# 71. *Synthetic Analgesics. Part IV. Synthesis of 3-Substituted Piperidines and Pyrrolidines.**

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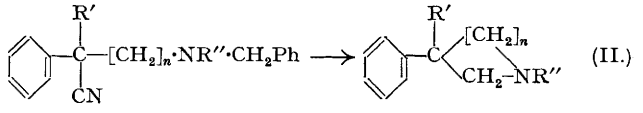
New syntheses of 3-phenyl-pyrrolidine and -piperidine compounds are described. When benzylalkylaminoalkyl derivatives of phenylacetonitrile or ethyl phenylcyanoacetate were submitted to catalytic hydrogenation, reduction of the nitrile group occurred with simultaneous removal of the benzyl group and elimination of ammonia under ring closure. When *N*-dibenzylaminoalkyl derivatives were used, ring closure was followed by hydrogenolysis of the second benzyl group, yielding secondary cyclic bases. Catalytic hydrogenation of ω-cyanoalkyl derivatives of ethyl phenylcyanoacetate also gave secondary cyclic bases.

In the three preceding papers certain aspects of the chemistry of 4-arylpiperidine compounds were discussed. We now present new syntheses of 3-phenyl-pyrrolidine and -piperidine compounds, some of which possess analgesic properties.

While attempting to prepare γ-methylamino-α-phenylbutyronitrile by selective hydrogenolysis of γ-benzylmethylamino-α-phenylbutyronitrile (I; R′ = H, R″ = $CH_3$; $n = 2$), we observed that 4-phenyl-1-methylpyrrolidine (II; R = H, R″ = $CH_3$; $n = 2$) was always formed. This is undoubtedly due to simultaneous reduction of the nitrile group, followed by elimination of ammonia to give a ring compound. This reaction




obviously afforded a general method of synthesising substituted pyrrolidines, and it was found that it could be extended to the preparation of substituted piperidines by hydrogenation of δ-benzylalkylamino-α-phenylvaleronitriles. Where R″ = $CH_2Ph$, it was found that the second benzyl radical was removed after ring closure, and secondary bases were formed (II; R″ = H).

Esters of 3-phenyl-1-methyl-pyrrolidine- and -piperidine-3-carboxylic acids were readily prepared by this method, starting from ethyl phenylcyanoacetate derivatives (I; R′ = $CO_2Et$, R″ = $CH_3$; $n = 2$ or 3). 3-Phenyl-1-methylpyrrolidine was also isolated from an attempt to prepare γ-methylamino-α-phenylbutyronitrile by hydrogenation of β-aldehydo-α-phenylpropionitrile in presence of methylamine.

3-Phenyl-1-methylpyrrolidine (II; R′ = H, R″ = $CH_3$; $n = 2$) was prepared by condensing phenylacetonitrile with β-chloroethylbenzylmethylamine in the presence of sodamide and hydrogenating the resulting *γ-benzylmethylamino-α-phenylbutyronitrile* (I; R′ = H, R″ = $CH_3$; $n = 2$). In a similar way *ethyl 3-phenyl-1-methylpyrrolidine-3-carboxylate* (II; R′ = $CO_2Et$, R″ = $CH_3$; $n = 2$) was obtained by catalytic hydrogenation of *ethyl α-cyano-γ-benzylmethylamino-α-phenylbutyrate* (I; R′ = $CO_2Et$, R″ = $CH_3$; $n = 2$).

For the syntheses of the corresponding piperidine derivatives *γ-chloropropylbenzylmethylamine* was prepared by the condensation of α-chloro-γ-bromopropane (from allyl chloride and hydrogen bromide) with benzylmethylamine (cf. Marxer, *Helv. Chim. Acta*, 1941, *E*, **24**, 214). Ethyl sodiophenylcyanoacetate when condensed with γ-chloropropylbenzylmethylamine gave *ethyl α-cyano-δ-benzylmethylamino-α-phenylvalerate* (I; R′ = $CO_2Et$, R″ = $CH_3$; $n = 3$), which on hydrogenation gave *ethyl 3-phenyl-1-methylpiperidine-3-carboxylate*. By starting from ethyl *o*-tolylcyanoacetate, the *o-tolyl* analogue was synthesised in the same manner.

As we also wished to prepare a piperidine derivative with a group other than phenyl in the 3-position, we condensed ethyl benzylcyanoacetate with γ-chloropropylbenzylmethylamine to give *ethyl α-cyano-δ-benzylmethylamino-α-benzylvalerate*, which on hydrogenation yielded *ethyl 3-benzyl-1-methylpiperidine-3-carboxylate*. *Ethyl 3-phenylpiperidine-3-carboxylate* was prepared most conveniently by condensation of ethyl sodiophenylcyanoacetate with α-chloro-γ-bromopropane in alcohol to give *ethyl δ-chloro-α-cyano-α-phenylvalerate*, which on heating with 2 mols. of dibenzylamine yielded *ethyl α-cyano-δ-dibenzylamino-α-phenylvalerate* (I; R′ = $CO_2Et$, R″ = $CH_2Ph$; $n = 3$). Catalytic hydrogenation gave the desired piperidine compound. Ethyl 3-phenylpiperidine-3-carboxylate was also synthesised by catalytic hydrogenation of *ethyl αγ-dicyano-α-phenylbutyrate*, prepared by the condensation of ethyl phenylcyanoacetate with β-chloropropionitrile. Similarly, catalytic hydrogenation of *ethyl αβ-dicyano-α-phenylpropionate* (from ethyl phenylcyanoacetate and chloroacetonitrile) yielded *ethyl 3-phenylpyrrolidine-3-carboxylate*.

3-Phenyl-1-methylpyrrolidine was also prepared by catalytic hydrogenation of *β-aldehydo-α-phenyl-*

* Cf. B.P. 552,065 (1943); Pats. pend. Nos. 1310 and 3827 (1943).

*propionitrile* in presence of methylamine. The *acetal* of this aldehyde was formed by condensation of bromodiethylacetal with benzyl cyanide in presence of sodamide.

Studies of the resolution of the racemic compounds and of the properties of the optically active isomers will be published later. The pharmacology of the compounds will be reported in association with Professor A. D. Macdonald and Dr. G. Woolfe, University of Manchester (Department of Pharmacology).

## Experimental.

*γ-Chloropropylbenzylmethylamine.*—Benzylmethylamine (37·8 g.) was added slowly with stirring to a solution of α-chloro-γ-bromopropane (24·5 g.) in ether (25 c.c.) at room temperature. The mixture was warmed at 30° for 90 minutes, the water-bath then heated to 40—45°, and stirring continued for 7 hours. The crystalline benzylmethylamine hydrobromide was filtered off, and the ethereal solution extracted with dilute hydrochloric acid. The extract was made alkaline, and the oil which separated taken up in ether, and dried over anhydrous sodium sulphate. *γ-Chloropropylbenzylmethylamine* distilled at 137—138°/16 mm. as a colourless oil (19·4 g.) (Found: N, 7·2; Cl, 18·3. $C_{11}H_{16}NCl$ requires N, 7·1; Cl, 18·0%). On prolonged standing it underwent autocondensation.

*β-Cyano-β-phenylpropaldehyde Diethylacetal.*—Phenylacetonitrile (13·0 g.) was added slowly with stirring to powdered sodamide (4·3 g.) suspended in dry ether (50 c.c.), the mixture refluxed for 10 minutes, then cooled to 0°; bromoacetal (21·7 g.) was then added slowly (2 hours), and stirring continued at room temperature overnight. The reaction mixture was poured on ice, the ethereal layer separated, washed with water, dried over anhydrous sodium sulphate, and evaporated. The residue was distilled, and the *acetal* obtained as a colourless oil (10 g.), b. p. 120—121°/0·2 mm. (Found: N, 5·8. $C_{14}H_{19}O_2N$ requires N, 6·0%).

*β-Cyano-β-phenylpropaldehyde.*—The acetal (5 g.) was shaken with 15% hydrochloric acid (20 c.c.) for 24 hours in nitrogen. The mixture was then extracted with ether, and the extract washed with dilute potassium carbonate solution, dried over anhydrous sodium sulphate, and evaporated. The residue on distillation gave the *aldehyde* (2·7 g.) as a colourless oil, b. p. 109—111°/0·1 mm. (Found: N, 8·6. $C_{10}H_9ON$ requires N, 8·8%).

*γ-Benzylmethylamino-α-phenylbutyronitrile* (I; R′ = H, R″ = $CH_3$; *n* = 2).—Phenylacetonitrile (48 g.) was added slowly with stirring to powdered sodamide (16·2 g.) suspended in dry ether (260 c.c.), and the mixture refluxed for 20 minutes and then cooled to 15°; β-chloroethylbenzylmethylamine (69 g.) was now added slowly (30 minutes), and stirring continued overnight. The mixture was poured into water, the ethereal layer extracted with dilute hydrochloric acid, the extract made alkaline, and the oil which separated taken up in ether. After being washed, and dried over anhydrous sodium sulphate, the ether was evaporated. The residue was distilled, giving *γ-benzylmethylamino-α-phenylbutyronitrile* (74 g.) as a yellow oil, b. p. 158°/0·1 mm. (Found: N, 10·7. $C_{18}H_{20}N_2$ requires N, 10·6%). Its *reineckate* melted at 104—107° (Found: N, 19·0. $C_{22}H_{26}N_8S_2Cr$ requires N, 19·2%).

*3-Phenyl-1-methylpyrrolidine* (I; R′ = H; R″ = $CH_3$).—(A) β-Cyano-β-phenylpropaldehyde (2 g.) was reduced catalytically with palladium–charcoal (1 g. of charcoal + 5 c.c. of 5% aqueous palladium chloride) in a mixture of alcohol and a 33% aqueous solution of methylamine (5 c.c.). When the hydrogen absorption had ceased, the mixture was filtered and the solvents evaporated. The residue was extracted with dilute hydrochloric acid, the extract made alkaline, the precipitated base taken up in ether, the ethereal solution dried (potassium carbonate), and the ether evaporated; the residue was distilled to give a small amount of 3-phenyl-1-methylpyrrolidine. Recrystallised from water, its *picrate* melted at 155—158° (Found: C, 52·5; H, 5·3; N, 14·5. $C_{17}H_{18}O_7N_4$ requires C, 52·4; H, 4·6; N, 14·4%).

(B) γ-Benzylmethylamino-α-phenylbutyronitrile (9·2 g.) was reduced catalytically in methanol solution, the catalyst being 2 g. of charcoal and 12 c.c. of 5% aqueous palladium chloride solution containing 6% hydrogen chloride. When hydrogen absorption had ceased, the mixture was worked up in the usual manner, giving 3-phenyl-1-methylpyrrolidine as a colourless oil, b. p. 105—110°/11 mm. Its picrate melted at 155—158° alone and when mixed with that described in (A).

*Ethyl α-Cyano-γ-benzylmethylamino-α-phenylbutyrate* (I; R′ = $CO_2Et$, R″ = $CH_3$; *n* = 2).—(A) Sodium wire (0·43 g.) was covered with dry ether (50 c.c.), and ethyl phenylcyanoacetate (3·5 g.) added slowly with stirring. When the sodium had dissolved, a solution of β-chloroethylbenzylmethylamine (3·5 g.) in dry toluene (50 c.c.) was added, the ether distilled off, and the toluene solution heated on the water-bath for 16 hours. After cooling, the reaction mixture was poured into water, and the toluene layer separated. After removal of the solvent, the product was distilled, giving *ethyl α-cyano-γ-benzylmethylamino-α-phenylbutyrate* as a yellow oil (5·4 g.), b. p. 176—178°/0·2 mm. (Found: C, 75·6; H, 7·2; N, 8·1. $C_{21}H_{24}O_2N_2$ requires C, 75·0; H, 7·1; N, 8·3%).

(B) Ethylene dibromide (7·6 g.) was added to a solution of ethyl sodiophenylcyanoacetate (7·6 g. ester, 0·5 g. sodium) in absolute alcohol (12 c.c.), and the mixture heated in a sealed tube at 115° for 3 hours. The sodium bromide was filtered off, and the alcohol evaporated. The residue was taken up in ether, the solution washed with water, and dried by distilling with benzene. The remaining oil (9·2 g.) was heated in alcoholic benzylmethylamine solution (6·1 g. in 10 c.c.) in a sealed tube at 100° for 2 hours, the product filtered, and the solvent evaporated. The residual oil was taken up in ether, and the ethereal solution extracted with dilute hydrochloric acid, the acid extract made alkaline, and the oil which separated taken up in ether. After washing, drying, and evaporation of the extract, the residue was distilled. The oil boiled at 174—180°/0·2 mm. Its identity was proved by hydrogenation, which gave (II; R′ = $CO_2Et$, R″ = $CH_3$; *n* = 2).

*Ethyl 3-Phenyl-1-methylpyrrolidine-3-carboxylate* (II; R′ = $CO_2Et$, R″ = $CH_3$; *n* = 2).—A mixture of aqueous 5% palladium chloride solution (10 c.c.) containing 6% of hydrogen chloride, charcoal (1 g.), and alcohol (50 c.c.) was shaken in a hydrogen atmosphere until absorption of hydrogen ceased. Ethyl α-cyano-γ-benzylmethylamino-α-phenylbutyrate (2·4 g.) was then added, and the hydrogenation continued. When the absorption of hydrogen had ceased, the reaction mixture was filtered and worked up as described above. The *ester* distilled at 114°/0·4 mm. as a colourless oil (Found: C, 72·2; H, 8·4. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·2%). Its *picrate* melted at 115—118° after recrystallisation from alcohol (Found: C, 51·7; H, 4·7; N, 12·3. $C_{20}H_{22}O_9N_4$ requires C, 51·9; H, 4·7; N, 12·1%).

*Ethyl α-Cyano-δ-benzylmethylamino-α-phenylvalerate* (I; R′ = $CO_2Et$, R″ = $CH_3$; *n* = 3).—Ethyl phenylcyanoacetate (18·9 g.) was dissolved in dry toluene (150 c.c.), and powdered sodamide (4·0 g.) added in several portions with mechanical stirring. The mixture was gradually heated to boiling, refluxed for 30 minutes, and cooled to room temperature; γ-chloropropylbenzylmethylamine (21 g.) was added, and the mixture slowly heated to boiling and refluxed for 2 hours. The product was treated with water, the toluene layer separated, washed with water, and evaporated under reduced pressure. The residue was distilled in a high vacuum. The *ester* distilled at 180°/0·2 mm. as a thick yellow oil (26·8 g.) (Found: C, 75·9; H, 7·7; N, 8·3. $C_{22}H_{26}O_2N_2$ requires C, 75·5; H, 7·5; N, 8·0%).

*Ethyl 3-Phenyl-1-methylpiperidine-3-carboxylate* (II; R′ = $CO_2Et$, R″ = $CH_3$; *n* = 3).—A mixture of aqueous 5% palladium chloride solution, containing 6% of hydrogen chloride (20 c.c.), charcoal (6 g.), and alcohol (200 c.c.) was shaken in a hydrogen atmosphere until hydrogen absorption ceased. Ethyl α-cyano-δ-benzylmethylamino-α-phenylvalerate (12·8 g.) was then added, and shaking resumed. The absorption of hydrogen was very rapid. When it had slackened, an additional portion of palladium chloride solution (5 c.c.) was added, and hydrogenation carried to completion. The

product was worked up as described in previous experiments. The *ester* (5·6 g.) distilled as a colourless oil at 104°/0·2 mm. (Found : C, 72·9; H, 8·6; N, 5·7. $C_{15}H_{21}O_2N$ requires C, 72·8; H, 8·5; N, 5·7%). Its *hydrochloride*, a white, hygroscopic crystalline solid melted at 177—180° after recrystallisation from alcohol–ether (Found : C, 62·9; H, 7·9; N, 5·0; Cl, 12·4. $C_{15}H_{22}O_2NCl$ requires C, 63·6; H, 7·8; N, 5·0; Cl, 12·4%). The *hydriodide* after recrystallisation from alcohol had m. p. 207° (Found : C, 48·3; H, 6·0; N, 3·7; I, 34·3. $C_{15}H_{22}O_2NI$ requires C, 48·0; H, 5·9; N, 3·7; I, 33·9%).

3-*Phenyl*-1-*methylpiperidine*-3-*carboxylic Acid*.—The above ester (2·5 g.) was refluxed with 10% alcoholic potash solution (50 c.c.) for 2 hours, the solvent evaporated, and the residue made acid to Congo-red with dilute hydrochloric acid. The acid solution was evaporated to dryness under reduced pressure, and the salts were dried over phosphoric oxide. After extraction with absolute alcohol, filtration, and evaporation of the alcohol, the residue was sublimed in a high vacuum (oil bath : 200°/0·1 mm.). The hydrochloride of the acid was obtained in white needles, m. p. 265°. The *picrate* had m. p. 196—199° after recrystallisation from alcohol (Found C, 50·3; H, 4·5; N, 12·5. $C_{19}H_{20}O_9N_4$ requires C, 50·9; H, 4·5; N, 12·5%).

*Methyl ester*. Thionyl chloride (50 c.c.) was added to the crude mixture of potassium chloride and acid hydrochloride obtained as described above. After refluxing for 15 minutes, the excess of thionyl chloride was distilled off under reduced pressure. Dry methanol (15 c.c.) was added, the mixture refluxed for 15 minutes, the excess of methanol distilled off, and the residue taken up in ice-cold dilute hydrochloric acid and extracted with ether. The aqueous layer was made alkaline and extracted with ether; the extract was washed with water, dried (sodium sulphate), and evaporated; distillation of the residue gave the methyl ester (1·4 g.) as a colourless oil, b. p. 110°/0·4 mm. Recrystallised from methanol–ether, its *hydrochloride* melted at 177—179° (Found : C, 61·2; H, 7·4; N, 5·6; Cl, 12·6. $C_{14}H_{20}O_2NCl$ requires C, 62·4; H, 7·5; N, 5·2; Cl, 13·0%).

The *n*-propyl ester, similarly prepared, was a colourless oil, b. p. 110°/0·2 mm.; *hydrochloride*, m. p. 174—175° (Found : C, 63·1; H, 8·2; N, 4·8; Cl, 12·5. $C_{16}H_{24}O_2NCl$ requires C, 64·6; H, 8·1; N, 4·7; Cl, 11·8%). The *iso*propyl ester had b. p. 110°/0·2 mm., and gave a *hydrochloride*, m. p. 191—193° (Found : C, 64·6; H, 8·4; N, 4·6; Cl, 11·5%).

The *diethylamide*, prepared by treatment of the acid chloride with an excess of diethylamine at 0°, distilled at 125—128°/0·1 mm. as a thick yellow oil; yield 74% (Found : C, 74·7; H, 9·5; N, 10·6. $C_{17}H_{26}O_2N_2$ requires C, 74·5; H, 9·5; N, 10·2%).

*Ethyl* o-*Tolylcyanoacetate*.—A solution of *o*-tolylacetonitrile (21·5 g.) in dry ether (40 c.c.) was added slowly to powdered sodamide (7·2 g.) suspended in dry ether (70 c.c.) with mechanical stirring, and the mixture refluxed for 15 minutes. Ethyl carbonate (25 g.) was then added slowly with external cooling, and the reaction completed by refluxing for 90 minutes. The mixture was then poured into ice water, the ethereal layer separated, washed with water, dried over anhydrous sodium sulphate, and evaporated. The residue on distillation gave *ethyl* o-*tolylcyanoacetate* (19·8 g.) as a faintly yellow oil, b. p. 110—114°/0·1 mm. (Found : N, 7·1. $C_{12}H_{13}O_2N$ requires N, 6·9%).

*Ethyl* α-*Cyano*-δ-*benzylmethylamino*-α-o-*tolylvalerate*.—Powdered sodamide (1·2 g.) was added in several portions to a solution of the above ester (6·1 g.) in dry toluene (50 c.c.) with mechanical stirring, and the mixture finally refluxed for 15 minutes. γ-Chloropropylbenzylmethylamine (6·0 g.) was then added gradually with external cooling, and the reaction completed by 3 hours' refluxing. The mixture was then treated with dilute hydrochloric acid, and the insoluble oily hydrochloride separated, treated with alkali, and extracted with ether. The ethereal extract was washed with water, dried (potassium carbonate), and evaporated. The *nitrile* (7·1 g.) distilled at 199—200°/0·2 mm. as a yellow, viscous oil (Found : C, 75·1; H, 7·9; N, 7·7. $C_{23}H_{28}O_2N_2$ requires C, 75·8; H, 7·8; N, 7·7%).

*Ethyl* 3-(o-*Tolyl*)-1-*methylpiperidine*-3-*carboxylate*.—A mixture of charcoal (6 g.), 5% aqueous palladium chloride solution containing 6% of hydrogen chloride (10 c.c.), and alcohol (250 c.c.) was shaken in a hydrogen atmosphere until hydrogen absorption ceased. The foregoing ester (6·6 g.) and an additional portion of palladium chloride solution (5 c.c.) were then added, and hydrogenation continued until no more hydrogen was absorbed. The product was worked up as described in previous examples. The *ester*, a colourless oil (3·2 g.), distilled at 126—128°/0·2 mm. (Found : N, 5·9. $C_{16}H_{23}O_2N$ requires N, 5·4%). Recrystallised from alcohol–ether, the *hydrochloride* had m. p. 200—201° (Found : C, 64·8; H, 8·2; Cl, 11·9. $C_{16}H_{24}O_2NCl$ requires C, 64·7; H, 8·1; Cl, 11·8%). The *hydriodide*, recrystallised from alcohol, had m. p. 178—180° (Found : N, 3·5. $C_{16}H_{24}O_2NI$ requires N, 3·6%).

*Ethyl* α-*Cyano*-δ-*benzylmethylamino*-α-*benzylvalerate*.—Ethyl benzylcyanoacetate (10 g.) and γ-chloropropylbenzylmethylamine (11 g.) were dissolved in toluene (100 c.c.), and powdered sodamide (2·4 g.) added gradually with vigorous stirring. The mixture was then refluxed for 7 hours. On being worked up in the usual manner, the basic *ester* was obtained as a viscous oil, b. p. 225—235°/0·4 mm. (Found : C, 76·3; H, 8·0; N, 7·5. $C_{23}H_{28}O_2N_2$ requires C, 75·8; H, 7·7; N, 7·7%).

*Ethyl* 3-*Benzyl*-1-*methylpiperidine*-3-*carboxylate*.—The above ester (5 g.) was hydrogenated in alcohol with a catalyst prepared from charcoal (2 g.) and 5% palladium chloride (10 c.c.), with the addition of a further 2 c.c. of the latter after hydrogenation had started. When hydrogen uptake had ceased, the catalyst was filtered off, the filtrate concentrated, water added, and the aqueous solution made alkaline with sodium hydroxide solution. The liberated base was taken up in ether, the solution dried, concentrated, and the residue distilled, giving *ethyl* 3-*benzyl*-1-*methylpiperidine*-3-*carboxylate* (2·1 g.), b. p. 125—135°/0·3 mm. (Found : C, 74·3; H, 9·2; N, 5·6. $C_{16}H_{23}O_2N$ requires C, 73·6; H, 8·8; N, 5·4%).

*Ethyl* δ-*Chloro*-α-*cyano*-α-*phenylvalerate*.—To a solution of sodium (0·92 g.) in absolute alcohol (40 c.c.) and ethyl phenylcyanoacetate (8·0 g.), α-chloro-γ-bromopropane (12·6 g.; 2 mols.) was added, and the mixture heated on a water-bath with mechanical stirring for 7 hours. The product was filtered, the alcohol evaporated, and the residual oil taken up in ether. The extract was washed with water, dried over anhydrous sodium sulphate, and evaporated. The *ester* distilled at 128—129°/0·1 mm. as a colourless oil (9·6 g.) (Found : N, 5·0. $C_{14}H_{16}O_2NCl$ requires N, 5·3%).

*Ethyl* α-*Cyano*-δ-*dibenzylamino*-α-*phenylvalerate* (I; R′ = $CO_2Et$, R″ = $CH_2Ph$; *n* = 3).—A solution of ethyl δ-chloro-α-cyano-α-phenylvalerate (43·5 g.), dibenzylamine (65·25 g.), and sodium iodide (26·95 g.) in dry acetone (200 c.c.) was refluxed for 21 hours. After cooling, the reaction mixture was filtered, the acetone evaporated, and the residue taken up in ether. After being washed with dilute sodium hydroxide solution and water, and dried over potassium carbonate, the extract was evaporated. The *ester* distilled as a yellow, viscous oil (64·5 g.) at 215—217°/0·1 mm. (Found : C, 79·8; H, 7·2; N, 7·0. $C_{28}H_{30}O_2N_2$ requires C, 78·8; H, 7·0; N, 6·6%).

*Ethyl* αγ-*Dicyano*-α-*phenylbutyrate*.—To a solution of ethyl phenylcyanoacetate (15·0 g.) in dry toluene (75 c.c.), powdered sodamide (3·1 g.) was added with mechanical stirring, and the mixture refluxed for 15 minutes. A solution of β-chloropropionitrile (7·0 g.) in dry toluene (5 c.c.) was then added, and refluxing continued for 2 hours. The product was cooled, poured into water, and the toluene layer separated, washed with water, and evaporated under reduced pressure. The *ester* distilled as a colourless oil (12·2 g.) at 145°/0·1 mm. (Found : C, 69·5; H, 5·8; N, 11·7. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8; N, 11·6%).

*Ethyl* αβ-*Dicyano*-α-*phenylpropionate*.—To a solution of ethyl phenylcyanoacetate (11 g.) in dry toluene (50 c.c.), powdered sodamide (2·1 g.) was added, and the sodio-derivative prepared as in the above experiment. Chloroacetonitrile (4·0 g.) was then added, and after refluxing for 2 hours the reaction mixture was worked up as above. The *ester* distilled as a colourless oil (8·1 g.) at 141—142°/0·1 mm. (Found : C, 68·9; H, 5·6; N, 11·8. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3; N, 12·3%).

*Ethyl* 3-*Phenylpiperidine*-3-*carboxylate* (II; R′ = $CO_2Et$, R″ = H; $n = 3$).—(A) A mixture of charcoal (12 g.), 10% aqueous palladium chloride solution (5 c.c.) containing 6% of hydrogen chloride, alcohol (200 c.c.), and water (50 c.c.) was shaken in a hydrogen atmosphere until no more hydrogen was taken up. Ethyl α-cyano-δ-dibenzylamino-α-phenylvalerate (12·9 g.) and an alcoholic solution of hydrogen chloride (4 c.c. of 5·67N) were then added, and the hydrogenation continued, the temperature being kept at approx. 40°. When the absorption of hydrogen had slackened, a further 3 c.c. of palladium chloride solution were added, and the hydrogenation carried to completion. After filtration, the product was worked up as previously described. The *ester* (5·3 g.) distilled at 115—117°/0·1 mm. as a colourless oil (Found C, 70·6, 70·7; H, 8·4, 8·1; N, 6·2. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·2; N, 6·1%). It formed a solid *nitroso*-derivative, m. p. 88—89° after recrystallisation from light petroleum (b. p. 60—80°) (Found : C, 63·9; H, 6·9; N, 10·6. $C_{14}H_{18}O_3N_2$ requires C, 64·1; H, 6·9; N, 10·7%).

(B) Hydrogenation of ethyl αγ-dicyanobutyrate (2·2 g.) was effected as before by means of a mixture of charcoal (3 g.), 10% aqueous palladium chloride solution (10 c.c.) containing 6% of hydrogen chloride, and alcohol (100 c.c.), a further 0·2 g. of catalyst being used later. The product was worked up as in the previous experiment. A colourless oil (0·8 g.) was obtained, b. p. 115—117°/0·1 mm., which gave a nitroso-derivative identical with that obtained in the preceding experiment.

*Ethyl* 3-*Phenylpyrrolidine*-3-*carboxylate* (II; R′ = $CO_2Et$, R″ = H; $n = 2$).—Ethyl αβ-dicyano-α-phenylpropionate (2·3 g.) was hydrogenated, palladised charcoal being used as catalyst [prepared from charcoal (4 g.), 5% aqueous palladium chloride solution (10 c.c.), and alcohol (75 c.c.)]. Hydrogenation proceeded very slowly and several portions of palladium chloride solution (total 17 c.c.) and platinum oxide (0·2 g.) had to be added to complete it. The product was worked up as above. The *ester* (0·6 g.) distilled at 97°/0·1 mm. as a colourless oil (Found : C, 71·8; H, 8·0; N, 6·6. $C_{13}H_{17}O_2N$ requires C, 71·3; H, 7·8; N, 6·4%).

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