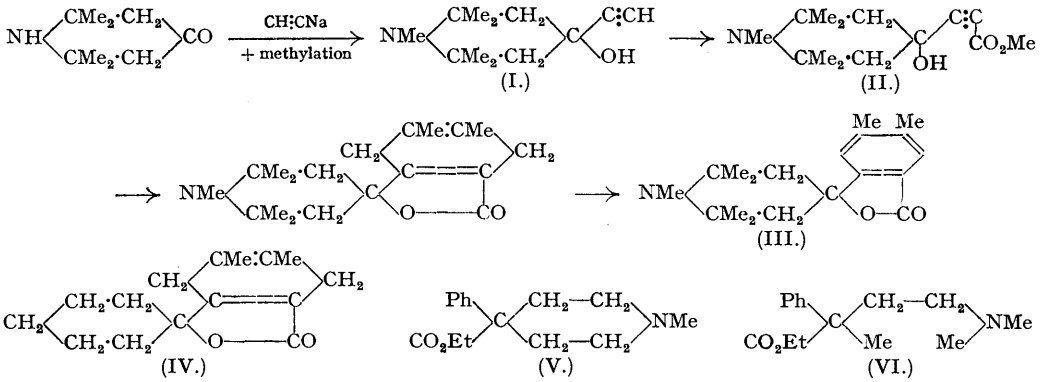
161. *Experiments in the Piperidine Series. Part IV.*

By R. M. Anker and A. H. Cook.

Unsuccessful attempts to obtain " angular " arylpiperidine derivatives such as (III) are described. A number of tertiary bases derived from ethyl γ-amino-α-phenylbutyrate and ε-amino-α-phenylhexoate were prepared as possibly possessing analgesic properties. They may be related to the analgesic piperidine derivative pethidine (V).

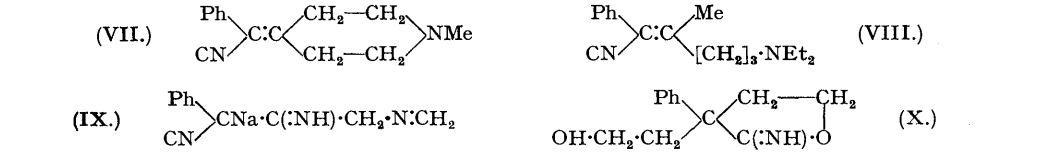
In an earlier paper (*J.*, 1946, 59) attempts to devise structures containing an aryl grouping maintained at an angle with respect to a piperidine ring were described. Such structures were desired because of their spatial resemblance to that of morphine, so that they might have had analgesic properties. In the first part of the present work this possibility was pursued in an attempt to build up the " angular " aryl grouping in the following manner :



Triacetonamine was selected for study as it was more readily available than simpler piperidones, and the feasibility of the earlier stages was first investigated in the carbocyclic series. Here methyl 2-(1′-hydroxy*cyclo*hexyl)propiolate (Jones and Whiting, *J.*, in the press) underwent the Diels–Alder reaction with 2 : 3-dimethylbutadiene to give 5 : 6-*dimethyl*-3-spirocyclo*hexyldihydrophthalide* (IV). Triacetonamine and sodium acetylide afforded 4-*hydroxy*-2 : 2 : 6-*tetramethyl*-4-*ethynylpiperidine* which on methylation gave 4-*hydroxy*-1 : 2 : 2 : 6 : 6-*pentamethyl*-4-*ethynylpiperidine* (I); the latter was characterised as the corresponding acetoxy-compound which formed a *perchlorate* so confirming the presence of a *N*-Me grouping in the acetyl-pentamethyl compound. However, attempts to convert (I) into the ester (II) resulted in a low yield of an oil which was analytically unsatisfactory and which on heating with butadiene only reverted to a low boiling base, so that this synthesis was abandoned.

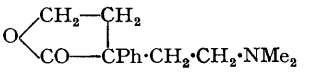
These experiements were originally suggested by comparing the structures of morphine and pethidine (V), but it was also thought possible that the analgesic properties of these compounds might be exhibited by " open-chain " analogues of (V), *e.g.*, by (VI) among others, and accordingly the preparation of some simpler compounds of this general type was undertaken. For preparative convenience the present study was restricted to aminoalkylphenylacetic esters having suitable substituents on the basic grouping. Since this work was initiated the analgesic properties of (VI) have been mentioned by Macdonald *et al.* (*Brit. J. Pharmacol.*, 1946, **1**, 4) though the compound itself has not so far been described.

Benzyl cyanide could be condensed with 1-methyl-4-piperidone or with 5-diethylaminopentan-2-one to give 1-methyl-4-(cyanophenylmethylene)piperidine (VII) (analysed as *hydrochloride*) or 1-*cyano*-1-*phenyl*-2-*methyl*-2-3′-*diethylaminopropylethylene* (VIII) respectively, but these could not be converted into the corresponding esters by alcoholysis satisfactorily and were therefore not further examined. Methyleneaminoacetonitrile reacted with sodiobenzyl cyanide



to give what may be presumed to be the sodio-compound (IX) but attempts to isolate any related keto-nitrile were unsuccessful. Other attempts to utilise keto-nitriles, *e.g.*, by reaction of sodiobenzyl cyanide with crotonyl chloride, were also unpromising.

Efforts to condense sodiobenzyl cyanide with ethylene chloro(or bromo)hydrin (cf. Knowles and Cloke, *J. Amer. Chem. Soc.*, 1932, **54**, 2028) in the desired manner were unavailing. 1-Bromo-3-phthalimidopropane did not react with sodiobenzyl cyanide in the anticipated manner, and a similar reaction with epichlorohydrin gave rise only to tarry products. In liquid ammonia sodiobenzyl cyanide gave with ethylene oxide the required hydroxyethylbenzyl cyanide but in a yield of only 20%; much of the benzyl cyanide was converted into 2-*imino*-3-*phenyl*-3-2′-*hydroxyethyltetrahydrofuran* (X) which formed the sole product when 2 molecular proportions of ethylene oxide were used. This compound was readily hydrolysed to the corresponding lactone, which was converted into the bromoethyl-lactone and thence into the piperidino-compound as described by Bergel *et al.* (*J.*, 1944, 267), and into the *dimethylamino*-compound (XI), characterised as its *hydrochloride*. [A number of homologues of (XI) have been

(XI.) 

$Cl\cdot[CH_2]_n\cdot O\cdot CH_2\cdot O\cdot[CH_2]_n\cdot Cl$ (XII.)

prepared by Walton and Green (*J.*, 1945, 315).] It was hoped to effect the *gem*-dimethylation of the above dimethylaminoethyl-lactone but only an unidentified *product*, $C_{15}H_{23}ONCl_2$, was obtained by the action of methylmagnesium iodide followed by hydrogen chloride.

Ultimately the required compounds were obtained by condensing sodiobenzyl cyanide with di-2-chloroethylformal (cf. Bergel *et al.*, *J.*, 1944, 265) (XII, $n = 2$), whereby *di*-3-*cyano*-3-*phenylpropylformal* (XIII, $n = 2$) was satisfactorily obtained; this was hydrolysed to 2-hydroxyethylbenzyl cyanide (XIV, $n = 2$) and thence converted into 2-chloroethylbenzyl cyanide (XV, $n = 2$). Reaction of the last compound with the appropriate bases gave 2-dimethylamino- (XVI, $n = 2$), 2-piperidino-, and 2-*morpholino-ethylbenzyl cyanide*; the first base was described in another connection while this work was in progress (Kwarther and Lucas, *J. Amer. Chem. Soc.*, 1946, **68**, 2395). *Ethyl* γ-*dimethylamino*- (XVII, $n = 2$), γ-*piperidino*-,

$CN\cdot CHPh\cdot[CH_2]_n\cdot O\cdot CH_2\cdot O\cdot[CH_2]_n\cdot CHPhCN$ (XIII.)

$CN\cdot CHPh\cdot[CH_2]_n\cdot OH$ (XIV.)

$CN\cdot CHPh\cdot[CH_2]_n\cdot Cl$ (XV.)

(XVI.) $CN\cdot CHPh\cdot[CH_2]_n\cdot NMe_2$

$CO_2Et\cdot CHPh\cdot[CH_2]_n\cdot NMe_2$ (XVII.)

and γ-morpholino-α-*phenylbutyrate* (the last two characterised as *hydrochlorides*) were obtained by alcoholysis of the nitriles. By similar methods tetramethylene chlorohydrin was converted into *di*-4-*chlorobutylformal* (XII, $n = 4$) and thence into *di*-5-*cyano*-5-*phenylamylformal* (XIII, $n = 4$) and 4-*hydroxybutylbenzyl cyanide* (XIV, $n = 4$) (characterised as its α-*naphthylurethane*), 4-*chlorobutylbenzyl cyanide* (XV, $n = 4$), 4-*dimethylamino*- (XVI, $n = 4$), 4-*methylamino*-, and 4-*morpholino-benzyl cyanide*, and finally into *ethyl* ε-*dimethylamino*- (XVII, $n = 4$), and ε-*morpholino*-α-*phenylhexoate*.

The effectiveness of most of the above nitriles and esters, of types (XVI) and (XVII) respectively, as analgesics was examined in the biological laboratories of I.C.I. Ltd. (Dyestuffs Division). They usually had only a low degree of activity but that of the morpholino-esters was higher, being about one-third of that of pethidine. This seems to be the first indication of the possible superiority of morpholine derivatives in this connection as analgesics, and further implications of this finding are being examined.

Experimental.

Methyl 2-(1′-hydroxy*cyclo*hexyl)propiolate (3·5 g.), 2 : 3-dimethylbutadiene (3 g.), and dry xylene (5 g.) were heated (sealed tube) to 170° for 18 hrs. The original acetylenic compound (1·1 g.) was recovered by distillation at 120°/0·05 mm., and the adduct sublimed at a higher temperature, leaving a residue of rubber-like material. 5 : 6-*Dimethyl*-3-spirocyclo*hexyldihydrophthalide* crystallised from light petroleum in platelets, m. p. 123° (Found: C, 77·4; H, 8·6. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·7%). Light absorption (ethanol): $\lambda_{max.} = 2150$ A., $E_1^1 = 400$.

Sodamide was prepared from sodium (28 g.) in liquid ammonia (700 c.c.) in presnece of ferric nitrate as catalyst. An excess of acetylene was passed in, followed by anhydrous triacetonamine (175 g.) (prepared by distilling the monohydrate at 15 mm.) in ether (175 c.c.) during 15 mins. The mixture was stirred overnight, neutralised with ammonium chloride, and evaporated. The residue was extracted with ether to remove triacetonamine and then with hot glycol monomethyl ether. 4-*Hydroxy*-2 : 2 : 6 : 6-*tetramethyl*-4-*ethynylpiperidine* crystallised on cooling in cubes or rectangular prisms, m. p. 212° (Found: C, 72·6; H, 10·4. $C_{11}H_{19}ON$ requires C, 72·9; H, 10·6%) (yield, 80 g. or 80% calc. on the triacetonamine used). The acetylenic carbinol (9 g.), suspended in dioxan (50 c.c.), was heated (sealed tube) with

methyl iodide (16 g.) to 100° for 90 mins. The product was poured into water (500 c.c.), excess of methyl iodide removed, and excess of 10% aqueous sodium hydroxide added. The solid, together with a further quantity extracted from the filtrate by ether, was crystallised from light petroleum to give *4-hydroxy-1 : 2 : 2 : 6 : 6-pentamethyl-4-ethynylpiperidine* (yield, 8·4 g. or 90%), m. p. 120° (Found C, 73·6; H, 10·65. $C_{12}H_{21}ON$ requires C, 73·8; H, 10·85%). The preceding carbinol (3 g.) was refluxed for 15 mins. with acetic anhydride (10 c.c.) and sodium acetate (3 g.), the solution cooled and poured into an excess of aqueous sodium hydrogen carbonate, and the acetoxy-compound extracted with ether. It could not itself be crystallised but *4-acetoxy-1 : 2 : 2 : 6 : 6-pentamethyl-4-ethynylpiperidine perchlorate* crystallised from glycol monomethyl ether in pointed prisms, m. p. 247° (decomp.) (Found : C, 50·0; H, 7·2. $C_{14}H_{24}O_6NCl$ requires C, 49·8; H, 7·2%).

5-Diethylaminopentan-2-one (18 g.), benzyl cyanide (25 g.), sodium methoxide (5 g.), and ethanol (70 c.c.) were refluxed together for 30 mins., the solution cooled, diluted with water (300 c.c.), and acidified, and material extracted by ether was rejected. The aqueous phase was treated with an excess of potassium carbonate, extracted with ether, and the extract fractionated. *1-Cyano-1-phenyl-2-methyl-2-3′-diethylaminopropylethylene* (yield, 11 g. or 38%) had b. p. 140°/0·1 mm., $n_D^{19°}$ 1·5261 (Found : C, 79·6; H, 9·1; N, 10·6. $C_{17}H_{24}N_2$ requires C, 79·7; H, 9·4; N, 10·9%). 1-Methyl-4-piperidone (5 g.) and benzyl cyanide (10 g.) were similarly condensed. 1-Methyl-4-(cyanophenylmethylene)-piperidine, b. p. 150°/0·5 mm., was precipitated as its *hydrochloride* (yield, 5·7 g. or 52%) by treating the ethereal solution with hydrogen chloride. The salt crystallised from ethanol in rectangular prisms, m. p. 203° (Found : C, 67·25; H, 7·0. $C_{14}H_{17}N_2Cl$ requires C, 67·55; H, 6·9%).

Sodamide from sodium (24 g.) and ferric nitrate (1·2 g.) in liquid ammonia (500 c.c.) was treated slowly with benzyl cyanide (60 g.), and stirring continued for a further 30 mins. Ethylene oxide (45 g.) in ether (250 c.c.) was introduced dropwise, and the mixture stirred for 40 hrs., neutralised with ammonium chloride (60 g.), evaporated, and the residue extracted with water. *2-Imino-3-phenyl-3-2′-hydroxyethyltetrahydrofuran* (61 g., 58%) crystallised from methanol in prisms, m. p. 130° (Found : C, 70·45; H, 7·4; N, 6·6. $C_{12}H_{15}O_2N$ requires C, 70·3; H, 7·4; N, 6·8%). The imino-compound (10 g.) in 1N-hydrochloric acid (55 c.c.) at 0° was slowly treated with sodium nitrite (3·5 g.) in a small volume of water at 0°. Nitrogen was evolved and an oil separated which solidified on keeping overnight. α-Phenyl-α-β′-hydroxyethylbutyrolactone (yield, 9·7 g.) crystallised from carbon tetrachloride–benzene (3 : 1) in prisms, m. p. 77° (Found : C, 69·7; H, 6·8. Calc. for $C_{12}H_{14}O_3$: C, 69·9; H, 6·9%). It was also formed on keeping an acid solution of the imino-compound overnight. It was probably identical with the compound described by Bergel *et al.* (*J.*, 1944, 268; cf. also Walton and Green, *loc. cit.*) as an oil, as the α-phenyl-α-(2-piperidinoethyl)butyrolactone hydrochloride derived from the present compound agreed with that described by Bergel *et al.* The iminotetrahydrofuran (37·5 g.) was boiled gently for 1 hr. with 48% aqueous hydrobromic acid (36 c.c.) and concentrated sulphuric acid (15 c.c.). After dilution with water and ether, the extract was distilled to give α-phenyl-α-(2-bromoethyl)-γ-butyrolactone, b. p. 140°/0·02 mm. (46 g., 94%). This lactone (25 g.) and dimethylamine (7·5 g.) in ether (60 c.c.) were kept at room temperature for 24 hrs. and then at 50° for 7 hrs. Dimethylamine hydrobromide was filtered off, and the filtrate and washings were distilled to give *α-phenyl-α-(2-dimethylaminoethyl)butyrolactone*, b. p. 215°/20 mm. or 140°/0·1 mm. (20·5 g., 95%) (Found : C, 72·3; H, 8·3. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·3%). The *hydrochloride* was precipitated from ethereal solution by hydrogen chloride; it crystallised from ethanol in prisms, m. p. 193° (Found : C, 62·6; H, 7·6. $C_{14}H_{20}O_2NCl$ requires C, 62·3; H, 7·5%). Methylmagnesium iodide [from magnesium (6·5 g.) and methyl iodide (36 g.) in ether (160 c.c.)] was treated dropwise and with stirring with phenyldimethylaminoethylbutyrolactone (10·3 g.) in ether (30 c.c.), and the mixture refluxed for 20 hrs. Excess of Grignard reagent was decomposed by dropwise addition of methanol followed by water. Magnesium compounds were filtered off, and the aqueous layer extracted with ether. The combined extracts were dried and treated with hydrogen chloride. The solid was taken up in ethanolic hydrogen chloride, and the solution boiled for a few minutes, evaporated to small bulk, and allowed to crystallise. The *hydrochloride* recrystallised from ethanol in needles, m. p. 174° (yield, 2·5 g.) (Found : C, 59·25, 59·35; H, 7·5, 7·6; N, 4·2. $C_{15}H_{23}ONCl_2$ requires C, 59·3; H, 7·6; N, 4·6%).

A rapid stream of dry hydrogen chloride was passed for 2 hrs. into an ice-cold mixture of redistilled ethylene chlorohydrin (320 g.), trioxymethylene (65 g.), and anhydrous calcium chloride (55 g.). The mixture was kept at 0° for 2 days, filtered, the solid washed with dry ether, and the combined filtrate and washings were distilled to give di-2-chloroethylformal, b. p. 105°/14 mm. (250 g., 84%).

Fresh sodamide (190 g.) was finely ground under toluene, and suspended in dry toluene (4 l.) in a flask fitted with an efficient stirrer preferably of the Hershberg type (*Org. Synth.*, Coll. Vol. II, 117). Benzyl cyanide (600 g.) was added dropwise with stirring to maintain the temperature of the mixture at about 40°, and the latter was finally warmed gradually and boiled to expel ammonia (15—60 mins.). Dichloroethylformal (410 g.) was added so as to keep the temperature at 40°, and the mixture finally refluxed for 60—90 mins. until the solid had given place to an almost clear brown solution. After cooling and addition of water (500 c.c.), the solution was acidified to Congo-red, any solid (phenylacetamide) rejected, and the toluene layer separated and distilled. *Di-3-cyano-3-phenylpropylformal* (330 g., 65%) had b. p. 115°/0·001 mm. but was difficult to obtain free from phenylacetamide and a chlorinated impurity (Found : C, 75·0; H, 6·5. $C_{21}H_{22}O_2N_2$ requires C, 75·5; H, 6·65%).

The preceding formal (53 g.), ethanol (60 c.c.), water (200 c.c.), and concentrated hydrochloric acid (40 c.c.) were stirred vigorously at 85° for 30 mins., formaldehyde being evolved. After cooling and dilution with water to 400 c.c., the oil was separated, and the aqueous layer extracted twice with ether. The combined oil and extract on distillation gave 2-hydroxyethylbenzyl cyanide (39 g., 75%) (cf. Knowles and Cloke, *loc. cit.*). Thionyl chloride (116 g.) was added slowly to a mixture of hydroxyethylbenzyl cyanide (91 g.) and dimethylaniline (190 g.) which was stirred vigorously and cooled to keep the internal temperature at $\not>$ 20°. The mixture was warmed, kept at 80° for 30 mins., then poured into ice-water, acidified, and extracted with ether. On distilling the extract, 2-chloroethylbenzyl cyanide was collected at 160—180°/14 mm. (yield 66 g., 65%).

Chloroethylbenzyl cyanide (18 g.), piperidine (17 g.), and dioxan (30 c.c.) were heated together to 100°

for 6 hrs.; water (200 c.c.) was added, and the solution acidified and extracted with ether to remove unchanged chloro-compound (35 g.). The aqueous layer was treated with solid potassium carbonate and again extracted with ether. Distillation of the extract gave 2-piperidinoethylbenzyl cyanide (13·5 g., or 60% calc. on the chloro-compound used), b. p. 150°/0·1 mm., the *picrate* of which crystallised from glycol monomethyl ether in rhombic prisms, m. p. 161° (Found: C, 55·4; H, 5·2. $C_{21}H_{23}O_7N_5$ requires C, 55·1; H, 5·1%). 2-Chloroethylbenzyl cyanide (15 g.) and dimethylamine (9·5 g.) in dioxan (40 c.c.) were heated together (sealed tube) to 100° for 20 hrs. The mixture was diluted with water to 200 c.c., neutral products removed from the acidified solution, and excess of potassium carbonate added to the aqueous layer. Extraction with ether and distillation gave 2-dimethylaminoethylbenzyl cyanide (11·5 g., 73%), b. p. 85°/0·05 mm., $n_D^{22°}$ 1·5116 (Found: C, 76·6; H, 8·6. Calc. for $C_{12}H_{16}N_2$: C, 76·55; H, 8·6%) (cf. Kwartler and Lucas, *loc. cit.*). 2-Chloroethylbenzyl cyanide (13·5 g.) and morpholine (14·2 g.) were heated together to 100° for 7 hrs., the solution diluted with water (80 c.c.), and the product isolated as in the preceding preparation. 2-*Morpholinoethylbenzyl cyanide* (yield 10·3 g., 60%) had b. p. 140°/0·05 mm., $n_D^{23°}$ 1·5280 (Found: C, 73·0; H, 7·6. $C_{14}H_{18}ON_2$ requires C, 73·0; H, 7·9%.

Piperidinoethylbenzyl cyanide (12·5 g.), ethanol (30 c.c.), and concentrated sulphuric acid (11 g.) were heated (sealed tube) to 135° for 5 hrs., the solution poured into ice-water (200 c.c.), and the basic ester salted out with an excess of potassium carbonate. The aqueous layer was extracted three times with ether, and the combined oil and extracts on distillation gave *ethyl γ-piperidino-α-phenylbutyrate* (10·3 g., 68%), b. p. 115°/0·05 mm., $n_D^{20°}$ 1·5162 (Found: C, 74·4; H, 8·8. $C_{17}H_{25}O_2N$ requires C, 74·2; H, 9·2%). Dry hydrogen chloride was passed into a solution of the basic ester in ether; the precipitated *hydrochloride* crystallised from dioxan in rectangular prisms, m. p. 176° (Found: C, 65·6; H, 8·2; N, 4·4. $C_{17}H_{26}O_2NCl$ requires C, 65·4; H, 8·4; N, 4·5%). *Ethyl γ-dimethylamino-α-phenylbutyrate* (yield, 8·2 g., 73%) was similarly prepared from dimethylaminoethylbenzyl cyanide (9 g.), ethanol (35 c.c.), and sulphuric acid (10 g.); it had b. p. 100°/1·5 mm., $n_D^{29°}$ 1·5010 (Found: C, 71·4; H, 9·0. $C_{14}H_{21}O_2N$ requires C, 71·4; H, 9·0%). Ethyl γ-morpholino-α-phenylbutyrate (8·5 g., 70%) was similarly obtained from morpholinoethylbenzyl cyanide (10 g.), ethanol (30 c.c.), and sulphuric acid (8·5 g.). The ester had b. p. 135°/1·5 mm., $n_D^{21·5°}$ 1·5207, $n_D^{17°}$ 1·5190; the *hydrochloride*, prepared with ethereal hydrogen chloride, crystallised from chloroform or dioxan in rectangular prisms, m. p. 169° (Found: C, 61·8; H, 7·5. $C_{16}H_{24}O_3NCl$ requires C, 61·3; H, 7·7%).

A slow stream of dry hydrogen chloride was passed into boiling tetrahydrofuran (200 g.) until the temperature of the liquid was 102° (*ca.* 6 hrs.). The solution was cooled to 0°, trioxymethylene (35 g.) added, and a rapid stream of hydrogen chloride passed in for 1 hr. After addition of anhydrous calcium chloride (50 g.), the mixture was kept at room temperature for 5 days, the solid removed, and the liquid distilled. Small quantities of unchanged tetrahydrofuran, tetramethylene dichloride, and tetramethylene chlorohydrin (30 g.) were recovered, and *di-4-chlorobutylformal* (150 g., 47%) collected at 100°/0·01 mm. (Found: C, 47·2; H, 8·1. $C_9H_{18}O_2Cl_2$ requires C, 47·2; H, 7·9%). A further product (30 g.) had b. p. 130°/0·01 mm.

Sodiobenzyl cyanide was prepared from benzyl cyanide (310 g.) and sodamide (105 g.) in toluene (2 l.) as described above. Di-4-chlorobutylformal (197 g.) was added to the sodio-compound, and the whole refluxed with stirring for 1 hr. After cooling, water (600 c.c.) was added, followed by excess of acetic acid. The aqueous layer was extracted twice with ether, and the combined toluene and ether extracts were distilled. Unchanged benzyl cyanide was recovered, followed by phenylacetamide, and *di-5-phenyl-5-cyanoamylformal* (120 g.) was collected at 125°/0·002 mm.; it had $n_D^{18°}$ 1·5268 (Found: C, 77·1; H, 7·6; N, 7·6. $C_{25}H_{30}O_2N_2$ requires C, 76·9; H, 7·7; N, 7·2%).

The above formal (43 g.) was hydrolysed with ethanol (50 c.c.), water (150 c.c.), and concentrated hydrochloric acid (30 c.c.), and the product isolated as described for hydroxyethylbenzyl cyanide. 4-*Hydroxybutylbenzyl cyanide* (34 g., 80%) had b. p. 160°/0·2 mm. (Found: C, 75·8; H, 7·5. $C_{12}H_{15}ON$ requires C, 76·1; H, 8·0%). The *α-naphthylurethane* was prepared by heating the carbinol with the equivalent quantity of α-naphthyl *iso*cyanate at 80° for 15 mins. (sealed tube). The gum was washed with light petroleum and eventually recrystallised from benzene, carbon tetrachloride, or *cyclo*hexane in small needles, m. p. 96° (Found: C, 77·1; H, 6·3. $C_{23}H_{22}O_2N_2$ requires C, 77·05; H, 6·2%). 4-*Chlorobutylbenzyl cyanide* (125 g. or 78%) was prepared from the preceding carbinol (145 g.), dimethylaniline (220 g.), and thionyl chloride (125 g.) by the method used for chloroethylbenzyl cyanide; the chlorobutyl compound had b. p. 125°/0·1 mm., $n_D^{21°}$ 1·5276 (Found: C, 69·5; H, 6·8. $C_{12}H_{14}NCl$ requires C, 69·5; H, 6·8%).

Chlorobutylbenzyl cyanide (14 g.), 33% methylamine in ethanol (12 g.), and ether (80 c.c.) were heated to 100° for 16 hrs. (sealed tube), the product diluted with water to 200 c.c., and potassium carbonate added. The aqueous layer was extracted twice with ether, distillation of the extract giving 4-*methylaminobutylbenzyl cyanide* (10 g., 73%), b. p. 125°/0·5 mm., $n_D^{30°}$ 1·5117 (Found: C, 77·3; H, 9·1. $C_{13}H_{18}N_2$ requires C, 77·2; H, 9·0%). 4-*Dimethylaminobutylbenzyl cyanide* (13·7 g., 80%) was prepared from the appropriate chloro-compound (36·5 g.) and dimethylamine (9·5 g.) in dioxan (40 c.c.) as described for the dimethylaminoethyl compound; it had b. p. 110°/0·5 mm., $n_D^{24°}$ 1·5053 (Found: C, 77·8; H, 9·0. $C_{14}H_{20}N_2$ requires C, 77·7; H, 9·3%). Similarly 4-*morpholinobutylbenzyl cyanide* (15·5 g., 78%) was obtained from the chloro-compound (16 g.) and morpholine (14·4 g.). It had b. p. 190°/0·5 mm., n_D^{25} 1·5210 (Found: C, 74·5; H, 8·5; N, 10·8. $C_{16}H_{22}ON_2$ requires C, 74·4; H, 8·6; N, 10·85%); the *picrate* crystallised from glycol monoethyl ether in prismatic needles, m. p. 123° (Found: C, 53·9; H, 5·3; N, 14·9. $C_{22}H_{25}O_8N_5$ requires C, 54·2; H, 5·2; N, 14·4%).

Alcoholysis of the nitrile group in the above substituted butylbenzyl cyanides was effected as in the preparation of the substituted aminobutyric esters above. 4-Dimethylaminobutylbenzyl cyanide (11·5 g.), ethanol (40 c.c.), and concentrated sulphuric acid (10·4 g.) gave *ethyl ε-dimethylamino-α-phenylhexoate* (12·3 g., 88%), b. p. 115°/1·5 mm., $n_D^{25°}$ 1·4945 (Found: C, 73·2; H, 9·7. $C_{16}H_{25}O_2N$ requires C, 73·1; H, 9·6%). 4-Morpholinobutylbenzyl cyanide (13 g.), ethanol (35 c.c.), and sulphuric acid (10 g.) gave *ethyl ε-morpholino-α-phenylhexoate* (12·4 g., 80%), b. p. 145°/0·2 mm., $n_D^{27°}$ 1·5128 (Found: C, 70·8; H, 8·6. $C_{18}H_{27}O_3N$ requires C, 70·8; H, 8·9%); its hydrochloride, precipitated from ether by hydrogen chloride, crystallised from ethyl acetate in small prisms, m. p. 133—135°.

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W.7.

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