# 69. *Synthetic Analgesics. Part II. A New Synthesis of Pethidine and Similar Compounds.**

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A new method of synthesising 4-arylpiperidine-4-nitriles is described. Arylacetonitriles were condensed with 2 mols. of β-chloroethyl vinyl ether, and the resulting αα-bis-(β′-vinyloxyethyl)arylacetonitriles hydrolysed to the corresponding di-alcohols, which were chlorinated and then treated with primary amines to give the above nitriles. The same di-alcohols were obtained by hydrolysis of αα-bis-(β′-alkoxymethyloxyethyl)arylacetonitriles, which were prepared by condensation of arylacetonitriles with 2 mols. of alkyl-β-chloroethylformals.

In this way, 4-phenyl-1-methylpiperidine-4-nitrile and 4-o-*tolyl*-1-*methylpiperidine*-4-*nitrile* were prepared. Hydrolysis with concentrated hydrochloric acid gave the corresponding carboxylic acids. Several esters of 4-phenyl-1-methylpiperidine-4-carboxylic acid have been prepared. The ethyl ester was also obtained by direct alcoholysis of the nitrile.

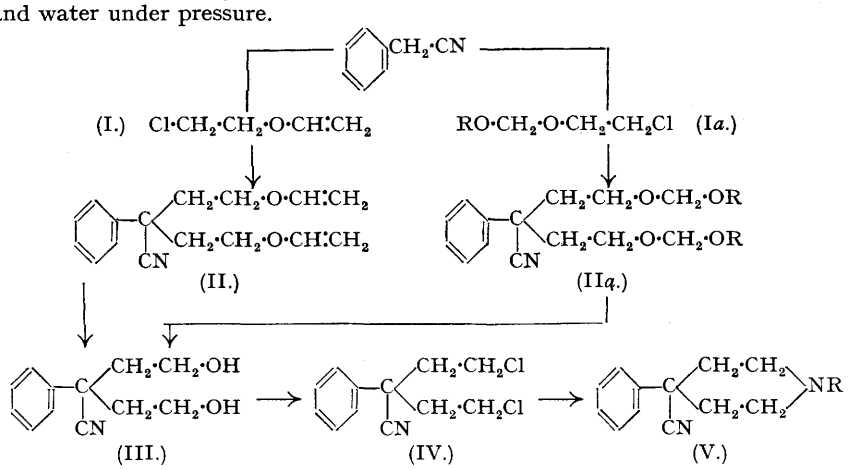
Condensation of phenylacetonitrile with alkyl halides and alkylene dihalides, in the latter case to give phenyl-*cyclo*paraffin nitriles, in presence of sodamide was described by Bodroux and Taboury (*Compt. rend.*, 1910, **150**, 1241, etc.) and Case (*J. Amer. Chem. Soc.*, 1934, **56**, 715). Eisleb later (*Ber.*, 1941, **75**, 1435) reported the synthesis of heterocyclic compounds by the condensation of phenylacetonitriles with ββ′-dihalogenoethylalkylamines, ethers, and sulphides. In view of the pronounced vesicant nature of ββ′-dihalogenoethylmethylamine, we looked for another method of preparing 4-arylpiperidine-4-nitriles, which are intermediates of important analgesics. One of the alternative methods considered was the preparation of αα-bis-(β′-halogenoethyl)arylacetonitriles which, on condensation with primary amines, would give the desired piperidine nitriles. Attempts to prepare such dihalogeno-compounds by condensation of phenylacetonitriles with 2 mols. of chlorobromoethane were unsuccessful, *cyclo*propane derivatives being the main products. Although ethylene chlorohydrin may be condensed with the sodio-derivative of phenylacetonitrile (Knowles and Cloke, *J. Amer. Chem. Soc.*, 1932, **54**, 2028), the introduction of a second hydroxyethyl group was found to be impossible. The use of β-halogenoethyl alkyl ethers gave products which could not be converted into the desired dihalogenonitriles, as the agent used for fission of the ether linkage also hydrolysed the nitrile group to the carboxylic acid, the resulting product being a derivative of α-phenylbutyrolactone, which was of no use for the projected syntheses. We finally achieved our aim by condensation of phenylacetonitrile in presence of sodamide with 2 mols. of β-chloroethyl vinyl ether (I) to give αα-*bis*-(β′-*vinyloxyethyl*)*phenylacetonitrile* (II), which on mild acid hydrolysis yielded αα-*bis*-(β′-*hydroxyethyl*)*phenylacetonitrile* (III) (cf. Cretcher, Koch, and Pittenger, *ibid.*, 1925, **47**, 3083). The same dialcohol was also obtained by mild acid hydrolysis of αα-*bis*-(β′-*methoxymethyloxyethyl*)*phenylacetonitrile* (II*a*; R = Me), formed by condensation of phenylacetonitrile with 2 mols. of *methyl*-β-*chloroethylformal* (I*a*; R = Me) in presence of sodamide. This di-alcohol on treatment with thionyl chloride in presence of diethylaniline yielded αα-*bis*-(β′-*chloroethyl*)*phenylacetonitrile* (IV), which, when condensed with primary amines such as methylamine or benzylamine in aqueous-alcoholic solution, gave 1-alkyl- or 1-aralkyl-4-phenylpiperidine-4-nitriles (V). 4-Phenyl-1-methylpiperidine-4-nitrile thus prepared possessed all the properties described by Eisleb (*loc. cit.*).

The above β-chloroethylalkylformals were more readily prepared by the action of ethylene oxide on chloromethyl ethers at low temperature (cf. Blanchard, *Bull. Soc. chim.*, 1936, **39**, 1263) than by the methods suggested in the literature (Henry, *Ber.*, 1895, **28**, Ref. 851).

The hydrolysis of 4-phenyl-1-methylpiperidine-4-nitrile to the corresponding carboxylic acid was easily achieved by boiling with concentrated hydrochloric acid. In addition to the ethyl ester (pethidine) and those esters mentioned by Schaumann (*Arch. Path. Exp. Pharm.*, 1940, **196**, 109), we have prepared the n-*propyl*,

* Cf. B.PP. 550,963 (1943), 550,970 (1943), and 556,976 (1943).

iso*propyl*, β-*hydroxyethyl*, cyclo*hexyl* and *allyl* esters of 4-phenyl-1-methylpiperidine-4-carboxylic acid. The ethyl ester was also obtained directly from the nitrile by heating it with an appropriate mixture of alcohol, sulphuric acid, and water under pressure.




We also synthesised 4-o-*tolyl*-1-*methylpiperidine*-4-*nitrile*, the corresponding *carboxylic acid*, and its *ethyl* ester, according to the above method.

The results of pharmacological tests of the above compounds, obtained in association with Professor A. D. Macdonald and Dr. G. Woolfe, University of Manchester (Department of Pharmacology), will be published elsewhere.

## Experimental.

*Methyl-β-chloroethylformal* (Ia; R = $CH_3$).—Chloromethyl methyl ether (80 g.) was added slowly with stirring to mercuric chloride (0·6 g.) in dry liquid ethylene oxide (44 g.), the temperature being maintained at −10° by external cooling. After standing at room temperature overnight, the colourless product was washed with dilute sodium carbonate solution and water, dried over anhydrous potassium carbonate, and distilled. The *formal* was a colourless liquid, b. p. 134—139° (Found : Cl, 25·2. $C_4H_9O_2Cl$ requires Cl, 28·5%); yield 78·5 g. It may be obtained pure by washing repeatedly with water (Found : Cl, 28·8%), but can be employed in the impure state for condensation with phenylacetonitrile.

*β-Chloroethylethylformal* (Ia; R = Et), prepared in a similar manner (yield, 72%), was a colourless liquid, b. p. 62—65°/50 mm. (Found : Cl, 20·7. $C_5H_{11}O_2Cl$ requires Cl, 25·4%).

*αα-Bis-(β′-vinyloxyethyl)phenylacetonitrile* (II).—Phenylacetonitrile (431 g.) was added gradually with mechanical stirring to a suspension of powdered sodamide (317 g.) in a mixture of chloroethyl vinyl ether (867 g.) and dry benzene (4400 c.c.). The temperature of the reaction mixture was kept between 40° and 50° until all the nitrile had been added; it was then slowly raised to boiling point, and refluxing continued for 1 hour. The resulting product was poured into a large separating funnel and washed twice with water. The benzene was then distilled off, and the residue distilled in a high vacuum. The *nitrile* (730 g.) distilled at 125—135°/0·15 mm. as a colourless oil (Found : C, 73·9, 75·8; H, 7·4, 7·6; N, 6·4, 6·6. $C_{16}H_{19}O_2N$ requires C, 74·7; H, 7·4; N, 5·4%). It was difficult to effect complete separation from α-(β′-vinyloxyethyl)phenylacetonitrile, b. p. 110°/0·15 mm., formed as a by-product.

*αα-Bis-(β′-methoxymethoxyethyl)phenylacetonitrile* (IIa; R = $CH_3$), prepared by condensation of phenylacetonitrile with β-chloroethylmethylformal (Ia) in a similar manner, was obtained as a faintly yellow oil, b. p. 147—155°/0·05—0·1 mm. (Found : C, 66·0; H, 7·8; N, 4·9. $C_{16}H_{23}O_4N$ requires C, 65·6; H, 7·8; N, 4·8); yield 61%. The β′-ethoxy-homologue was obtained in an analogous manner from phenylacetonitrile and β-chloroethylethylformal as a slightly yellow oil, b. p. 167—169°/0·05 mm.; yield 77%.

*αα-Bis-(β′-hydroxyethyl)phenylacetonitrile* (III).—(A) αα-Bis-(β′-vinyloxyethyl)phenylacetonitrile (7·9 g.) was suspended in water (60 c.c.) and heated to 80° with vigorous stirring. Concentrated hydrochloric acid (2 c.c.) was then added, whereupon hydrolysis set in with evolution of acetaldehyde. After 10 minutes' stirring, on completion of the reaction, the mixture was cooled, and the aqueous layer separated from the oil. The oil soon solidified, and was recrystallised from ethyl acetate, chloroform, or water, the *di-alcohol* being obtained as a white crystalline powder. A further small quantity crystallised out from the aqueous part on cooling to 0°. Yield of crystalline material, 4·4 g.; m. p. 96—98° (Found : C, 70·3; H, 7·4; N, 6·7. $C_{12}H_{15}O_2N$ requires C, 70·3; H, 7·3; N, 6·8%)

(B) αα-Bis-(β′-ethoxymethoxyethyl)phenylacetonitrile (13 g.) was suspended in water (260 c.c.) and heated to 92°, concentrated hydrochloric acid (5·2 c.c.) then being added. Formaldehyde and ethyl alcohol were evolved. The mixture was kept at 90—92° for 20—25 minutes to complete hydrolysis. After cooling, the di-alcohol was extracted with ethyl acetate, from which it crystallised after evaporation of some solvent (yield 5·9 g.). It had m. p. 96—98° alone and when mixed with the product obtained in (A).

*αα-Bis-(β′-chloroethyl)phenylacetonitrile* (IV).—αα-Bis-(β′-hydroxyethyl)phenylacetonitrile (6·0 g.) was suspended in diethylaniline (12·0 g.), and thionyl chloride (12·0 g.) added dropwise with efficient stirring and cooling. The mixture was then warmed to 80° for 30 minutes, cooled to 40°, and poured into a mixture of ice water and ether with vigorous stirring. The ethereal layer was separated, washed with cold sodium hydroxide solution and water, dried over anhydrous sodium sulphate, and evaporated. The product distilled at 135—138°/0·1—0·2 mm. as a yellow oil (6·6 g.) which solidified on standing; m. p. 52°. The *nitrile* (IV) may also be purified by recrystallising from alcohol (Found : C, 59·8; H, 5·4; N, 5·8; Cl, 29·0. $C_{12}H_{13}NCl_2$ requires C, 59·5; H, 5·7; N, 5·6; Cl, 28·8%).

4-*Phenyl*-1-*methylpiperidine*-4-*nitrile* (V).—A mixture of αα-bis-(β′-chloroethyl)phenylacetonitrile (5·0 g.), alcohol (10 c.c.), and a 50% aqueous solution of methylamine (5·1 g.) was heated in a sealed tube at 145° for 17 hours. After cooling, the solvents were distilled off under reduced pressure, and the residue taken up in dilute hydrochloric acid. Non-basic material was removed by extraction with ether, the aqueous part made alkaline, and the liberated base extracted with ether. The extract was washed with water, dried over anhydrous sodium sulphate, and evaporated. The product distilled at 126°/0·5 mm. as a faintly yellow oil (3·4 g.), which solidified on standing, m. p. 53°. Its picrate

melted at 239—240° after recrystallisation from alcohol and gave no depression in m. p. when mixed with a sample obtained by Eisleb's method (*loc. cit.*) (Found : C, 53·5; H, 4·5; N, 15·9. Calc. for $C_{19}H_{19}O_7N_5$ : C, 53·2; H, 4·4; N, 16·3%).

*Ethyl 4-Phenyl-1-methylpiperidine-4-carboxylate.*—A mixture of 4-phenyl-1-methylpiperidine-4-nitrile (20 g.), concentrated sulphuric acid (30 g., 98%), water (0·26 g.), ethanol (46 g.), and ammonium chloride (5·36 g.) was heated in an autoclave at 160° for 7 hours, then made alkaline with cold sodium hydroxide solution, and extracted with ether. After being washed and dried over anhydrous sodium sulphate, the extract was evaporated. The product distilled at 115°/0·2 mm. as a colourless oil (11·1 g.) and was identical with ethyl 4-phenyl-1-methylpiperidine-4-carboxylate obtained by successive hydrolysis of the nitrile and esterification of the acid. From the alkaline mother-liquor, 4-phenyl-1-methylpiperidine-4-carboxylic acid (6·5 g.) was recovered. *n-Propyl 4-phenyl-1-methylpiperidine-4-carboxylate hydrochloride* was prepared from the corresponding acid chloride hydrochloride and *n*-propyl alcohol according to Eisleb (*loc. cit.*); m. p. 181—183° (Found : Cl, 11·9. $C_{16}H_{24}O_2NCl$ requires Cl, 11·8%). The *isopropyl hydrochloride* had m. p. 192—195° (Found : Cl, 12·1. $C_{16}H_{24}O_2NCl$ requires Cl, 11·8%), and the *β-hydroxyethyl hydrochloride* m. p. 195—200° (Found : Cl, 11·6. $C_{15}H_{22}O_3NCl$ requires Cl, 12·0%).

The *allyl ester hydrochloride* had m. p. 155—158° (Found : N, 4·5; Cl, 11·3. $C_{16}H_{22}O_2NCl$ requires N, 4·8; Cl, 11·9%) [in the preparation of the free ester a mixture of allyl alcohol and pyridine (2 mols.) was added to the acid chloride hydrochloride in order to prevent addition of hydrogen chloride to the double bond of the allyl group]; and the *cyclohexyl hydrochloride* had m. p. 234—236° (Found : C, 67·4; H, 8·5; N, 4·4; Cl, 10·7. $C_{19}H_{28}O_2NCl$ requires C, 67·6; H, 8·3; N, 4·2; Cl, 10·4%). The five foregoing hydrochlorides were recrystallised from alcohol–ether.

*αα-Bis-(β′-vinyloxyethyl)-o-tolylacetonitrile.*—Powdered sodamide (10 g.) was added in several portions to a solution of *o*-tolylacetonitrile (11 g.) and *β*-chloroethyl vinyl ether (39 g.) in dry toluene (80 c.c.), the temperature of the reaction mixture being maintained at about 40°. The reaction was completed by refluxing for 2 hours; the cooled reaction mixture was then poured into water, the toluene layer separated, washed with water, and evaporated under reduced pressure. The residue on distillation gave the *nitrile* as a yellowish oil, b. p. 135—140°/0·1 mm. (Found : N, 4·9. $C_{17}H_{21}O_2N$ requires N, 4·9%).

*αα-Bis-(β′-hydroxyethyl)-o-tolylacetonitrile.*—The foregoing nitrile was hydrolysed with dilute hydrochloric acid according to the method given above, the temperature being kept at 90°. On cooling, the *di-alcohol* crystallised in white needles; recrystallised from benzene, it had m. p. 95—100° (Found : C, 71·3; H, 7·8. $C_{13}H_{17}O_2N$ requires C, 71·3; H, 7·8%).

4-(*o-Tolyl*)-1-*methylpiperidine-4-nitrile.*—αα-Bis-(*β′*-hydroxyethyl)-*o*-tolylacetonitrile was treated with thionyl chloride as described above, and the crude dichloride used directly for the condensation with methylamine. Crude dichloride (5 g.) was heated with 33% aqueous solution of methylamine (11 c.c.) and alcohol (27 c.c.) in a sealed tube at 120—140° for 8 hours. The solvents were then removed under reduced pressure, and the residue taken up in 2N-hydrochloric acid (12·5 c.c.). On cooling, 4-(*o*-tolyl)-1-methylpiperidine-4-nitrile hydrochloride (4·0 g.) crystallised; m. p. 279—280°. The *picrate* had m. p. 265° (decomp.) (Found : C, 54·9; H, 5·3; N, 16·0. $C_{20}H_{21}O_7N_5$ requires C, 54·3; H, 4·8; N, 15·8%).

*Ethyl* 4-(*o-Tolyl*)-1-*methylpiperidine-4-carboxylate.*—The corresponding piperidine nitrile hydrochloride (4 g.) was heated at 130° with concentrated hydrochloric acid (16 c.c.) in a sealed tube for 5 hours. The reaction mixture was made alkaline with 4N-sodium hydroxide solution, and carbon dioxide passed through; the piperidine carboxylic acid (3 g.) was precipitated in white needles, m. p. 300—310° (decomp.). It was filtered off, dried over phosphoric oxide, and treated with thionyl chloride (8 c.c.). After refluxing for 15 minutes, the excess thionyl chloride was removed, and after addition of ethyl alcohol (8·6 c.c.) to the residue, the mixture was heated on the water-bath for 15 minutes and then filtered from insoluble material. After removal of solvent, the residual oil was distilled, to give the *ethyl ester*, b. p. 175°/11 mm., as a colourless oil (2·9 g.) (Found : C, 73·2; H, 8·6; N, 5·9. $C_{16}H_{23}O_2N$ requires C, 73·6; H, 8·8; N, 5·5%). The *hydriodide*, a white crystalline solid, had m. p. 175—176° (Found : I, 32·6. $C_{16}H_{24}O_2NI$ requires I, 32·6%).

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