302. *Synthetic Analgesics. Part V. Compounds Related to Pethidine.*

By A. L. Morrison and H. Rinderknecht.

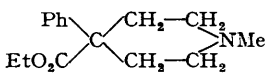
Various substances related to pethidine have been prepared but none was found to be superior in analgesic action.

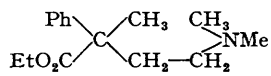
As a continuation of work on synthetic analgesics (Parts I—IV, *J.*, 1944, 261 *et seq.*) a number of new compounds related to pethidine were prepared several years ago and submitted to pharmacological tests, but none was found to be markedly superior to pethidine (I) in analgesic properties (Macdonald, Wolfe, Bergel, Morrison, and Rinderknecht, *Brit. J. Pharmacol.*, 1946, **1**, 4).

To simulate the phenolic group in morphine, ethyl 4-(*m*-hydroxyphenyl)-1-methylpiperidine-4-carboxylate was prepared essentially by the method which later came to our knowledge through Report No. PB-981 of the U.S.A. Office of the Publications Board, Department of Commerce. This compound, prepared by the I.G. Farbenindustrie at Hoechst, is known as bemidone. Ethyl 4-(*m*-acetoxyphenyl)-1-methylpiperidine-4-carboxylate was also made by us and characterised as its hydrochloride.

The German workers prepared a number of ketones from 4-cyano-4-phenyl-1-methylpiperidine but seem to have investigated only one of the secondary alcohols which can be derived from them, namely, 4-phenyl-1-methyl-4-(1-hydroxybutyl)piperidine (Report PB-981). These alcohols can be prepared from the ketones either by reduction with sodium and alcohol or, as recently found, by the action of lithium aluminium hydride. 4-Phenyl-1-methyl-4-(1-hydroxyethyl)piperidine and 4-phenyl-1-methyl-4-(1-hydroxypropyl)piperidine and the corresponding acetyl derivatives were prepared. Contrary to the experience of May and Mosettig in the amidone series (*J. Org. Chem.*, 1948, **13**, 459) where it was found that, although the secondary alcohol obtained by reduction of amidone was inactive, the acetyl derivative was at least as active as the original ketone, it was established that the secondary alcohols were much less active as analgesics than the parent ketones, but that formation of acetyl derivatives did not restore completely the analgesic activity.

Ethyl γ-dimethylamino-α-phenyl-α-methylbutyrate (II), obtained by alcoholysis of the corresponding nitrile, was made to determine if the intact piperidine ring was necessary for full analgesic action in the pethidine series, but it was found to be practically inactive.

(I.) 

 (II.)

Recently Thorp and Walton (*J.*, 1948, 559) reported the preparation of ethyl 4-phenyl-1-allylpiperidine-4-carboxylate by allylation of norpethidine. This compound, in view of the work of Hart and McCawley (*J. Pharm. Exp. Ther.*, 1944, **82**, 339) and of Unna (*ibid.*, 1943, **79**, 27) on *N*-allylnormorphine, had been of interest to us for some time, and it was found that it was readily prepared by alcoholysis of the corresponding nitrile, which could be made either by condensation of 1 : 5-dichloro-3-cyano-3-phenylpentane with allylamine or by condensation of benzyl cyanide with di-(2-chloroethyl)allylamine. The latter compound was readily formed by

the action of thionyl chloride on di-(2-hydroxyethyl)allylamine (Ford-Moore, Lidstone, and Waters, *J.*, 1946, 819) which was made by the action of ethylene oxide on allylamine.

It is well known that in the series of esters of 4-phenyl-1-methylpiperidine-4-carboxylic acid the optimal analgesic effect is found in the ethyl ester (pethidine). It was of theoretical interest to determine if this relationship also held with thio-esters. Ethyl and methyl 4-phenyl-1-methylpiperidine-4-thiocarboxylate were prepared and it was found that, although both were less potent than pethidine itself, the methyl ester was slightly more active than the ethyl ester.

Experimental.

4-Cyano-4-(m-methoxyphenyl)-1-methylpiperidine.—This compound was prepared from *m*-methoxybenzyl cyanide and methyldi-(2-chloroethyl)amine as described in Washington Report PB-981, p. 85, and obtained as an oil, b. p. 134—136°/0·5 mm. It formed a *picrate*, m. p. 231—232° (Found: C, 52·7; H, 4·8; N, 14·8. $C_{20}H_{21}O_8N_5$ requires C, 52·3; H, 4·6; N, 15·3%).

4-(m-Hydroxyphenyl)-1-methylpiperidine-4-carboxylic Acid.—The above nitrile (2 g.) was heated at 120—130° with 60% hydrobromic acid (25 ml.) for 3·5 hours. After cooling, the excess of hydrobromic acid was distilled off under reduced pressure, the solid residue dissolved in water, made alkaline with sodium hydroxide and extracted with ether, and carbon dioxide passed into the aqueous solution, whereupon the acid was obtained as a solid, which, recrystallised from water, had m. p. 329—331° (decomp.) (60%). After drying in a vacuum at 50° over phosphoric oxide for several hours it still contained more than 1 mole of water (Found: C, 60·4; H, 7·1; N, 6·1. Calc. for $C_{13}H_{17}O_3N,H_2O$: C, 61·6; H, 7·5; N, 5·5%).

Ethyl 4-(m-Hydroxyphenyl)-1-methylpiperidine-4-carboxylate.—The above acid (1 g.) was esterified by being heated for 4 hours with a saturated solution of hydrogen chloride in ethanol (60 ml.). The ester was obtained as a solid, m. p. 110°, which was converted into the hydrochloride, m. p. 173—174° (70%) (Found: C, 59·6; H, 7·2; N, 4·8; Cl, 12·0. Calc. for $C_{15}H_{22}O_3NCl$: C, 60·1; H, 7·3; N, 4·7; Cl, 11·8%). Acetylation of the ester with acetic anhydride and pyridine gave the *m*-acetoxy-derivative which gave a *hydrochloride*, m. p. 149—150° (Found: C, 59·4; H, 6·4; N, 3·7. $C_{17}H_{24}O_4NCl$ requires C, 59·7; H, 7·0; N, 4·1%).

4-Phenyl-1-methyl-4-(1-hydroxyethyl)piperidine.—(*a*) To 4-acetyl-4-phenyl-1-methylpiperidine (2 g.), dissolved in ethyl alcohol (50 ml.), was added sodium (4 g.) in small portions, and the solution then heated at 120° for 2 hours. On addition of water and extraction with ether the secondary alcohol was obtained as a solid which, recrystallised from light petroleum (b. p. 60—80°), had m. p. 123·5—124°. (*b*) Reaction of the ketone (7·5 g.) in dry ether (50 ml.) with lithium aluminium anhydride (0·3 g.) during 3 hours in a nitrogen atmosphere gave an 84% yield of the secondary *alcohol* (Found: C, 76·4; H, 9·6; N, 6·9. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·6; N, 6·4%). The *acetate*, prepared by the action of acetic anhydride on a pyridine solution of the alcohol, was a liquid, b. p. 114—116°/0·3 mm. (Found: C, 73·7; H, 8·9; N, 5·4. $C_{16}H_{23}O_2N$ requires C, 73·6; H, 8·8; N, 5·4%).

4-Phenyl-1-methyl-4-(1-hydroxypropyl)piperidine.—A solution of 4-propionyl-4-phenyl-1-methylpiperidine (8 g.) in dry ether (20 ml.) was added to a stirred solution of lithium aluminium hydride (0·25 g.) in dry ether in an atmosphere of nitrogen, and the mixture left at room temperature for 3 hours. When the product was worked up in the usual way the secondary *alcohol* was obtained as a viscous oil, b. p. 125—127°/0·7 mm. (80%) (Found: N, 5·9. $C_{15}H_{23}ON$ requires N, 6·0%). The *acetoxy*-derivative was an oil, b. p. 138—142°/0·8 mm. (Found: C, 74·5; H, 8·75; N, 5·25. $C_{17}H_{25}O_2N$ requires C, 74·2; H, 9·0; N, 5·1%).

Dimethyl-3-cyano-3-phenylbutylamine.—1-Phenylethyl cyanide (13·6 g.) and dimethyl-2-chloroethylamine (10·4 g.) were dissolved in toluene (100 ml.), and powdered sodamide (3·4 g.) was added gradually with stirring. The solution was heated under reflux for 1 hour and after cooling worked up in the normal manner to give the *nitrile* as an oil, b. p. 145—150°/12 mm. (Found: C, 76·9; H, 9·3; N, 13·7. $C_{13}H_{18}N_2$ requires C, 77·3; H, 8·9; N, 13·9%).

Ethyl γ-Dimethylamino-α-phenyl-α-methylbutyrate.—The above nitrile (5 g.) was heated with a mixture of 98% sulphuric acid (4 ml.), water (0·08 ml.), ethyl alcohol (13·9 g.), and ammonium chloride (1 g.) in a sealed tube at 100° for 7 hours. The *ester* was obtained as an oil, b. p. 170—175°/13 mm. (Found: N, 6·1. $C_{15}H_{23}O_2N$ requires N, 5·6%). It formed a crystalline *hydriodide*, m. p. 141—143° (Found: N, 3·75; I^-, 33·7. $C_{15}H_{24}O_2NI$ requires N, 3·7; I^-, 33·7%).

4-Cyano-4-phenyl-1-allylpiperidine.—(*a*) Crude 1:5-dichloro-3-cyano-3-phenylpentane (42 g.), prepared from the corresponding dialcohol (32 g.), was heated with allylamine (35 g.) in methylated spirits (50 ml.) at 130—140° for 8 hours. The basic product gave an oil, b. p. 130—135°/0·5 mm. (70% yield), the *picrate* of which had m. p. 204—205° when recrystallised from alcohol (Found: C, 55·2; H, 4·7; N, 15·4. $C_{21}H_{21}O_7N_5$ requires C, 55·2; H, 4·6; N, 15·0%).

(*b*) Allylamine (12·5 g.) in water (25 ml.) was cooled to 0° and ethylene oxide (30 ml.) gradually added. The sudden rise in temperature could be controlled by addition of ice to the reaction mixture. When all the oxide had been added, the pressure flask was stoppered and left at room temperature for 16 hours. Fractionation of the aqueous solution gave di-(2-hydroxyethyl)allylamine, b. p. 149—150°/15 mm. in 70—80% yield (Found: C, 58·3; H, 10·4; N, 9·3. Calc. for $C_7H_{15}O_2N$: C, 57·9; H, 10·3; N, 9·65%). Condensation of undistilled di-(2-chloroethyl)allylamine (5·4 g.) with benzyl cyanide (3·5 g.) in presence of sodamide (2 g.) in the usual manner gave 4-cyano-4-phenyl-1-allylpiperidine, characterised as its picrate, m. p. 205—206°.

4-Phenyl-1-allylpiperidine-4-carboxylic Acid.—The above nitrile (3 g.) was heated at 135—140° with a mixture of sulphuric acid (5 g.) and water (1 g.) for 1 hour. The reaction mixture was poured into excess of ice-cold sodium hydroxide solution, which was then extracted with ether and saturated with carbon dioxide, whereupon the *acid* was precipitated. After recrystallisation from aqueous alcohol it had m. p. 245—248°. It still contained one mole of water after drying over P_2O_5 [Found: C, 68·3; H, 7·7; N, 5·5%; $\overline{F}$, 1·06 (Wijs). $C_{15}H_{19}O_2N,H_2O$ requires C, 68·5; H, 8·0; N, 5·3%; $\overline{F}$, 1].

Ethyl 4-Phenyl-1-allylpiperidine-4-carboxylate.—This ester was made by esterification of the acid, and obtained as an oil, b. p. 130—135°/0·3 mm. It formed a *picrate*, m. p. 134—135°, from alcohol (Found: C, 54·8; H, 5·1; N, 10·75. $C_{23}H_{26}O_9N_4$ requires C, 55·0; H, 5·2; N, 11·2%).

Ethyl 4-Phenyl-1-methylpiperidine-4-thiocarboxylate.—4-Phenyl-1-methylpiperidine-4-carboxyl chloride hydrochloride, prepared from the corresponding acid (5 g.) with thionyl chloride, was added in portions to a well-cooled mixture of ethanethiol (6 g.) and pyridine (4 g.). The mixture was finally refluxed, with carbon dioxide–acetone in the condenser, for 2 hours. The excess of thiol was then driven off with carbon dioxide, an ice-cold solution of sodium hydroxide added, and the mixture extracted with ether. The ethereal solution gave the *thio-ester* as an oil, b. p. 138—139°/0·8 mm. (Found: C, 68·6; H, 8·1; N, 5·2. $C_{15}H_{21}ONS$ requires C, 68·5; H, 8·0; N, 5·3%). The *hydrochloride*, crystallised from acetone, had m. p. 197—200° (Found: Cl^-, 11·3. $C_{15}H_{22}ONClS$ requires Cl^-, 11·7%). The *methyl* ester was prepared similarly from methanethiol, except that the reaction was carried out in a sealed tube at 80° for 1·5 hours, and was obtained as an oil, b. p. 148—149°/1·5 mm. (Found: C, 67·5; H, 7·6; N, 5·25. $C_{14}H_{19}ONS$ requires C, 67·5; H, 7·6; N, 5·6%). The *hydrochloride* (from acetone) had m. p. 224—226° (Found: Cl^-, 12·0. $C_{14}H_{20}ONSCl$ requires Cl^-, 12·3%).

RESEARCH DEPARTMENT, ROCHE PRODUCTS LIMITED,
WELWYN GARDEN CITY, HERTS.

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