304. *Synthetic Analgesics. Part VII. Metadine and Related 3-Phenylpiperidine Derivatives.*

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Cyclisation of ethyl 5-chloro-1-amino-2-phenylpentane-2-carboxylate (II), formed by reduction of the corresponding nitrile (I) and methylation of the resulting piperidine derivative, provides an alternative synthesis of ethyl 3-phenyl-1-methylpiperidine-3-carboxylate (metadine), the pethidine isomer previously described (Part IV).

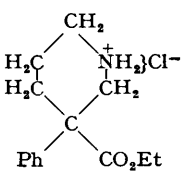
Treatment of metadine with ethylmagnesium iodide produces 3-phenyl-1-methyl-3-piperidyl ethyl ketone (V).

An improved method is described for the preparation of 1-methyl-3-piperidone which was used for the synthesis of 3-propionoxy-3-phenyl-1-methylpiperidine (VI). Neither (V) nor (VI) exceeded metadine in analgesic potency in rats.

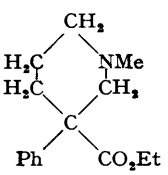
After the preparation of metadine (β-pethidine) (IV) described in Part IV (Bergel, Hindley, Morrison, and Rinderknecht, *J.*, 1944, 269) and the demonstration of its analgesic activity (Glazebrook and Branwood, *Lancet*, 1945, **249**, 528; Macdonald *et al.*, *Brit. J. Pharmacol.*, 1946, **1**, 4) it was decided to make further compounds with the 3-phenylpiperidine skeleton for comparison with the known 4-phenylpiperidines related to pethidine.

The synthesis of metadine itself was previously carried out by the hydrogenation of ethyl δ-benzylmethylamino-α-cyano-α-phenylvalerate. This has now been modified so that the use of the benzylmethylamine is unnecessary. Ethyl δ-chloro-α-cyano-α-phenylvalerate (I) was

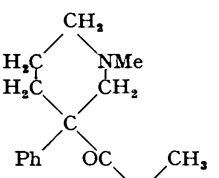
(I.) $CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CPh(CO_2Et){\cdot}CN$ $CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CPh(CO_2Et){\cdot}CH_2{\cdot}NH_2$ (II.)



(III.)



(IV.)



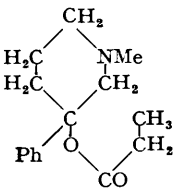
(V.)

reduced in acid solution with hydrogen and palladised charcoal (but not platinum) to the amine (II) which cyclised, slowly on storage or rapidly when heated, to the hydrochloride (III) of ethyl 3-phenylpiperidine-3-carboxylate. The latter base was described in Part IV but the present method of preparation is considerably more satisfactory. Attempted *N*-methylation by catalytic reductive condensation with formaldehyde under the conditions used in the final step of the German synthesis of pethidine (B.I.O.S. Final Report No. 766, p. 60) was unsuccessful. However, methylation proceeded smoothly and in high yield on heating of the base with formaldehyde and formic acid (Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571).

Treatment of metadine with ethylmagnesium iodide gave the ethyl ketone (V) in 60% yield. Similar " incomplete " Grignard reactions on esters have been observed with pethidine derivatives (Ciba Ltd., B.P. 614,567). As was found with the ethyl ketone corresponding to pethidine (Schaumann, *Arch. exp. Path. Pharm.*, 1940, **196**, 109; Macdonald *et al.*, *loc. cit.*) the analgesic potency of (V) was lower than that of metadine.

In view of the high analgesic activity of 4-acyloxy-4-phenylpiperidines (Jensen *et al.*, *Dansk Tidsskr. Farm.*, 1943, **17**, 173; *Chem. Abstr.*, 1945, **39**, 2506; Lee *et al.*, *J. Org. Chem.*, 1947, **12**, 894, 904, 911) it was a necessary part of our programme to investigate the corresponding 3-acyloxy-3-phenyl compounds. Owing to suspension of the work only one such compound

has been made, *viz.*, 3-propionoxy-3-phenyl-1-methylpiperidine (VI). The next lower homologue, 3-acetoxy-3-phenyl-1-methylpiperidine has recently been prepared by McElvain and Vozza (*J. Amer. Chem. Soc.*, 1949, **71**, 896) but not apparently in relation to analgesic studies. Our preparation, though very similar, presents some features worth recording. Ethyl methylaminoacetate was prepared according to Staudt (*Z. physiol. Chem.*, 1925, **146**, 286) by the alcoholysis of the " methylaminoacetonitrile " obtained by reaction between methylamine sulphate, formaldehyde, and potassium cyanide. The high boiling point of the so-called methylaminoacetonitrile obviously pointed to a higher molecular weight than that shown by the simple formulation. Dalgleish and Mann (*J.*, 1947, 658), whose data agree with our own, did not question the structure in spite of an enormous difference in boiling point between ethyl methylaminoacetate and the intermediate nitrile. From its analysis and molecular weight our product would seem to have resulted from condensation of two molecules of methylaminoacetonitrile and one of formaldehyde, presumably having the structure: $CN{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}CN$. Treatment with picric acid or dilute hydrochloric acid gave the salt of methylaminoacetonitrile and liberated formaldehyde. This result is interesting since very recently Cook and Cox (*J.*, 1949, 2334), by a preparation very similar to this, isolated the expected low-boiling monomeric methylaminoacetonitrile together with a high-boiling product which they stated appeared to be derived by condensation of two molecules of formaldehyde with one molecule of methylaminoacetonitrile and also readily yielded salts of the parent substance.



(VI.)

$CO_2Et{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Et$
(VII.)

Treatment of butyrolactone with hydrobromic acid (Henry, *Compt. rend.*, 1886, **102**, 368; *Ber.*, 1886, **19**, 165R) and esterification of the resulting acid gave a 74% yield of ethyl γ-bromobutyrate, which with ethyl methylaminoacetate (cf. Prill and McElvain, *J. Amer. Chem. Soc.*, 1933, **55**, 1233) afforded the diester (VII). Dieckmann cyclisation of (VII) with powdered sodium, followed by acid hydrolysis and decarboxylation of the resulting cyclic keto-ester following closely the method described by Fuson (*J. Amer. Chem. Soc.*, 1946, **68**, 1239) for 1-methyl-4-piperidone, gave the required 1-methyl-3-piperidone hydrochloride in 86% yield. Thus this seems to represent an altogether simpler route to the piperidone than McElvain and Vozza's improved procedure (*loc. cit.*) and the overall yield is appreciably better. 1-Methyl-3-piperidone hydrochloride with phenylmagnesium bromide and then propionic anhydride and pyridine gave the ester (VI).

Analgesic tests with rats showed that this compound too had a reduced activity compared with metadine, illustrating that the relation between structure and activity does not follow parallel paths in the two series of 3- and 4-phenylpiperidine derivatives. Indeed this is not surprising for metadine itself does not exhibit the other pharmacological effects common to morphine, pethidine, amidone, and their analogues, such as respiratory depression and the characteristic Straub phenomenon in mice. Metadine, on the contrary, stimulates respiration and antagonises the morphine-induced Straub reaction (private communications from Prof. K. Fromherz, Department of Pharmacology, Hoffmann–La Roche, Basle, and Mr. M. W. Parkes of our own laboratories). Its analgesic action (and that of related compounds) may thus be exerted through a mechanism different from that of the morphine-like analgesic drugs.

Experimental.

Ethyl δ-Chloro-α-cyano-α-phenylvalerate (I).—Sodium (5·5 g.) was dissolved in absolute alcohol (240 ml.), and ethyl phenylcyanoacetate (48 g.) added with stirring. 1-Chloro-3-bromopropane (75·4 g.) was run in slowly to the cooled solution and then the mixture was boiled for 9—10 hours. The alcohol and most of the excess of halide were then removed *in vacuo*, the residue was treated with cold water, and the resulting oil taken up in ether. After separation and a further two ether-extractions of the aqueous part, the combined ethereal solutions were washed with two small portions of water, dried, and distilled. The required *cyano*-ester was obtained as a colourless oil (54·9 g., 78%), b. p. 125—127°/0·4 mm. (Found: N, 5·0. $C_{14}H_{16}O_2NCl$ requires N, 5·3%).

Ethyl 3-Phenylpiperidine-3-carboxylate.—Ethyl δ-chloro-α-cyano-α-phenylvalerate (8·9 g.) was hydrogenated in alcohol (110 ml.) with 10% palladised charcoal (5 g.), after addition of alcoholic hydrogen

chloride (20 ml.; 5N.). After absorption of hydrogen was complete the catalyst was filtered off and the solution concentrated *in vacuo*. The residue was dissolved in ice-water and washed twice with ether, and the aqueous solution made strongly alkaline with 30% sodium hydroxide solution. The oil which separated was extracted with ether, dried rapidly, and concentrated. The residue (3·4 g.) became increasingly viscous and was ultimately ether-insoluble. On storage, crystallisation began and was completed by trituration with dry ether. The *ethyl 3-phenylpiperidine-3-carboxylate hydrochloride* (2·5 g.) had m. p. 140° which was increased to 143° on recrystallisation from ethyl acetate (Found : N, 5·6. $C_{14}H_{20}O_2NCl$ requires N, 5·2%). The picrate had m. p. 110—111° and did not depress the m. p. of the picrate of authentic material.

Addition of the cyano-ester in portions to an equal weight of catalyst during the hydrogenation improved the yield considerably in this preparation, the product usually being isolated as the free base, b. p. 105°/0·1 mm. Hydrogenation using platinum gave none of the desired product.

Ethyl 3-Phenyl-1-methylpiperidine-3-carboxylate (IV) (*Metadine*).—The above base (4·7 g.) was treated, with cooling, with 98% formic acid (2·5 g.) and then with 40% aqueous formaldehyde (1·8 g.). Warming induced a vigorous evolution of carbon dioxide and the yellow colour at first produced was discharged. The mixture was heated on the water-bath for 4 hours after gas evolution had ceased. It was then cooled, diluted with twice its volume of water, and made strongly alkaline with 30% aqueous sodium hydroxide, with cooling in ice. The oil which separated was extracted with ether, and the extract washed with water, dried, and distilled, to give metadine as a colourless oil (4·4 g.), b. p. 160°/12 mm. n_D^{20} 1·5193 (Found : C, 72·9; H, 8·4; N, 5·8. Calc. for $C_{15}H_{21}O_2N$: C, 72·9; H, 8·5; N, 5·7%).

3-Phenyl-1-methyl-3-piperidyl Ethyl Ketone (V).—Metadine (2·5 g.) was dissolved in dry ether (10 ml.) and added to the Grignard reagent from ethyl iodide (3·2 g.) and magnesium (0·5 g.) in ether (10 ml.). The ether was then replaced by toluene (25 ml.) by distillation and the mixture heated for 5½ hours on the boiling water-bath. After cooling, it was poured on ice, and 2N-hydrochloric acid (20 ml.) added. The layers were separated and the aqueous layer was washed once more with ether and then made strongly alkaline. The resulting oil was extracted 3 times with ether, and the extract dried and distilled. The *ketone* (1·4 g.) was obtained as a colourless oil, b. p. 162—163°/12 mm. (Found : C, 77·2; H, 9·1; N, 6·0. $C_{15}H_{21}ON$ requires C, 77·9; H, 9·15; N, 6·1%).

Ethyl γ-Bromobutyrate.—Butyrolactone (21·5 g.) was dissolved in water (20 ml.) and the solution saturated with gaseous hydrogen bromide in the cold. It was then heated on the water-bath for 1 hour and, with cooling, ether and water were added and the layers separated. The aqueous layer was washed 4 times with ether, and the combined ethereal solutions were washed once with a little water, dried, and concentrated. After being dried thoroughly by dissolution in benzene and repeated distillation *in vacuo*, the residual γ-bromobutyric acid was obtained as a yellow oil (36·7 g.) which set solid on cooling in ice. The crude acid so prepared was next heated with thionyl chloride (35 ml.) under reflux for 2 hours. The excess of thionyl chloride was then removed *in vacuo* and the pale yellow oil thus obtained was treated with absolute alcohol (25 ml.) with good ice-cooling and shaking. When the reaction subsided, the solution was warmed to room temperature, kept for 2 hours, and then poured into ice-water. Extraction of the product with ether gave the required ethyl γ-bromobutyrate as a colourless, fruity-smelling, heavy oil (36·3 g., 74% from the lactone), b. p. 83—85°/13 mm., n_D^{25} 1·4545.

Ethyl Methylaminoacetate.—Crude methylaminoacetonitrile was obtained from methylamine (62 g.) according to the directions of Staudt (*Z. physiol. Chem.*, 1925, **146**, 286) as a light brown oil (120 g.). The bulk of this (80 g.) did not distil below 150°/12 mm. and the low-boiling material was not capable of ready separation into distinct fractions. Continuation of the distillation at 0·1 mm. gave a colourless oil (74·3 g.), b. p. 86—87° (Dalgleish and Mann, *J.*, 1947, 658, give 95—100°/0·2 mm. as the b. p. of "methylaminoacetonitrile") (Found : N, 36·1%; *M*, 148. $C_7H_{12}N_4$ requires N, 36·8%; *M*, 152). The *compound* produced a pronounced odour of formaldehyde on dissolution in dilute hydrochloric acid and gave a picrate, m. p. 141—141·5°, agreeing with that found by Dalgleish and Mann.

Conversion of the distilled nitrile (70 g.) into the hygroscopic crystalline ethyl methylaminoacetate hydrochloride by boiling it with alcoholic hydrogen chloride followed the procedure of Staudt (*loc. cit.*). The free base was best obtained from its salt by suspension in dry ether and passage of dry ammonia according to Prill and McElvain (*J. Amer. Chem. Soc.*, 1933, **55**, 1233), much loss occurring in aqueous solution. The ester (48·5 g.) had b. p. 46—48°/12 mm. It was used immediately for the next step.

1-Methyl-3-piperidone.—The above ester (68 g.) was treated with ethyl γ-bromobutyrate (48·8 g.), and the mixture kept 16 hours at room temperature, a crystalline mass of the sarcosine ester hydrobromide separating. This was filtered off and washed with dry ether, and the combined filtrates were distilled. The tertiary amino-ester (VII) was obtained as a colourless oil (42·5 g.), b. p. 145—147°/12 mm., n_D^{24} 1·4390.

Cyclisation of this compound was based on the method described by Fuson *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1239) for the preparation of 1-methyl-4-piperidone. The diester (VII) (42·5 g.) was added slowly to powdered sodium (3·9 g.) suspended in xylene (45 ml.) with the preliminary addition of 2 drops of alcohol. Addition to the stirred reaction mixture was carried out at such a rate that a gentle reflux was maintained. After the addition the mixture was boiled gently for a further 45 minutes. It was then cooled and poured into ice-water. The separated xylene layer was further washed with water, and the combined aqueous layers were washed with ether. The aqueous solution was then cooled and acidified (to Congo-red) with concentrated hydrochloric acid below 10°. The solution was neutralised by the addition of solid potassium carbonate and transferred to a separating funnel. Solid potassium carbonate (100 g.) was then added in two portions. The base separated as a red oil which was removed, and the aqueous phase was again treated with potassium carbonate (50 g.) below 10° and extracted twice with ether. The extracts and oil were combined and washed twice with saturated sodium chloride solution (5—10 ml.). The extract was then washed with hydrochloric acid (30 ml. of concentrated acid + 20 ml. of water) in two portions, the acid solution treated with additional concentrated acid (15 ml.), and the dissolved ether removed. It was then boiled until no colour could be observed with ferric chloride (1 hour) and concentrated *in vacuo*. The residue, after drying *in vacuo* with potassium hydroxide pellets, was triturated with dry acetone and filtered, giving the 1-methyl-3-piperidone hydrochloride as a

white solid (23·7 g., 86%), m. p. 110—112° (Prill and McElvain give 110—111°). After a single recrystallisation from alcohol–acetone–ether it melted sharply at 111°.

3-*Propionoxy*-3-*phenyl*-1-*methylpiperidine* (VI).—Phenylmagnesium bromide was prepared by the action of bromobenzene (11·6 g.) on magnesium (1·8 g.) in ether (50 ml.) and to the stirred and cooled solution was added 1-methyl-3-piperidone hydrochloride (5·0 g.). Reaction set in as the mixture was allowed to warm to room temperature, with the separation of a putty-like magnesium complex. The mixture was boiled for 2 hours to complete the reaction and then cooled and decomposed with ice-water and saturated ammonium chloride solution. Distillation of the ethereal extract gave some unchanged piperidone derivative, b. p. 60—70°/12 mm., with the main fraction distilling at *ca.* 70°/0·1 mm. Acylation of the latter with propionic anhydride and pyridine gave a base whose *hydrochloride* had m. p. 190·5° on crystallisation from alcohol–ethyl acetate–ether (Found: C, 63·8; H, 8·3; N, 4·9; Cl^-, 13·0. $C_{15}H_{22}O_2NCl$ requires C, 63·5; H, 7·8; N, 4·9; Cl^-, 12·5%).

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