{25}H_{34}N_2,2HBr$ requires N, 5·3; Br, 30·5%). The *dihydrochloride*, purified in the same way, melted at 192—194° (Found : N, 6·1; Cl, 16·2. $C_{25}H_{34}N_2,2HCl$ requires N, 6·4; Cl, 16·3%).

The dihydrobromide (I*e*) (6 g.), refluxed for 2 hours with 20% hydrobromic acid (30 ml.), gave an oily lower layer, which, after being washed with water and recrystallised first from methyl ethyl ketone and then from alcohol–ether, gave the *ketone hydrobromide* (as I*f*) as rectangular plates, m. p. 205—206° (Found : N, 3·25; Br, 17·7. $C_{25}H_{23}ON,HBr$ requires N, 3·15; Br, 18·0%).

5-*Piperidino*-3 : 3-*diphenylhexan*-2-*one* (II*b*).—The basic oily product (14 g.) from the cyanide (II*a*) (18 g.) in xylene (25 ml.) and methylmagnesium iodide (28·3 g.) in ether (45 ml.), prepared and isolated as described in previous examples, gave the *ketone hydrochloride* (as II*b*) as crystalline granules (5·5 g.), m. p. 174—175°, from alcohol–ether (Found : N, 3·8; Cl, 9·6. $C_{23}H_{29}ON$,HCl requires N, 3·8; Cl, 9·5%).

6-*Piperidino*-4 : 4-*diphenylheptan*-3-*one* (II*c*).—The basic reaction product from (II*a*) (10·6 g.) in xylene (50 ml.) and ethylmagnesium bromide (13·5 g.) in ether (50 ml.) was extracted with hydrochloric acid. On cooling, crude *ketone hydrochloride* (as II*c*) separated and was purified by crystallisation first from water (plus a little hydrochloric acid) and then from wet alcohol–ether. It formed minute prisms, m. p. 123—126° (Found : N, 3·45; Cl, 9·3. $C_{24}H_{31}ON$,HCl requires N, 3·6; Cl, 9·2%) (Bockmühl and Ehrhart, *loc. cit.*, have recorded m. p. 189° for this hydrochloride). The *hydrobromide*, m. p. 103—106°, crystallised from water (Found : N, 3·4; Br, 18·5. $C_{24}H_{31}ON$,HBr requires N, 3·3; Br, 18·6%), and the *picrate* from alcohol in rectangular prisms, m. p. 137—138° (Found : N, 9·65. $C_{24}H_{31}ON,C_6H_3O_7N_3$ requires N, 9·7%).

7-*Piperidino*-5 : 5-*diphenyloctan*-4-*one* (II*d*).—The product (9·5 g.), from the cyanide (II*a*) (10 g.) and *n*-propylmagnesium iodide (18·5 g.), gave a deliquescent hydrochloride, but its *nitrate* was sparingly soluble in water and crystallised from alcohol in pyramidal tablets, m. p. 167° (decomp.) (Found : N, 6·5. $C_{25}H_{33}ON,HNO_3$ requires N, 6·6%).

γ-*Piperidino*-αα-*diphenylvaleramide* (II*e*).—The cyanide (II*a*) (4 g.) was heated with 66% v/v sulphuric acid at 180° for 5 minutes. The mixture, which had darkened considerably, was then diluted with water and made alkaline. The semi-solid *amide* that separated crystallised from dilute alcohol in tablets, m. p. 156—157° (Found : N, 8·4. $C_{22}H_{26}ON_2$ requires N, 8·3%).

3-*Piperidino*-1 : 1-*diphenylbutane* (II*f*).—*Method* (a). A well-stirred suspension of sodamide (5 g.) in a solution of the cyanide (II*a*) (5 g.) in toluene (20 ml.) was refluxed for 6 hours and then decomposed with dilute hydrochloric acid. The ether-washed aqueous layer was made alkaline and extracted with ether. The ethereal residue with light petroleum afforded some unchanged cyanide (II*a*) (3 g.), m. p. 83°, but the oil from the mother-liquors gave the butane hydrochloride (as II*f*) as rectangular plates, m. p. 211—212°, from alcohol–ether (Found : N, 4·3; Cl, 10·7. Calc. for $C_{21}H_{27}N$,HCl : N, 4·25; Cl, 10·7%) (Bockmühl and Ehrhart, *loc. cit.*, give m. p. 214—215°). *Method* (b). The propionyl (II*c*) hydrochloride (1·6 g.), ethylene glycol (10 ml.), and finely-divided potassium hydroxide (2 g.) were refluxed together for 17 hours. The basic product, extracted with ether, was dissolved in hydrochloric acid, and from this the butane hydrochloride (as II*f*) (0·5 g.) was readily isolated by reason of its low solubility in hot methyl ethyl ketone.

Determination of the Structure of the Cyanide (I*a*) *by Exhaustive Methylation*.—The methiodide of the cyanide (I*a*) (42 g.), dissolved in water (3 l.) at 90—95°, was treated with moist silver oxide freshly prepared from silver nitrate (46·5 g.). After being stirred vigorously for 30 minutes at this temperature, the suspension was filtered and the filtrate concentrated *in vacuo* to a syrup (*A*). The distillate, absorbed in dilute hydrochloric acid and made alkaline, gave an ethereal extract which, on distillation, afforded 1-methylpiperidine (4·2 g.), b. p. 105—107°; picrate, m. p. 222° (Found : C, 43·9; H, 4·9; N, 17·0. Calc. for $C_6H_{13}N,C_6H_3O_7N_3$: C, 43·9; H, 4·9; N, 17·1%). The undistilled syrup (*A*) was shaken with water and ether. The ethereal extract on distillation gave 1 : 1-diphenyl-2-methylallyl cyanide (III) (12·5 g.), b. p. 162—165°/4 mm., m. p. 64—65° (Found : C, 87·4; H, 6·3; N, 6·2. Calc. for $C_{17}H_{15}N$: C, 87·5; H, 6·4; N, 6·0%) [cf. Schultz, Robb, and Sprague, *loc. cit.*], and a residual solid, which on being washed with ether and crystallised from aqueous alcohol gave 1 : 1-*diphenyl*-2-*methylallylformamide* (IV) as slender needles, m. p. 180—181° (Found : C, 81·2; H, 6·85; N, 5·5. $C_{17}H_{17}ON$ requires C, 81·2; H, 6·8; N, 5·6%).

Hydrogenation of (III) (11·8 g.), as described by Schultz, Robb, and Sprague (*loc. cit.*), gave 2 : 2-diphenyl-3-methyl-*n*-butylamine (V) (10·3 g.), b. p. 128—136°/0·1 mm. (Found : N, 5·5. Calc. for $C_{17}H_{17}N$: N, 5·85%). Its *phenylureido*-derivative (needles, m. p. 204—205°, from alcohol) (Found : C, 80·3; H, 7·2; N, 7·8. $C_{24}H_{26}ON_2$ requires C, 80·5; H, 7·3; N, 7·8%) gave no m. p. depression on admixture with the same derivative of the butylamine synthesised from diphenylmethyl cyanide and *iso*propyl iodide (Schultz *et al.*, *loc. cit.*). For purposes of comparison the isomeric 2 : 2-diphenyl-*n*-amylamine was synthesised from diphenylmethyl cyanide and *n*-propyl iodide (Schultz *et al.*, *loc. cit.*) and its *phenylureido*-derivative prepared (needles, m. p. 194°, from alcohol) (Found : C, 80·6; H, 7·5; N, 7·8. $C_{24}H_{26}ON_2$ requires C, 80·5; H, 7·3; N, 7·8%).

Confirmation of the Structure of the Cyanide (II*a*) *by an Alternative Synthesis*.—3-Bromo-1 : 1-diphenyl-*n*-butyl cyanide (X) (20 g.) (prepared by the method of Easton *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 2941), was refluxed with piperidine (14·5 g.) for 12 hours, and, after cooling, excess of 40% sodium hydroxide was added. The mixture was extracted with ether, and the ethereal solution shaken with dilute acid. Fractionation of the base, liberated from the acid extract, yielded the cyanide (II*a*) as a viscous oil, b. p. 224—228°/2·5 mm., which crystallised from light petroleum in hexagonal leaflets, m. p. 81—82°, identical with the product already described.

1-*Chloro*-3-*piperidinopropane*.—3-Piperidinopropan-1-ol (174 g.) (prepared in 94% yield from piperidine, allyl alcohol, and sodium, as described by Hromatka, *loc. cit.*) in benzene (175 ml.) was added to a stirred solution of thionyl chloride (145 g.) in the same solvent (145 ml.) at 0°. After 2 hours' refluxing, the resulting solid hydrochloride (231 g.) was collected and washed with benzene and ether. It crystallised from alcohol–ether in slender rectangular plates, m. p. 213—214° (Found : N, 6·9; Cl, 35·8. Calc. for $C_8H_{16}NCl$,HCl : N, 7·1; Cl, 35·8%).

4-*Piperidino*-1 : 1-*diphenyl*-n-*butyl Cyanide* (XI*a*).—1-Chloro-3-piperidinopropane [from the hydrochloride (34 g.)] reacted with diphenylmethyl cyanide (42 g.) in dry benzene (85 ml.) in the presence of sodamide (6·8 g.), and the basic product (38 g.) was isolated as described for the cyanides (I*a*) and (II*a*). Distillation yielded an oily base (35 g., 64%), b. p. 223—228°/3·5 mm., which gave a *hydrochloride* crystallising from methyl ethyl ketone in octahedral plates, m. p. 187—188° (Found : N, 8·0; Cl, 10·0. $C_{22}H_{26}N_2$,HCl requires N, 7·9; Cl, 10·0%). The *hydrogen sulphate* crystallised from alcohol in long

slender prisms, m. p. 160—161°, almost insoluble in methyl ethyl ketone (Found : N, 6·75; S, 7·7. $C_{22}H_{26}N_2,H_2SO_4$ requires N, 6·7; S, 7·7%).

6-*Piperidino*-3 : 3-*diphenylhexan*-2-*one* (XI*b*).—The product from the reaction of (XI*a*) (16·5 g.) in xylene with methylmagnesium iodide (25·8 g.) in ether was isolated. This oily ketone (XI*b*), b. p. 220—224°/2·5 mm., gave a *hydrogen sulphate* crystallising from alcohol in slender prisms, m. p. 172—173° (Found : N, 3·3; S, 7·4. $C_{23}H_{29}ON,H_2SO_4$ requires N, 3·2; S, 7·4%), and a *hydrobromide* as rectangular plates, m. p. 209—210°, from the same solvent (Found : N, 3·4; Br, 19·3. $C_{23}H_{29}ON,HBr$ requires N, 3·4; Br, 19·2%).

7-*Piperidino*-4 : 4-*diphenylheptan*-3-*one* (XI*c*).—Distillation of the basic oil from interaction of (XI*a*) (12·5 g.) and ethylmagnesium bromide (15·9 g.) in xylene gave the *ketone* (XI*c*), b. p. 228—232°/2·5 mm. (Found : N, 4·0. $C_{24}H_{31}ON$ requires N, 4·0%), which afforded a *hydrobromide* as rectangular prisms, m. p. 150—151°, from methyl ethyl ketone–ether (Found : N, 3·3; Br, 18·7. $C_{24}H_{31}ON,HBr$ requires N, 3·25; Br, 18·6%), and a microcrystalline *hydrogen sulphate*, m. p. 192—193°, from ethyl alcohol (Found : N, 3·5; S, 7·1. $C_{24}H_{31}ON,H_2SO_4$ requires N, 3·1; S, 7·15%).

8-*Piperidino*-5 : 5-*diphenyloctan*-4-*one* (XI*d*).—This was prepared from (XI*a*) (14·6 g.) and *n*-propylmagnesium iodide (3 mols.). It boiled at 231—233°/2 mm., and was purified by conversion into the *hydrogen sulphate*; micro-crystals, m. p. 193—194°, from alcohol (Found : N, 3·35; S, 7·0. $C_{25}H_{33}ON,H_2SO_4$ requires N, 3·0; S, 6·9%). Its *hydrobromide* formed parallelogrammatic plates, m. p. 154—155°, from methyl ethyl ketone–ether (Found : N, 3·2; Br, 18·3. $C_{25}H_{33}ON,HBr$ requires N, 3·15; Br, 18·0%).

Preparation of Compounds of the Type (XII).—3-Diethylamino-1 : 1-diphenylpropyl cyanide (XII*a*) was prepared in a manner similar to that subsequently described by Dupré *et al.* (*loc. cit.*). It formed a *hydrobromide*, crystallising from alcohol–ether in rectangular leaflets, m. p. 131—132° (Found : N, 7·4; Br, 21·4. $C_{20}H_{24}N_2,HBr$ requires N, 7·5; Br, 21·4%), and a *methiodide*, crystallising from alcohol in long needles, m. p. 185—190° (Found : N, 6·8; I, 28·9. $C_{21}H_{27}N_2I$ requires N, 6·4; I, 29·3%).

With ethylmagnesium bromide (XII*a*) afforded the ketone (XII*b*) (cf. Dupré *et al.*, *loc. cit.*), the *hydrobromide* of which crystallised from alcohol–ether in prisms, m. p. 116—119° (Found : N, 3·4. $C_{22}H_{29}ON,HBr$ requires N, 3·5%).

A solution of (XII*a*) (2 g.) in 50% sulphuric acid (5 ml.), refluxed for 1 hour, diluted, made alkaline, and cooled, gave *γ-diethylamino-αα-diphenylbutyramide* (XII*c*) as a crystalline precipitate, m. p. 80—86° (Found : N, 8·8. $C_{20}H_{26}ON_2$ requires N, 9·0%). The neutralised filtrate, on concentration *in vacuo*, gave the corresponding carboxylic acid (XII*d*) as a white precipitate, m. p. 183—184° (decomp.) (Found : N, 4·6. Calc. for $C_{20}H_{25}O_2N$: N, 4·5%).

Treatment of (XII*d*) with excess of diazomethane in ether for 3 days at room temperature gave a solution of the ethyl ester (XII*e*), the *methiodide* of which crystallised from alcohol–ether in clusters of needles, m. p. 133—135° (Found : OEt, 9·4; I, 26·3. $C_{23}H_{32}O_2NI$ requires OEt, 9·4; I, 26·4%). The same acid, heated at 200° for 20 minutes, made alkaline and extracted with ether, afforded 3-diethylamino-1 : 1-diphenylpropane (XII*f*) (Eisleb, *Ber.*, 1941, **74**, 1438), which formed a *hydrobromide*, crystallising in needles, m. p. 131—132° (Found : N, 4·0; Br, 23·3. $C_{19}H_{25}N,HBr$ requires N, 4·0; Br, 23·0%), and a methiodide crystallising in prisms, m. p. 158—159° (Adamson, *loc. cit.*) (Found : N, 3·6; I, 30·9. Calc. for $C_{20}H_{28}NI$: N, 3·4; I, 31·1%), both from alcohol–ether.

3-*Diethylamino*-1 : 1-*diphenyl*-2-*methyl*-n-*propyl Cyanide* (XIII*a*) and 3-*Diethylamino*-1 : 1-*diphenyl*-n-*butyl Cyanide* (XIV*a*).—A well-stirred solution of 2-chloro-1-diethylaminopropane (48 g.) (from its hydrochloride; Kerwin *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 2964) and diphenylmethyl cyanide (65 g.) in dry benzene (200 ml.) at 70—80° was treated with sodamide (13 g.) in small portions and the reaction completed by heating and stirring the solution for 1 hour more. The mixture was then decomposed with water, the benzene removed *in vacuo*, and the residual oily mixture extracted with ether. The ethereal extract was shaken with dilute hydrochloric acid, and the acid extract taken to dryness. Fractional crystallisation of the residue from alcohol eventually gave the less-soluble cyanide (XIII*a*) *hydrochloride* as tablets, m. p. 234—238° (Found : N, 8·3; Cl, 10·7. $C_{21}H_{26}N_2,HCl$ requires N, 8·2; Cl, 10·4%), and the more-soluble cyanide (XIV*a*) *hydrochloride* as rectangular prisms, m. p. 165—167° (Found : N, 8·3; Cl, 10·6. $C_{21}H_{26}N_2,HCl$ requires N, 8·2; Cl, 10·4%). The *hydrobromide* of (XIII*a*) [tablets, m. p. 241—242° (Found : N, 7·5; Br, 21·1. $C_{21}H_{26}N_2,HBr$ requires N, 7·2; Br, 20·7%)] was likewise less soluble in both alcohol and water than the *hydrobromide* of (XIV*a*) [rectangular plates, m. p. 189—190° (Found : N, 7·5; Br, 21·2. $C_{21}H_{26}N_2,HBr$ requires N, 7·2; Br, 20·7%)], but this difference could not be used in their separation as they appeared to form a eutectic mixture (1 : 1), which melted steadily at 185—190°, despite several recrystallisations.

The *base* (XIII*a*) crystallised slowly from its evaporating solution in light petroleum (b. p. 60—80°) in rectangular plates, m. p. 43—46° (Found : N, 9·2. $C_{21}H_{26}N_2$ requires N, 9·15%), but the base (XIV*a*) could not be induced to crystallise.

The *methiodide* of (XIII*a*) crystallised from alcohol in slender prisms, m. p. 228° (decomp.), sparingly soluble in water (Found : N, 5·5; I, 26·0. $C_{22}H_{29}N_2I$ requires N, 6·25; I, 28·3%). The *methiodide* of (XIV*a*) crystallised from alcohol–ether in needles, m. p. 177—179° (Found : N, 5·8; I, 25·5. $C_{22}H_{29}N_2I$ requires N, 6·25; I, 28·3%), but separated from water as an oil.

Determination of the Structure of (XIII*a*) *and of* (XIV*a*).—A solution of the methiodide of (XIII*a*) (7 g.) in hot water (250 ml.) was poured into silver oxide (from 7·5 g. of silver nitrate) suspended in water (50 ml.). After being boiled gently for 1 hour and filtered, the liquid was evaporated *in vacuo*, and the oil that separated was extracted with ether. On removal of the solvent, this oil solidified and was crystallised from light petroleum (b. p. 40—60°) to give 1 : 1-diphenyl-2-methylallyl cyanide (III), m. p. 62—63°, identical with that obtained as already described. The methiodide of (XIV*a*), similarly treated with

silver oxide, afforded a product which on being washed with light petroleum (b. p. 60—80°) gave a solid crystallising from benzene–light petroleum in square tablets, m. p. 156—158° (Found : N, 5·6. Calc. for $C_{17}H_{17}ON$: N, 5·6%). This very probably consisted of αα-diphenyl-β-vinylpropionamide (XV), as it differed from (IV) but was apparently identical with the amide obtained from 3-dimethylamino-1 : 1-diphenyl-*n*-butyl cyanide by Schultz *et al.* (*loc. cit.*). The ether-extracted mother-liquors on acidification gave the lactone (IX), m. p. 111—112° (Found : C, 81·0; H, 6·4. Calc. for $C_{17}H_{16}O_2$: C, 81·2; H, 6·3%), identical with that obtained by hydrolysis of 1 : 1-diphenylbut-3-enyl cyanide (VII) (Easton *et al.*, *loc. cit.*).

6-*Diethylamino*-4 : 4-*diphenyl*-5-*methylhexan*-3-*one* (XIII*c*).—A portion of the basic oil (11 g.) from the interaction of (XIII*a*) (12 g.) and ethylmagnesium bromide (11·8 g.) in xylene on distillation gave a fraction, b. p. 148—150°/0·05 mm., probably (analysis) the intermediate *ketimine* (XIII*b*) (Found : N, 8·3. $C_{23}H_{32}N_2$ requires N, 8·3%), which afforded a *dihydrochloride*, crystallising from alcohol–ether in leaflets, m. p. 179—180° (Found : N, 6·4; Cl, 17·0. $C_{23}H_{32}N_2$,2HCl requires N, 6·8; Cl, 17·3%). The bulk of the basic oil was therefore refluxed with 20% hydrobromic acid for 3 hours and the product diluted with water. After 2 days at 0°, the solid that had separated was crystallised from alcohol–ether to give the ketone (XIII*c*) *hydrobromide* as prisms, m. p. 189—191° (Found : N, 3·2; Br, 19·3. $C_{23}H_{31}ON$,HBr requires N, 3·35; Br, 19·1%). The corresponding *hydrochloride*, m. p. 166—169° (Found : N, 3·7; Cl, 9·7. $C_{23}H_{31}ON$,HCl requires N, 3·75; Cl, 9·5%), showed a depression in m. p. on admixture with the above ketimine dihydrochloride.

6-*Diethylamino*-4 : 4-*diphenylheptan*-3-*one* (XIV*b*).—The basic oil from the interaction of (XIV*a*) (17 g.) and ethylmagnesium bromide (17 g.) was dissolved in hydrochloric acid, and the solution evaporated to dryness. The residue when treated with acetone gave some ammonium chloride, which was removed, and a filtrate, which on evaporation and reconversion into the base afforded the ketone (XIV*b*) *hydrobromide* as well-defined needles, m. p. 135—138° (shrinking at 115—120°), from alcohol–ether (Found : N, 3·2. $C_{23}H_{31}ON$,HBr requires N, 3·35%).

N-*Benzyl*-N-*methyl*-2-*aminoethyl Chloride*.*—*N*-Benzyl-*N*-methyl-2-aminoethanol (33 g.), b. p. 133—136°/14 mm., was prepared by interaction of benzylmethylamine (56 g.) and ethylene oxide (28 ml.) under pressure at 65° for 3 hours and fractionation of the product (Mannich and Kuphal used benzylmethylamine and ethylene chlorohydrin, *Arch. Pharm.*, 1912, **250**, 542). With thionyl chloride (19·5 ml.) in chloroform (50 ml.) this gave N-*benzyl*-N-*methyl*-2-*aminoethyl chloride hydrochloride* (30 g.), which crystallised readily from alcohol–ether in needles, m. p. 140—141° (Found : N, 6·6; Cl, 32·3. $C_{10}H_{14}NCl$,HCl requires N, 6·4; Cl, 32·3%).

3-(*Benzylmethylamino*)-1 : 1-*diphenylpropyl Cyanide*.—Dupré *et al.* (*loc. cit.*) have recently prepared this compound and the corresponding ketone by way of 3-bromo-1 : 1-diphenylpropyl cyanide.

Diphenylmethyl cyanide (8 g.), *N*-benzyl-*N*-methyl-2-aminoethyl chloride (9 g.), and sodamide (2 g.) reacted in dry benzene as described for the preparation of the cyanides (XIII*a*) and (XIV*a*). The product was decomposed with water, evaporated to remove benzene, and extracted with ether. The ethereal extract, with hydrochloric acid, was converted into a sparingly-soluble oily hydrochloride which, after being washed with ether, was dissolved in chloroform. As the hydrochloride failed to crystallise it was converted into the base and distilled; the fraction, b. p. 220—230°/0·4 mm., gave a *methiodide* which crystallised from alcohol in rectangular prisms, m. p. 204—206° (Found : N, 5·5; I, 26·9. $C_{25}H_{27}N_2I$ requires N, 5·8; I, 26·4%).

6-(*Benzylmethylamino*)-4 : 4-*diphenylhexan*-3-*one*.—This was prepared from the corresponding cyanide and ethylmagnesium bromide and gave an oily, sparingly-soluble hydrochloride,† and a crystalline *methiodide* [needles, m. p. 189—190°, from alcohol–ether (Found : I, 25·1. $C_{27}H_{32}ONI$ requires I, 24·8%)], which showed a depression in m. p. on admixture with the corresponding cyanide methiodide.

2-*Dicyclohexylaminoethyl Chloride*.—2-Di*cyclo*hexylaminoethanol (55 g.), b. p. 178—182°/14 mm., was prepared in improved yield (73%) by the interaction of ethylene oxide (15 ml.) and di*cyclo*hexylamine (60 ml.) under pressure at 100° for 2 hours, then at 150° for two more hours, and finally at 200° for 6 hours, followed by fractionation of the product (Blicke and Maxwell, *J. Amer. Chem. Soc.*, 1942, **64**, 429, obtained a 55% yield from di*cyclo*hexylamine and ethylene chlorohydrin). Di*cyclo*hexylaminoethyl chloride hydrochloride, from the alcohol and thionyl chloride (B.P. 351,605), crystallised from alcohol–ether in minute cubes, m. p. 184° (Found : N, 5·0; Cl, 25·8. Calc. for $C_{14}H_{26}NCl$,HCl : N, 5·0; Cl, 25·4%).

3-*Dicyclohexylamino*-1 : 1-*diphenylpropyl Cyanide*.—The product from the interaction in benzene of diphenylmethyl cyanide (8 g.), di*cyclo*hexylaminoethyl chloride (12 g.), and sodamide (1·9 g.) [obtained as described under 3-benzylmethylamino-1 : 1-diphenylpropyl cyanide] was extracted with ether, and the extract washed with dilute hydrochloric acid. The residue obtained by evaporation of the acid washings was crystallised from alcohol–ether and gave the *cyanide hydrochloride* as hexagonal tablets, m. p. 196—198°, sparingly soluble in water (Found : N, 6·3; Cl, 8·0. $C_{28}H_{36}N_2$,HCl requires N, 6·4; Cl, 8·15%). The cyanide base, m. p. 71—75°, with methyl iodide under pressure at 100° gave a *methiodide*, m. p. 104—110°, from alcohol–ether (Found : N, 5·3; I, 23·4. $C_{29}H_{39}N_2I$ requires N, 5·2; I, 23·4%).

6-*Dicyclohexylamino*-4 : 4-*diphenylhexan*-3-*one*.—The product from the interaction of the preceding cyanide and ethylmagnesium bromide gave an amorphous *ketone hydrochloride* (Found : N, 3·3; Cl, 7·9. $C_{30}H_{41}ON$,HCl requires N, 3·0; Cl, 7·6%) and a crystalline methiodide, m. p. 187—192°.

4-*Dimethylamino*-2 : 2-*diphenylamylamine* (XVI; R = H).—3-Dimethylamino-1 : 1-diphenylbutyl cyanide (Part III, *loc. cit.*) (10 g.), liquid ammonia (20 ml.), and Raney nickel (3 g.) in methyl alcohol

* Bergel *et al.* (*J.*, 1944, 269) have used this base without describing it.

† Bockmühl and Ehrhart (*loc. cit.*) give m. p. 142—143° for this hydrochloride but do not describe its preparation.

(50 ml.) were treated with hydrogen at 170° (5 atmospheres) for 8 hours. The filtered product on distillation gave an oil, b. p. 214—218°/15 mm., which later solidified. Crystallisation from light petroleum (b. p. 60—80°) gave (XVI; R = H) as prisms, m. p. 67—70° (Found: N, 9·7. $C_{19}H_{26}N_2$ requires N, 9·5%). Its *acetyl* derivative (XVI; R = COMe) crystallised from light petroleum (b. p. 60—80°) in rectangular tablets, m. p. 119—121° (Found: N, 8·6. $C_{21}H_{28}ON_2$ requires N, 8·6%), and gave a *hydrobromide* as needles, m. p. 227—229°, from alcohol–ether (Found: N, 6·8; Br, 19·7. $C_{21}H_{28}ON_2$,HBr requires N, 6·9; Br, 19·7%). The *phenylureido*-derivative (XVI; R = CO·NHPh) crystallised from benzene-light petroleum in rectangular granules, m. p. 170—173° (Found: N, 10·6. $C_{26}H_{31}ON_3$ requires N, 10·5%), which gave a somewhat gelatinous *hydrochloride*, m. p. 234—238°, from water (Found: N, 9·7. $C_{26}H_{31}ON_3$,HCl requires N, 9·6%).

4-*Dimethylamino*-2 : 2-*diphenyl*-3-*methylbutylamine* (XVII; R = H).—This *amine*, b. p. 218—220°/15 mm., was prepared by hydrogenation of 3-dimethylamino-1 : 1-diphenyl-2-methylpropyl cyanide (Part III, *loc. cit.*) as described above for the amylamine (XVI; R = H); it gave a *dihydrobromide* as minute granules, m. p. 231—232°, from alcohol–ether (Found for the base: N, 10·3. $C_{19}H_{26}N_2$ requires N, 9·5%. Found for the dihydrobromide: N, 6·5; Br, 35·9. $C_{19}H_{26}N_2$,2HBr requires N, 6·3; Br, 36·0%). Its *acetyl* derivative (XVII; R = COMe) crystallised from light petroleum (b. p. 60—80°) in small needles, m. p. 104—106° (Found: N, 8·6. $C_{21}H_{28}ON_2$ requires N, 8·6%), and formed a *hydrobromide* crystallising from alcohol–ether in granules, m. p. 219—221° (Found: N, 6·6; Br, 19·8. $C_{21}H_{28}ON_2$,HBr requires N, 6·9; Br, 19·7%).

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