

#### 114. Analgesics. Part II. The Synthesis of Amidone and Some of its Analogues.

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Treatment of 1-chloro-2-dimethylaminopropane with diphenylmethyl cyanide in the presence of sodamide gave a mixture of compounds, from which 3-dimethylamino-1:1-diphenylbutyl cyanide (II) was isolated in 36% overall yield. Amidone (III) was obtained from (II) by treatment with ethylmagnesium iodide. Both 1-chloro-2-morpholinopropane and 2-chloro-1-morpholinopropane, on reaction with diphenylmethyl cyanide, gave a mixture of 1:1-diphenyl-3-morpholinobutyl cyanide (VIII) and 1:1-diphenyl-3-morpholinoisobutyl cyanide (XI), both of which have been converted into the corresponding ethyl ketones.

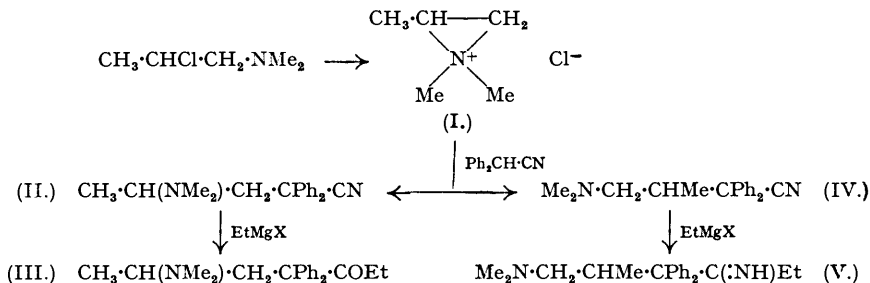
Treatment of diphenylmethyl cyanide with ethylene oxide or propylene oxide gave lactones instead of the hydroxy-cyanides required. Attempts to prepare the cyanide (VIII) by addition of hydrogen bromide or hydrogen iodide to 1:1-diphenylbut-3-enyl cyanide (XII) and reaction of the product with morpholine gave the required compound, but only in poor yield. Attempts to reduce selectively the double bond of 3-bromo-1:1-diphenylbut-3-enyl cyanide (XXI) were unsuccessful.

THE preparation in Germany of 6-dimethylamino-4:4-diphenylheptan-3-one (III; amidone) and the clinical testing of the compound as an analgesic were referred to in Part I. The German method of preparation, as described by Kleiderer *et al.* (Report No. 981, Office of the Publication Board, Department of Commerce, Washington, D.C.) involves the reaction of 2-chloro-1-dimethylaminopropane with diphenylmethyl cyanide in the presence of sodamide, and treatment of the resulting basic cyanide with ethylmagnesium bromide. A rearrangement

is clearly involved in this synthesis, since the product to be expected is 6-dimethylamino-4 : 4-diphenyl-5-methylhexan-3-one, and several workers have studied the reaction.

Schultz, Robb, and Sprague (*J. Amer. Chem. Soc.*, 1947, **69**, 2454) showed that the reaction of 2-chloro-1-dimethylaminopropane with diphenylmethyl cyanide gave roughly equal quantities of 3-dimethylamino-1 : 1-diphenylbutyl cyanide (II) and 3-dimethylamino-1 : 1-diphenylisobutyl cyanide (IV). The cyanide (II) reacted with ethylmagnesium bromide to give amidone, whereas the cyanide (IV) gave an imine (V), which was not hydrolysed under normal conditions. This imine has, however, been converted into the corresponding ketone by prolonged boiling with 20% hydrochloric acid (Easton, Gardner, and Stevens, *ibid.*, p. 976).

In order to explain the rearrangement, Schultz, Robb, and Sprague (*loc. cit.*) suggested that, under the conditions of reaction, the chloro-amine cyclised to the ethyleneiminium salt (I) which could then be opened in either of two ways :



Evidence that the rearrangement does occur during this stage and not, as suggested by Brode and Hill (*ibid.*, p. 724), during the preparation of the chloro-amines, has very recently been published by Schultz and Sprague (*ibid.*, 1948, **70**, 48) who showed that the chloro-amines prepared from 2-dimethylaminopropan-1-ol and from 1-dimethylaminopropan-2-ol were distinct compounds, no interconversion occurring at normal temperatures, but that each of these chloro-amines gave a similar mixture of cyanides (II) and (IV) on reaction with diphenylmethyl cyanide.

An alternative synthesis of the cyanide (II) has recently been described by Easton, Gardner, and Stevens (*ibid.*, 1947, **69**, 2941), and is referred to elsewhere in this paper.

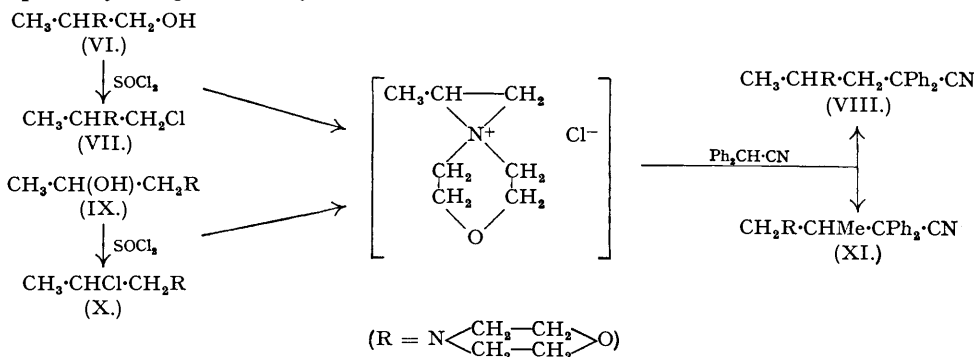
We have prepared the cyanide (II) as follows. 2-Aminopropan-1-ol was methylated with formaldehyde and formic acid, and the resulting 2-dimethylaminopropan-1-ol was treated with thionyl chloride in benzene. The hydrochloride so obtained gave a picrate melting at 158.5—161°, slightly lower, that is, than the melting point (166—167°) found by Schultz and Sprague (*loc. cit.*) for the picrate of 1-chloro-2-dimethylaminopropane. Further, a sample of the distilled base gave a picrate melting at the same temperature, in contradiction to the results of Schultz and Sprague, who found that the base isomerised on distillation, and then gave a picrate, m. p. 101—103°, identical with that prepared from 2-chloro-1-dimethylaminopropane. The undistilled 1-chloro-2-dimethylaminopropane reacted with diphenylmethyl cyanide in the presence of sodamide to give a solid product in 71% yield. Crystallisation from aqueous alcohol gave the pure cyanide (II) in 36% overall yield; no attempt was made to isolate the cyanide (IV) from the mother-liquors. [Schultz and Sprague, *loc. cit.*, using potassium *tert.*-butoxide in place of sodamide, and removing cyanide (IV) from the product by washing with ice-cold hexane, obtained a 40% yield.] Reaction of (II) with an excess of ethylmagnesium iodide in toluene gave amidone (III).

The high analgesic activity of 4 : 4-diphenyl-6-morpholinohexan-3-one as compared with its dimethylamine analogue (see Part I) made it desirable to prepare 4 : 4-diphenyl-6-morpholinohexan-3-one, the morpholine analogue of amidone.

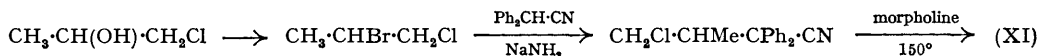
2-Morpholinopropan-1-ol was prepared by a Bouveault-Blanc reduction of ethyl  $\alpha$ -morpholinopropionate or, more conveniently, by reaction of 2-aminopropan-1-ol with di-(2-chloroethyl) ether. 1-Chloro-2-morpholinopropane (VII) reacted with sodiodiphenylmethyl cyanide to give a mixture of two isomeric cyanides melting at 140—141° (A) and 107—108° (B); the mixture contained about 40% of (A) and 60% of (B). A similar mixture resulted when 1-morpholinopropan-2-ol (IX), prepared from propylene oxide and morpholine, was subjected to the same series of reactions.

The two chloro-amines appeared to be distinct compounds, samples of the distilled bases giving picrates with fairly sharp and quite different melting points. Hence, the rearrangement

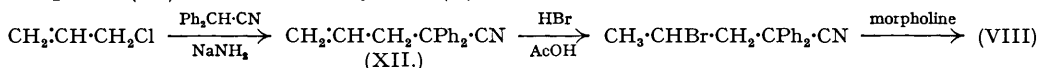
would again seem to occur during reaction with diphenylmethyl cyanide, an ethyleneiminium salt probably being transiently formed during the reaction.



Cyanides (A) and (B) were shown to be 1 : 1-diphenyl-3-morpholinoisobutyl cyanide (XI) and 1 : 1-diphenyl-3-morpholinobutyl cyanide (VIII), respectively, by the following syntheses :

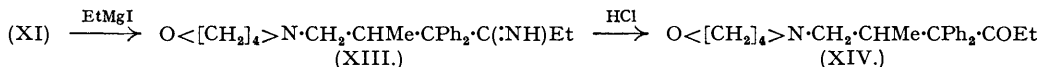


1-Chloropropan-2-ol was converted into 1-chloro-2-bromopropane which, on reaction with sodiodiphenylmethyl cyanide and treatment of the crude product with morpholine, gave compound (XI), identical with cyanide (A).



1 : 1-Diphenylbut-3-enyl cyanide (XII) was readily prepared by the reaction of sodiodiphenylmethyl cyanide with either allyl chloride or allyl bromide. (The same compound has recently been reported both by Easton, Gardner, and Stevens, *ibid.*, 1947, 69, 2941, and by Schultz, Robb, and Sprague, *loc. cit.*, the latter workers using potassium *tert.*-butoxide as condensing agent.) Hydrogen bromide was added in acetic acid at 120° in the presence of diphenylamine, and reaction of the crude product with morpholine gave a small yield of cyanide (B). The ambiguity in the mode of addition of hydrogen bromide to the double bond does not affect the validity of the proof of structure, since, apart from the improbability of either cyanide (A) or cyanide (B) being 1 : 1-diphenyl-4-morpholinobutyl cyanide, this last compound is known to have different properties from either of the cyanides (A) and (B) (see Part I).

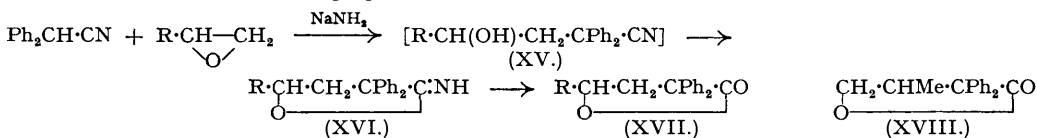
Cyanide (B) (VIII) was readily converted into 4 : 4-diphenyl-6-morpholinoheptan-3-one by treatment with ethylmagnesium iodide. Under the same conditions, cyanide (A) (XI) gave rise



to the imine (XIII) which could be hydrolysed to 4 : 4-diphenyl-6-morpholino-5-methylhexan-3-one (XIV) by vigorous treatment with concentrated hydrochloric acid (cf. Easton, Gardner, and Stevens, *loc. cit.*, p. 976).

The very high analgesic activity of 4 : 4-diphenyl-6-morpholinoheptan-3-one made it desirable to find a method of synthesis that would avoid the formation of mixtures, and the remainder of this paper deals with our attempts to devise such a synthesis.

It was hoped that it might be possible to prepare 3-hydroxy-1 : 1-diphenylbutyl cyanide (XV; R = Me) by the reaction of propylene oxide with diphenylmethyl cyanide. Preliminary experiments with ethylene oxide indicated that, in the presence of sodamide or sodium ethoxide in benzene, cyclisation occurred with the formation of  $\alpha$ -diphenyl- $\gamma$ -butyrolactone (XVII; R = H), presumably *via* the imino-compound (XVI; R = H). Alcoholic sodium ethoxide was ineffective as a condensing agent.



Reaction of propylene oxide with diphenylmethyl cyanide in the presence of sodamide in benzene gave the lactone (XVII; R = Me); that this compound was (XVII; R = Me) rather than (XVIII) is shown by its formation from 1:1-diphenylbut-3-enyl cyanide and hydrobromic acid (see below). In one preparation of the lactone, a small quantity of the hydrochloride of the imine (XVI; R = Me) was isolated. It was very rapidly hydrolysed by warm dilute hydrochloric acid to the lactone. The preparation of the imine (XVI; R = Me) and the lactone (XVII; R = Me) has recently been described by Easton, Gardner, and Stevens (*loc. cit.*, p. 2941), and by Schultz, Robb, and Sprague (*loc. cit.*).

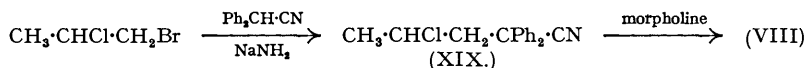
Some attempts were made to open the ring of the lactones as a preliminary to converting them into basic cyanides of the required type, but they were recovered unchanged after treatment with alcoholic sulphuric acid or a mixture of 48% hydrobromic acid and concentrated sulphuric acid. Since the completion of this work, Easton, Gardner, and Stevens (*loc. cit.*, p. 2941) have shown that the imine (XVI; R = Me) reacts with phosphorus trichloride and phosphorus tribromide to give 3-chloro- and 3-bromo-1:1-diphenylbutyl cyanide respectively.

The addition of hydrogen bromide to 1:1-diphenylbut-3-enyl cyanide (XII) has been described above. Attempts to increase the yield of 3-bromo-1:1-diphenylbutyl cyanide by heating the unsaturated compound with 50% hydrogen bromide in acetic acid at 120° for 48 hours gave the lactone (XVII; R = Me) as the sole product. Attempts to carry out the reaction without a solvent at 120°, or in a variety of solvents under various conditions gave products that, on treatment with morpholine, yielded very small quantities of 1:1-diphenyl-3-morpholinobutyl cyanide.

Reaction of (XII) with hydrogen iodide in acetic acid at 80° gave a crude iodine-containing compound which reacted with morpholine in xylene solution to give the compound (VIII) in about 20% overall yield. A wide range of reaction conditions was tried, but in every instance the yield was considerably less than this. Neither benzoyl peroxide nor ascaridole had any influence on the reaction at room temperature.

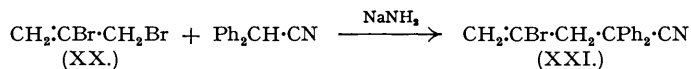
1:1-Diphenylbut-3-enyl cyanide (XII) readily yielded 3:4-dichloro- and 3:4-dibromo-1:1-diphenylbutyl cyanide on reaction with chlorine and bromine, respectively, in chloroform solution. (Schultz, Robb, and Sprague, *loc. cit.*, have recently reported that they were unable to add bromine to the unsaturated cyanide dissolved in carbon tetrachloride.) Both of these dihalides were treated with morpholine in the hope that the 3-halogeno-atom might react selectively, but the basic product consisted solely of 1:1-diphenyl-3:4-dimorpholinobutyl cyanide, even when only 2 mols. of morpholine were employed.

Reaction of 2-chloro-1-bromopropane with sodiodiphenylmethyl cyanide gave 3-chloro-1:1-diphenylbutyl cyanide (XIX) in fair yield, and reaction with morpholine at 150° gave the desired compound (VIII), but only in about 25% yield.



The poor yields obtained in the reaction of 3-halogeno-1:1-diphenylbutyl cyanides are in line with the results of Easton, Gardner, and Stevens (*loc. cit.*, p. 2941), who found that the chloro- and bromo-compounds gave less than 10% yields of 3-dimethylamine-1:1-diphenylbutyl cyanide (II) on reaction with dimethylamine in ethanol, the major part of the product being either (XII) or its isomer, 1:1-diphenylbut-2-enyl cyanide.

Reaction of 2:3-dibromopropene (XX) with sodiodiphenylmethyl cyanide gave a bromo-diphenylbutenyl cyanide which, in view of the low reactivity of vinyl halides, is assumed to be (XXI):



All attempts to reduce (XXI) to 3-bromo-1:1-diphenylbutyl cyanide were unsuccessful. Hydrogenation in alcoholic solution in the presence of palladised charcoal removed bromine as fast as it reduced the double bond, and the only product that could be isolated was 1:1-diphenylbutyl cyanide; the presence of hydrogen bromide made the hydrogenation slower without affecting the final result. Raney nickel was gradually inactivated by the hydrogen bromide liberated, and again there was no evidence of selective reduction of the double bond. Hydrogenation was very slow when ether, dioxan, or acetone was used as solvent with palladised charcoal as catalyst, though the use of a more active catalyst (Alexander and Cope, *J. Amer. Chem. Soc.*, 1944, 66, 886) increased the rate of hydrogenation. In no instance, however, was

there any indication of the formation of the required product. Treatment of (XXI) with activated aluminium failed to cause reduction.

The analgesic activities of the compounds tested are listed in the Table. An outline of the methods of testing is given in Part I, and a more detailed pharmacological report will be published elsewhere.

#### Analgesic Activities.

Compound.	Analgesic activity* (pethidine = 1).
$\text{NMe}_2\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{CPh}_2\cdot\text{COEt}$ (amidone)	8
$\text{O}<[\text{CH}_2]_4>\text{N}\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{CPh}_2\cdot\text{COEt}$	20
$\text{O}<[\text{CH}_2]_4>\text{N}\cdot\text{CH}_2\cdot\text{CHMe}\cdot\text{CPh}_2\cdot\text{COEt}$	1—2
$\text{O}<[\text{CH}_2]_4>\text{N}\cdot\text{CH}_2\cdot\text{CHMe}\cdot\text{CPh}_2\cdot\text{C}(\text{NH})\text{Et}$	1—3

\* The relative activities are quoted on a weight basis.

#### EXPERIMENTAL.

(M. p.s are corrected.)

**2-Nitropropan-1-ol.**—The method of Vanderbilt and Hass (*Ind. Eng. Chem.*, 1940, **32**, 34) gave a poor yield of 2-nitropropan-1-ol, together with 2-nitroisobutane-1 : 3-diol and unchanged nitroethane (cf. Blicke, Faust, Warzynski, and Gearien, *J. Amer. Chem. Soc.*, 1945, **67**, 205). The method of Earl, Ellsworth, Jones, and Kenner (*J.*, 1928, 2697) for the preparation of the sodium salt was found to be satisfactory, their yield being improved by concentration of the methanol mother-liquors from the first crop of sodium salt. The 2-nitropropan-1-ol was obtained by dissolving the sodium salt in a little water and adding ether and then a slight excess of 2N-sulphuric acid with stirring, the temperature being kept below 10°. The ether layer was separated, the aqueous layer was extracted thoroughly with ether, and the combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ). After removal of the solvent, 2-nitropropan-1-ol distilled at 100°/12 mm. (Vanderbilt and Hass, *loc. cit.*, give b. p. 99°/10 mm.). The overall yield was 65%.

**2-Aminopropan-1-ol.**—A solution of 2-nitropropan-1-ol (105 g.) in a mixture of methanol (300 c.c.) and water (30 c.c.) was hydrogenated at room temperature in the presence of Raney nickel (15 g.) (initial pressure, 50 atmospheres). The catalyst was filtered off, the methanol removed, and the residue fractionated under reduced pressure. 2-Aminopropan-1-ol boiled at 76—78°/15 mm. (Blicke, Faust, Warzynski, and Gearien, *loc. cit.*, give b. p. 80—86°/20 mm.). Yield 55.3 g., 74%.

**2-Dimethylaminopropan-1-ol.**—2-Aminopropan-1-ol (20 g.) was added gradually to a mixture of formic acid (61 g.) and water (7 c.c.) with ice cooling. Aqueous formaldehyde (36% ; 49 c.c.) was added, and the mixture was heated on the water-bath for about 20 hours. 10N-Hydrochloric acid (35 c.c.) was added, and the mixture was evaporated under reduced pressure from a steam-bath. The residue was treated with an excess of 40% sodium hydroxide solution with cooling, and was extracted thoroughly with ether. The extract was dried ( $\text{K}_2\text{CO}_3$ ), the ether removed, and the residue distilled. 2-Dimethylaminopropan-1-ol boiled at 65°/37 mm. (Karrer *et al.*, *Helv. Chim. Acta*, 1922, **5**, 468, give b.p. 140—141°/738 mm.). Yield 22.6 g., 82%.

**1-Chloro-2-dimethylaminopropane.**—A solution of 2-dimethylaminopropan-1-ol (22.0 g.) in benzene (250 c.c.) was treated with thionyl chloride (31 c.c.), added gradually with cooling and occasional shaking. When the addition was complete, the mixture was boiled under reflux for 2 hours and was then left overnight in the refrigerator. The white solid was filtered off and dried (32.2 g.). The picrate, prepared directly from the hydrochloride, or from a sample of distilled base (b. p. 124—126°), melted at 158.5—161° after crystallisation from ethanol (Found : N, 15.8 ; Cl, 10.1. Calc. for  $\text{C}_8\text{H}_{12}\text{NCl}$ ,  $\text{C}_6\text{H}_5\text{O}_7\text{N}_3$  : N, 16.0 ; Cl, 10.1%) (Schultz and Sprague, *loc. cit.*, give m. p. 166—167°).

**3-Dimethylamino-1 : 1-diphenylbutyl Cyanide.**—The above chloro-amine hydrochloride (15 g.) was dissolved in a little water. Excess of potassium carbonate solution was added, and the oil was extracted immediately with benzene (about 150 c.c. in all) ; the extract was dried ( $\text{K}_2\text{CO}_3$ ) and used without delay.

A solution of diphenylmethyl cyanide (18 g.) in dry benzene (125 c.c.) was treated with sodamide (3.75 g.), and the mixture was stirred at room temperature till there was no apparent further reaction. The benzene solution of the chloro-amine was added, and the mixture was stirred overnight at room temperature. The mixture was extracted with three 60 c.c. portions of 2N-hydrochloric acid, the acid extract was basified with 40% sodium hydroxide solution, and the oil was extracted with ether. The extract was dried ( $\text{K}_2\text{CO}_3$ ), the ether removed, and the residue distilled. The product (18.4 g., 71% yield) boiled at 128°/0.1 mm. and solidified on standing. Two crystallisations from aqueous alcohol gave colourless needles, m. p. 92—92.5° (Found : C, 82.2 ; H, 8.1 ; N, 10.0. Calc. for  $\text{C}_{19}\text{H}_{22}\text{N}_2$  : C, 82.0 ; H, 8.0 ; N, 10.1%) (Schultz, Robb, and Sprague, *J. Amer. Chem. Soc.*, 1947, **69**, 2454, give m. p. 90—91°). Yield of pure product 9.3 g., 36%.

**6-Dimethylamino-4 : 4-diphenylheptan-3-one.**—A solution of 3-dimethylamino-1 : 1-diphenylbutyl cyanide (11.1 g.) in dry toluene (30 c.c.) was added to a Grignard reagent prepared from magnesium (1.9 g.) and ethyl iodide (12.5 g.) in ether (30 c.c.). The ether was distilled from a water-bath till the temperature of the residue was 95—97°, and the residue was heated overnight on the water-bath. The mixture was decomposed with 2N-hydrochloric acid (200 c.c.), the decomposition being completed by heating on a water-bath for 30 minutes. The toluene layer was removed and extracted with hydrochloric acid. The combined acid solutions, together with a lower gummy layer, were made alkaline with 40% sodium hydroxide solution. The oil was extracted with ether, the extract was dried ( $\text{K}_2\text{CO}_3$ ), the ether was removed, and the residue distilled. The ketone (10.3 g. ; 83%) boiled at 154—160°/1 mm. The *hydrochloride*, after crystallisation from methyl cyanide, melted at 231—233° (Found : C, 72.8 ;

H, 8.6; N, 4.2; Cl, 10.1.  $C_{21}H_{27}ON_2Cl$  requires C, 72.9; H, 8.2; N, 4.05; Cl, 10.25% (Thorp, Walton, and Ofner, *Nature*, 1947, **159**, 679; 1947, **160**, 605, give m. p. 231° but quote no analytical figures).

*Ethyl  $\alpha$ -morpholinopropionate*.—Morpholine (88 g.) was added gradually to a solution of ethyl  $\alpha$ -bromopropionate (45 g.) in benzene (100 c.c.). The mixture was boiled under reflux for 1 hour, and, after cooling, the precipitate of morpholine hydrobromide was filtered off and washed with benzene. The combined filtrate and washings were extracted with an excess of 5*N*-hydrochloric acid, and the acid extract was made strongly alkaline with 2*N*-sodium hydroxide with cooling and extracted thoroughly with ether. The extract was dried ( $Na_2SO_4$ ), the ether removed, and the residue distilled. *Ethyl  $\alpha$ -morpholinopropionate* boiled at 110—113°/15 mm. (Found: C, 57.7; H, 9.2; N, 6.95.  $C_9H_{17}O_3N$  requires C, 57.7; H, 9.1; N, 7.5%).

*2-Morpholinopropan-1-ol*.—(a) *By reduction of ethyl  $\alpha$ -morpholinopropionate*. Sodium (125 g.) was covered with dry toluene in a 3-l. flask equipped with mercury-sealed wire stirrer, dropping funnel, and a long, wide-bore condenser. The toluene was heated to boiling, the flame was removed, and the mixture was stirred rapidly till it had cooled considerably. When the suspension of finely-divided sodium had cooled to room temperature, a solution of ethyl  $\alpha$ -morpholinopropionate (81 g.) in dry ethanol (125 c.c.) was added as rapidly as possible, followed by sufficient dry alcohol (also added rapidly) to decompose all the sodium, the mixture being stirred vigorously throughout. The reaction was completed by boiling under reflux for 30 minutes. After cooling, ice was added to decompose the sodium ethoxide, and the solution was distilled in steam until no further basic material passed over. The distillate was acidified to Congo-red with concentrated hydrochloric acid, and was then evaporated under reduced pressure to a syrup; the cooled residue was covered with ether, and made strongly alkaline by the addition of 40% sodium hydroxide. The ether layer was separated, and the aqueous layer was saturated with sodium hydroxide and extracted thoroughly with ether. The combined ether extracts were dried ( $K_2CO_3$ ), the ether removed, and the residue distilled. *2-Morpholinopropan-1-ol* boiled at 121—124°/18 mm. Yield 28.8 g., 46%. The  *$\alpha$ -naphthylurethane*, after crystallisation from benzene-petroleum, melted at 102—105° (Found: C, 69.2; H, 7.1; N, 8.85.  $C_{18}H_{22}O_3N_2$  requires C, 68.8; H, 7.05; N, 8.9%).

(b) *From 2-aminopropan-1-ol*. A mixture of di-(2-chloroethyl) ether (38 g.), 2-aminopropan-1-ol (20 g.), and anhydrous potassium carbonate (42 g.) was heated in an oil-bath at 150° for 8 hours. After cooling, ether was added, the mixture was filtered, and the solid was washed thoroughly with ether. The combined filtrate and washings were treated with solid potassium hydroxide, the ether layer was separated, and the aqueous layer extracted with ether. The combined extracts were dried ( $K_2CO_3$ ), the solvent removed, and the residue distilled. The fraction of b. p. 80—110°/15 mm. was redistilled to give *2-morpholinopropan-1-ol*, b. p. 105—107°/12 mm. Yield 23.4 g., 61%.

*1-Chloro-2-morpholinopropane*.—*2-Morpholinopropan-1-ol* (22.7 g.) in dry benzene (230 c.c.) was treated with thionyl chloride (28 c.c.), added gradually with occasional shaking, the solution being cooled in ice. When the addition was complete, the mixture was boiled under reflux for 2 hours, and was then left overnight in the refrigerator; the solid was filtered off, washed thoroughly with dry benzene, and dried. Yield 28 g., 89%.

The hydrochloride could be crystallised from ethyl acetate, but it was extremely deliquescent. The base, obtained in 83% yield, boiled at 88—91°/10 mm. It was used for the next stage without delay.

The *picrate*, prepared in ethanol, melted at 104—107°. After crystallisation from ethanol the m. p. was 105—107° (Found: N, 14.5; Cl, 9.1.  $C_7H_{14}ONCl, C_6H_3O_7N_3$  requires N, 14.3; Cl, 9.0%).

*Reaction of 1-Chloro-2-morpholinopropane with Diphenylmethyl Cyanide*.—A solution of diphenylmethyl cyanide (9.7 g.) in dry benzene (75 c.c.) was treated with sodamide (2.0 g.), and the mixture was stirred at room temperature for about 2 hours. A solution of 1-chloro-2-morpholinopropane (8.2 g.) in dry benzene (75 c.c.) was added, and the mixture was stirred overnight at room temperature. The mixture was extracted with excess of 2*N*-hydrochloric acid, the extract was made strongly alkaline with 40% sodium hydroxide, and the oil was extracted with ether. Removal of the ether, and crystallisation of the residue from petroleum gave a solid which melted between 94° and 124°. Yield 8.05 g., 50%. Crystallisation of the solid from benzene-petroleum (b. p. 60—80°) gave two types of crystals: clusters of small plates (*A*), and cubes (*B*). These were separated by hand, and each of the solids was crystallised from petroleum (b. p. 80—100°). Compound (*A*) melted at 140—141° alone or mixed with an authentic specimen of 1:1-diphenyl-3-morpholinobutyl cyanide (see below) (Found: C, 78.9; H, 7.6; N, 9.1.  $C_{21}H_{25}ON_2$  requires C, 78.7; H, 7.55; N, 8.7%). Compound (*B*) melted at 107—108° alone or mixed with an authentic specimen of 1:1-diphenyl-3-morpholinobutyl cyanide (Found: C, 78.5; H, 7.5; N, 9.3%).

Comparison of the melting range of the crude product with those of synthetic mixtures of the pure cyanides indicated that it contained approximately 60% of (*B*).

No simple method could be found for separating the isomers in good yield, but pure specimens of 1:1-diphenyl-3-morpholinobutyl cyanide could be obtained by crystallisation of the mixture from ether, and of 1:1-diphenyl-3-morpholinobutyl cyanide by crystallisation from acetone. In both cases the recovery was poor.

*1-Morpholinopropan-2-ol*.—Morpholine (43.5 g.), propylene oxide (30 g.), and methanol (10 c.c.) were boiled under reflux for 2 hours. Distillation under reduced pressure gave 1-morpholinopropan-2-ol as a colourless oil, b. p. 94—96°/17 mm. (Found: C, 57.85; H, 10.2; N, 10.1. Calc. for  $C_7H_{15}O_2N$ : C, 57.9; H, 10.4; N, 9.65%) (Cheney and Bywater, *J. Amer. Chem. Soc.*, 1942, **64**, 970, give b. p. 82—84°/1.5 mm.). Yield 63.5 g., 88%.

An attempt to prepare an  $\alpha$ -naphthylurethane by warming with  $\alpha$ -naphthyl isocyanate was unsuccessful.

*2-Chloro-1-morpholinopropane*.—The hydrochloride was prepared from 1-morpholinopropan-2-ol (35 g.), benzene (250 c.c.), and thionyl chloride (60 c.c.) by the method used for the preparation of 1-chloro-2-morpholinopropane hydrochloride. The *hydrochloride*, which was obtained in 89% yield, melted at 176—178° after crystallisation from ethyl acetate-ethanol (Found: C, 42.4; H, 7.5.  $C_7H_{14}ONCl$  requires C, 42.0; H, 7.6%). The base, obtained from the hydrochloride in 86% yield,

boiled at 82.5—83°/12 mm. The *picrate* separated from ethanol in yellow crystals, m. p. 117—119°, unchanged on crystallisation from the same solvent (Found : N, 14.4; Cl, 8.75.  $C_7H_{14}ONCl, C_6H_5O_7N_3$  requires N, 14.3; Cl, 9.0%).

*Reaction of 2-Chloro-1-morpholinopropane with Diphenylmethyl Cyanide.*—The reaction was carried out by precisely the same method as was used for the isomeric 1-chloro-2-morpholinopropane, the mixture of cyanides being obtained in 80% yield. The mixture again contained some 60% of 1:1-diphenyl-3-morpholinobutyl cyanide.

On one occasion the two cyanides were separated during their extraction from benzene solution with 2*N*-hydrochloric acid. The hydrochloride of 1:1-diphenyl-3-morpholinoisobutyl cyanide solidified, while that of 1:1-diphenyl-3-morpholinobutyl cyanide remained liquid. The two hydrochlorides were separated by filtration, and converted into the bases. Attempts to repeat this separation were always unsuccessful, both hydrochlorides solidifying simultaneously.

*Unambiguous Synthesis of 1:1-Diphenyl-3-morpholinoisobutyl Cyanide.*—3-Chloro-1:1-diphenylisobutyl cyanide. A solution of diphenylmethyl cyanide (19.3 g.) in benzene (150 c.c.) was treated with sodamide (4.0 g.), and the mixture was boiled under reflux with stirring until the separation of the solid was complete. The suspension was cooled to room temperature and 1-chloro-2-bromopropane (Dewael, *Bull. Soc. chim. Belg.*, 1930, **39**, 87) (15.75 g.) was added slowly. The mixture was boiled under reflux with stirring for 2 hours, and after cooling was washed successively with 2*N*-hydrochloric acid and water, and was dried ( $Na_2SO_4$ ). The benzene was removed and the residue distilled. The material boiling at 118—120°/0.2 mm. was redistilled giving 3-chloro-1:1-diphenylisobutyl cyanide, b. p. 110°/0.001 mm. (Found : N, 5.0; Cl, 13.1.  $C_{17}H_{16}NCl$  requires N, 5.2; Cl, 13.1%). Yield 18.9 g., 70%.

1:1-Diphenyl-3-morpholinoisobutyl cyanide. 3-Chloro-1:1-diphenylisobutyl cyanide (2.05 g.) and morpholine (10 c.c.) were heated at 150° in a sealed tube for 6 hours. After cooling, ether was added, and morpholine hydrochloride was filtered off. The filtrate was extracted with an excess of 2*N*-hydrochloric acid and the extract was made strongly alkaline with 40% sodium hydroxide and extracted with ether. The extract was dried ( $Na_2SO_4$ ) and evaporated, leaving a syrupy residue to which petrol (b. p. 80—100°) was added. The crystalline solid was filtered off, and recrystallised from benzene-petroleum (b. p. 40—60°), and then melted at 139—140°. Yield 0.43 g., 18%.

*Unambiguous Synthesis of 1:1-Diphenyl-3-morpholinobutyl Cyanide.*—1:1-Diphenylbut-3-enyl cyanide. Diphenylmethyl cyanide (193 g.) in benzene (1500 c.c.) was treated with sodamide (41 g.), and the mixture was boiled under reflux and stirred until the separation of solid was complete. After cooling, allyl chloride (80.5 g.) was added gradually, and the mixture was then boiled under reflux with stirring for 2 hours. The cooled solution was washed with 2*N*-hydrochloric acid, then with water, and was dried ( $Na_2SO_4$ ). The benzene was removed and the residue distilled, giving the cyanide, b. p. 125°/0.2 mm. The material solidified and then melted at 24.5°, but it could not be recrystallised (Found : C, 87.7; H, 6.3; N, 6.0. Calc. for  $C_{17}H_{16}N$  : C, 87.5; H, 6.5; N, 6.0%) (Schultz, Robb, and Sprague, *loc. cit.*, give b. p. 131°/1.5 mm.). Yield 219 g., 94%. Allyl bromide could be used in place of allyl chloride with very similar results.

1:1-Diphenyl-3-morpholinobutyl cyanide. 1:1-Diphenylbut-3-enyl cyanide (5 g.), a solution of hydrogen bromide in acetic acid (50%; 20 c.c.), and diphenylamine (0.2 g.) were placed in a nitrogen-filled Carius tube, and heated overnight at 120°. After cooling, the contents of the tube were diluted with water, and the oil was extracted with ether. The extract was washed first with water, then with sodium hydrogen carbonate solution till free from acid, and then again with water. It was dried ( $CaCl_2$ ), and the ether removed leaving a reddish oil (3.3 g.). Morpholine (2.1 c.c.) was added, and the mixture was heated overnight on the water-bath. Dry ether was added, the solid filtered off, and the filtrate extracted with three 20 c.c. portions of 2*N*-hydrochloric acid. The acid extract was made strongly alkaline with 40% sodium hydroxide, and extracted with ether. The extract was dried ( $K_2CO_3$ ), and the solvent removed. The residual oil (0.45 g.) was dissolved in hot petroleum (b. p. 80—100°). On standing, a solid (*A*) separated, and was filtered off; the filtrate, on concentration, yielded a second crystalline substance (*B*). The solid (*A*) (0.08 g.) melted at 135.5—137.5° after crystallisation from benzene-petroleum (Found : C, 74.75; H, 7.85; N, 8.0%). The structure of this compound is not known. Substance (*B*) (0.17 g.) melted at 105—107°, the melting point not being depressed on admixture with the material, m. p. 107—108°, obtained as described above.

The same result was obtained in the absence of diphenylamine. The addition of hydrogen bromide was attempted in a number of different solvents and under a wide range of conditions, but no appreciable increase in yield resulted.

4:4-Diphenyl-6-morpholinoheptan-3-one.—A solution of 1:1-diphenyl-3-morpholinobutyl cyanide (12.9 g.) in dry toluene (32 c.c.) was added to a Grignard reagent prepared from magnesium (1.98 g.), ethyl iodide (12.6 g.), and ether (30 c.c.). The ether was distilled off from a water-bath until the internal temperature reached 97°, and the residue was heated overnight on the water-bath. The reaction mixture was decomposed with 2*N*-hydrochloric acid (200 c.c.), the decomposition being completed by warming on the water-bath for 30 minutes. The toluene layer was separated and washed twice with small quantities of 2*N*-hydrochloric acid. The combined acid solutions, containing a heavy oily layer, were made strongly alkaline with 40% sodium hydroxide solution, and extracted with benzene. The extract was dried ( $K_2CO_3$ ) and the solvent removed, leaving a yellow oil (13.9 g.). A solution of this oil in dry ether was treated with dry hydrogen chloride, and the precipitated salt was crystallised from methyl cyanide. 4:4-Diphenyl-6-morpholinoheptan-3-one hydrochloride melted at 224—229° (Found : C, 70.8; H, 7.7; N, 3.6; Cl, 9.2.  $C_{23}H_{29}O_2N, HCl$  requires C, 71.2; H, 7.8; N, 3.6; Cl, 9.1%). Yield 11.4 g., 73%.

The base, liberated from the pure hydrochloride, melted at 75.5—77° after crystallisation from aqueous ethanol (Found : C, 78.5; H, 8.0; N, 4.4.  $C_{23}H_{29}O_2N$  requires C, 78.6; H, 8.3; N, 4.0%).

The hydrobromide, after crystallisation from water containing a trace of hydrobromic acid, melted at 235—237° (Found : N, 3.4; Br, 18.9.  $C_{23}H_{29}O_2N, HBr$  requires N, 3.2; Br, 18.5%). The nitrate melted at 175° after crystallisation from ethanol-ether (Found : C, 66.7; H, 7.25; N, 6.6.  $C_{23}H_{29}O_2N, HNO_3$  requires C, 66.6; H, 7.3; N, 6.8%). The oxalate had m. p. 162—163° after crystallis-

ation from ethanol-ether (Found: C, 68.3; H, 7.0; N, 3.3.  $C_{23}H_{29}O_2N, C_2H_5O_4$  requires C, 68.0; H, 7.1; N, 3.2%).

4 : 4-Diphenyl-6-morpholino-5-methylhexan-3-one.—A solution of 1 : 1-diphenyl-3-morpholinoisobutyl cyanide (3.2 g.) in toluene (15 c.c.) was added to a Grignard reagent prepared from magnesium (0.5 g.) and ethyl iodide (3.2 g.) in ether. Ether was removed by distillation until the internal temperature reached 97°, and the residue was heated overnight on the water-bath. The Grignard complex was decomposed with an excess of 2*N*-hydrochloric acid, and the resulting mixture was treated with ammonium chloride and ammonia. The oil was extracted with benzene, the extract dried ( $K_2CO_3$ ), and the solvent removed, leaving an oil (3.36 g.) from which 3-imino-4 : 4-diphenyl-6-morpholino-5-methylhexane was obtained by crystallisation from petroleum; the compound melted at 103—106° (Found: C, 79.2; H, 9.0; N, 7.8.  $C_{23}H_{30}ON_2$  requires C, 78.8; H, 8.6; N, 8.0%). The dihydrochloride, containing alcohol of crystallisation, melted at 200—203° after crystallisation from this solvent (Found: C, 64.2; H, 8.1; N, 5.9; Cl, 15.5.  $C_{23}H_{30}ON_2 \cdot 2HCl, C_2H_6O$  requires C, 63.95; H, 8.2; N, 6.0; Cl, 15.1%).

The imine (2 g.) was boiled under reflux overnight with concentrated hydrochloric acid (10 c.c.). The cooled solution was made strongly alkaline with sodium hydroxide, and extracted with benzene. Evaporation of the dry benzene extract left an oil which soon solidified. 4 : 4-Diphenyl-6-morpholino-5-methylhexan-3-one melted at 130—130.5° after crystallisation from ethanol (Found: C, 78.65; H, 8.5; N, 4.2.  $C_{23}H_{30}O_2N$  requires C, 78.6; H, 8.3; N, 4.0%). The hydrochloride melted at 218—222° after crystallisation from acetone-ether and drying at 100° (Found: C, 71.1; H, 7.65; N, 3.3; Cl, 8.6.  $C_{23}H_{30}O_2N, HCl$  requires C, 71.2; H, 7.8; N, 3.6; Cl, 9.1%).

$\alpha\alpha$ -Diphenyl- $\gamma$ -butyrolactone.—Diphenylmethyl cyanide (9.6 g.) in dry benzene (75 c.c.) was treated with sodamide (2 g.), and the mixture was boiled under reflux and stirred till no more solid separated. The mixture was cooled in ice and stirred while ethylene oxide (2.2 g.) was passed in; the suspended solid largely went into solution during this process. The mixture was stirred overnight at room temperature, and was then extracted with 2*N*-hydrochloric acid. The acid washings slowly deposited the lactone (6.8 g.; 57%) which melted at 80—80.5° after crystallisation from petroleum (b. p. 60—80°) (Found: C, 80.7; H, 6.1.  $C_{16}H_{14}O_2$  requires C, 80.7; H, 5.9%).

When sodium ethoxide replaced sodamide in the above experiment the same product was obtained in 46% yield; refluxing the solution for three hours after the addition of ethylene oxide increased the yield to 52%. When reaction was carried out in alcohol with sodium ethoxide as condensing agent, the diphenylmethyl cyanide was largely recovered unchanged, the only other pure product isolated being diphenylacetamide.

$\alpha\alpha$ -Diphenyl- $\gamma$ -valerolactone.—(a) From diphenylmethyl cyanide and propylene oxide. Diphenylmethyl cyanide (9.6 g.) was converted into its sodio-derivative by treatment with sodamide (2 g.) in boiling benzene (75 c.c.). A solution of propylene oxide (3.6 c.c.) in dry benzene (15 c.c.) was added gradually to the stirred, ice-cooled suspension. When the addition was complete, the mixture was stirred for 30 minutes at 0° and for three hours at room temperature. The mixture was extracted with an excess of 2*N*-hydrochloric acid. On standing, the extract deposited an oil which solidified. After several days, the solid (8.7 g.; 69% yield) was filtered off and crystallised from benzene-petroleum (b. p. 60—80°). The lactone melted at 115—116° alone or mixed with a specimen obtained as described below (Found: C, 80.8; H, 6.5. Calc. for  $C_{17}H_{16}O_2$ : C, 80.9; H, 6.4%).

In one experiment, crystallisation of the crude lactone yielded some benzene-insoluble material which melted at 221° after crystallisation from ethanol-ether, and which was rapidly hydrolysed to  $\alpha\alpha$ -diphenyl- $\gamma$ -valerolactone by means of warm 2*N*-hydrochloric acid. The analysis indicates that the substance is 2-imino-3 : 3-diphenyl-5-methyltetrahydrofuran hydrochloride (Found: N, 5.1; Cl, 12.5. Calc. for  $C_{17}H_{15}ON, HCl$ : N, 4.9; Cl, 12.3%) (Easton, Gardner, and Stevens, *loc. cit.*, p. 2941, give m. p. 112—113° for the lactone and m. p. 220—222° for the imine hydrochloride).

(b) From 1 : 1-diphenylbut-3-enyl cyanide. A solution of the cyanide (4.9 g.) in 50% hydrogen bromide in acetic acid (20 c.c.) was heated at 120° for 48 hours in a Carius tube. The contents of the tube, which were largely crystalline, were dissolved in benzene and the solution was washed first with water, then with sodium hydrogen carbonate solution; the solution was then dried ( $Na_2SO_4$ ) and evaporated to dryness. On trituration with ether the lactone was obtained, melting at 113—115°. Yield 3.5 g., 66%.

Reaction of 1 : 1-Diphenylbut-3-enyl Cyanide with Hydrogen Iodide and Conversion of the Product into 1 : 1-Diphenyl-3-morpholinobutyl Cyanide.—1 : 1-Diphenylbut-3-enyl cyanide (10.9 g.) was saturated with hydrogen iodide; the solution was cooled to -80° in a Carius tube, and hydrogen iodide (6 c.c.) was condensed into the solution. The tube was sealed and heated at 80° for 18 hours. The contents of the tube were diluted with water and extracted with ether. The extract was washed successively with water, sodium hydrogen carbonate solution, and sodium sulphite solution, and was then dried ( $CaCl_2$ ). The solvent was removed, and to the residue were added morpholine (8 c.c.) and xylene (40 c.c.). The mixture was heated on the water-bath for three hours, and the basic material was isolated. 1 : 1-Diphenyl-3-morpholinobutyl cyanide (2.8 g.; 19% yield) was obtained, melting at 107—108° after crystallisation from petroleum.

Variation of these conditions invariably resulted in a lower yield of product; neither ascaridole nor benzoyl peroxide had any effect on the yield. The use of ether as solvent was equally unsuccessful.

3 : 4-Dichloro-1 : 1-diphenylbutyl Cyanide.—1 : 1-Diphenylbut-3-enyl cyanide (23.3 g.) was dissolved in chloroform and an excess of chlorine was passed in, the temperature being kept below 20°. The chloroform solution was washed with 10% sodium sulphite solution, dried ( $Na_2SO_4$ ), and evaporated to dryness, leaving a gummy residue (29.5 g.) of the dichloro-compound which could not be made to crystallise (Found: Cl, 21.1.  $C_{17}H_{15}NCl_2$  requires Cl, 23.3%). A portion of the product was distilled, and had b. p. 138°/0.0005 mm.; the chlorine value was still low (Found: N, 4.5; Cl, 20.8.  $C_{17}H_{15}NCl_2$  requires N, 4.6; Cl, 23.3%).

Reaction of 3 : 4-Dichloro-1 : 1-diphenylbutyl Cyanide with Morpholine.—The cyanide (3.04 g.) was boiled under reflux with morpholine (10 c.c.) for 2 hours and, after cooling, ether was added, and



morpholine hydrochloride was filtered off. The filtrate was extracted with 2*N*-hydrochloric acid, and the extract was basified with sodium hydroxide solution, and extracted with ether. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to dryness. Trituration of the residue with ether, and addition of petroleum (b. p. 40—60°) yielded 1 : 1-*diphenyl-3 : 4-dimorpholinobutyl cyanide*, m. p. 133° after crystallisation from petroleum (b. p. 100—120°) (Found: C, 74.4; H, 7.6; N, 10.4.  $\text{C}_{25}\text{H}_{31}\text{O}_2\text{N}_3$  requires C, 74.0; H, 7.7; N, 10.4%). Yield 3.2 g.

When the dichloro-compound (3.04 g.) was refluxed with morpholine (1.74 c.c.) and xylene (15 c.c.) the only basic product isolated was the same dimorpholino-compound.

3 : 4-*Dibromo-1 : 1-diphenylbutyl Cyanide*.—1 : 1-Diphenylbut-3-enyl cyanide (23.3 g.) in chloroform (100 c.c.) was treated with a solution of bromine (16 g.) in chloroform (50 c.c.), the temperature being kept below 20°. The solution was washed with 10% sodium sulphite solution and dried ( $\text{MgSO}_4$ ). Evaporation to dryness followed by trituration with ether and addition of petroleum yielded 3 : 4-*dibromo-1 : 1-diphenylbutyl cyanide*, m. p. 71° after crystallisation from benzene-petroleum (b. p. 40—60°) (Found: C, 52.6; H, 4.1; N, 3.6; Br, 40.3.  $\text{C}_{17}\text{H}_{15}\text{NBr}_2$  requires C, 51.9; H, 3.85; N, 3.6; Br, 40.7%). Yield 28.6 g., 73%.

*Reaction of 3 : 4-Dibromo-1 : 1-diphenylbutyl Cyanide with Morpholine*.—The cyanide (7.25 g.) was boiled under reflux with morpholine (25 c.c.) for 2 hours. Ether was added to the cold solution, morpholine hydrobromide was filtered off, and the basic material was isolated from the filtrate. 1 : 1-Diphenyl-3 : 4-dimorpholinobutyl cyanide (5.3 g.; 71% yield) was obtained, m. p. 131°, undepressed on admixture with a specimen prepared as described above.

When the amount of morpholine was reduced to 2 mols. the only basic material isolated was the same dimorpholino-compound.

3-*Chloro-1 : 1-diphenylbutyl Cyanide*.—Diphenylmethyl cyanide (9.7 g.) was converted into its sodio-derivative by treatment with sodamide (2.0 g.) in boiling benzene (75 c.c.). The suspension was cooled while 2-chloro-1-bromopropane (Kharasch, Engelmann, and Mayo, *J. Org. Chem.*, 1937, 2, 288) (7.9 g.) was added, and the mixture was boiled under reflux for 2 hours. After cooling, the solution was washed successively with 2*N*-hydrochloric acid and sodium hydrogen carbonate solution, and was dried ( $\text{CaCl}_2$ ). After the benzene had been removed the residue was distilled, and the fraction, b. p. 115—120°/0.0003 mm., was collected. On crystallisation from petroleum (b. p. 40—60°) the compound melted at 59° (Found: C, 75.9; H, 5.95; N, 5.1; Cl, 12.7. Calc. for  $\text{C}_{17}\text{H}_{14}\text{NCl}$ : C, 75.7; H, 6.0; N, 5.2; Cl, 13.1%). Yield 6.4 g., 47% (Easton, Gardner, and Stevens, *loc. cit.*, p. 2941, give m. p. 53—55°).

1 : 1-*Diphenyl-3-morpholinobutyl Cyanide*.—3-Chloro-1 : 1-diphenylbutyl cyanide (2.0 g.) and morpholine (10 c.c.) were heated at 150° in a sealed tube for 6 hours. The mixture was worked up to yield 1 : 1-diphenyl-3-morpholinobutyl cyanide (0.5 g.; 21% yield), m. p. 105—107° after crystallisation from petroleum (b. p. 60—80°).

3-*Bromo-1 : 1-diphenylbut-3-enyl Cyanide*.—Diphenylmethyl cyanide (38.6 g.) was converted into its sodio-derivative by treatment with sodamide (8 g.) in boiling benzene (300 c.c.). 2 : 3-Dibromopropene (Lespieau and Bourguet, *Org. Synth.*, Coll. Vol. I, p. 203) (40 g.) was added slowly to the cooled suspension. The mixture was boiled under reflux for 2 hours with stirring. The cooled mixture was washed with 2*N*-hydrochloric acid and then with water, and was dried ( $\text{Na}_2\text{SO}_4$ ). The benzene was removed, and the residue distilled; the distillate crystallised on standing, and the *cyanide* melted at 54—55° after crystallisation from benzene-petroleum (b. p. 40—60°) (Found: C, 65.4; H, 4.6; N, 4.7; Br, 25.3.  $\text{C}_{17}\text{H}_{14}\text{NBr}$  requires C, 65.4; H, 4.5; N, 4.5; Br, 25.6%). Yield 44 g., 71%.

*Hydrogenation of 3-Bromo-1 : 1-diphenylbut-3-enyl Cyanide*.—Hydrogenation in ethanol solution in the presence of 10% palladised charcoal led to the absorption of 2 mols. of hydrogen without a break and to the formation of 1 : 1-diphenylbutyl cyanide; this compound boiled at 85°/0.01 mm. (Found: C, 87.1; H, 7.1; N, 6.1. Calc. for  $\text{C}_{17}\text{H}_{17}\text{N}$ : C, 86.8; H, 7.3; N, 5.95%) (Schultz, Robb, and Sprague, *loc. cit.*, give b. p. 125—127°/1 mm.).

Interruption of the hydrogenation at various stages, and titration of the hydrogen bromide liberated showed that for every g.-mol. of hydrogen absorbed roughly 0.5 g.-mol. of hydrogen bromide was formed, and hence that the bromine was being removed as rapidly as the double bond was being reduced.

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