788. *Some New Analogues of Pethidine.* Part I.†*

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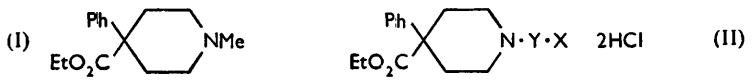
Substituted ethyl 1-alkyl-4-phenylpiperidine-4-carboxylates in which the alkyl group carries a nitrogenous heterocyclic residue have been prepared from ethyl 4-phenylpiperidine-4-carboxylate for pharmacological test as analgesics.

The discovery of the analgesic properties of pethidine (I) was followed by the synthesis and pharmacological evaluation of a large number of related substances. Pethidine, although not very potent on a weight basis, has held its place as the most widely used synthetic analgesic because of its low toxicity. In the present work, further analogues of pethidine have been synthesised in the hope that more potent substances retaining the low toxicity of pethidine might be obtained.



The substances synthesised have the general formula (II), in which Y represents an alkyl group carrying a heterocyclic residue (X) (cf. Table); the two heterocyclic systems in each case are linked through their nitrogen atoms by a two (or three) carbon-atom chain (Y). Although two derivatives of pethidine carrying a basic substituent at the nitrogen atom have been reported,[1] none has been described hitherto in which the 1-alkyl group was substituted by a heterocyclic residue.

The starting material for the syntheses reported here was ethyl 4-phenylpiperidine-4-carboxylate,[2] an intermediate in one of the commercial methods [3] of making pethidine. One of two methods was used for the preparation of the desired substituted substances: preferably the secondary base (I; H in place of Me) was treated with the desired substituted alkyl halide, but in the cases where difficulties might have arisen (Nos. 4, 7, 8, and 9 in Table) the

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[1] Schaumann, *Arch. Path. Pharmakol.*, 1940, **196**, 127.

[2] Eisleb, *Ber.*, 1941, **74**, 1433; cf. Walton, B.P. 592,016.

[3] B.I.O.S. Final Report No. 766, p. 60 *et seq.*

secondary base was first alkylated with ethylene chlorohydrin; the resulting 1-hydroxyethyl compound was converted into the chloroethyl compound which reacted readily with the heterocyclic bases chosen. The desired products were isolated and characterised as hydrochlorides.

The substances prepared were submitted to pharmacological tests, the results of which have been reported.[4] When this work was in progress (1954—55), it was generally accepted [5] that replacement of the *N*-methyl group of pethidine by other groups decreased or abolished analgesic activity. It was surprising therefore, that four of the substances, namely, Nos. 3, 5, 10, and 11 in the Table, had very considerable analgesic potency; ethyl

Pethidine analogues (II).

No.	Y	X	M. p. (decomp.)
1	$CH_2{\cdot}CH_2$	Pyrrolidino	259—262°
2	$CH_2{\cdot}CH_2$	Piperidino	270—272
3	$CH_2{\cdot}CH_2$	Morpholino	264—266
4	$CH_2{\cdot}CH_2$	Piperazino	244—246
5	$CH_2{\cdot}CH_2$	Tetrahydro-1 : 4-thiazin-4-yl	266
6	$CH_2{\cdot}CH_2$	4-Ethoxycarbonyl-4-phenylpiperidino	241—243
7	$CH_2{\cdot}CH_2$	4-Methylpiperidino	270—272
8	$CH_2{\cdot}CH_2$	1 : 2 : 3 : 6-Tetrahydropyridino	257—259
9	$CH_2{\cdot}CH_2$	4-Hydroxypiperidino	250—252
10	$CH_2{\cdot}CH_2{\cdot}CH_2$	Morpholino	240
11	$CHMe{\cdot}CH_2$	Morpholino	235—237

		Found (%)				Required (%)			
No.	Formula	C	H	N	Cl	C	H	N	Cl
1	$C_{20}H_{32}O_2N_2Cl_2$	59·0	8·0	7·15	17·65	59·5	7·9	6·95	17·6
2	$C_{20}H_{34}O_2N_2Cl_2$	59·7	7·6	6·75	17·2	60·4	8·2	6·7	17·0
3	$C_{20}H_{32}O_3N_2Cl_2$	56·9	7·65	6·65	16·9	57·3	7·7	6·7	16·9
4	$C_{20}H_{34}O_2N_2Cl_2$	53·0	7·6	—	—	52·9	7·5	—	—
5	$C_{20}H_{32}O_2N_2SCl_2$	55·6	7·55	6·35	—	55·15	7·4	6·45	—
6	$C_{30}H_{42}O_4N_2Cl_2$	62·9	7·35	4·75	12·5	63·7	7·4	4·95	12·55
7	$C_{22}H_{36}O_3N_2Cl_2$	61·25	7·9	6·3	—	61·2	8·4	6·5	—
8	$C_{21}H_{32}O_2N_2Cl_2$	59·9	7·35	6·75	—	60·7	7·7	6·75	—
9	$C_{21}H_{34}O_3N_2Cl_2$	58·0	7·8	6·15	—	58·2	7·9	6·45	—
10	$C_{21}H_{34}O_3N_2Cl_2$	57·9	7·9	6·4	15·9	58·2	7·9	6·45	16·3
11	$C_{21}H_{34}O_3N_2Cl_2$	57·7	7·9	6·8	16·0	58·2	7·9	6·45	16·3

1-2′-morpholinoethyl-4-phenylpiperidine-4-carboxylate, in particular, was 3—7 times as potent as pethidine. These appeared to be the first known cases of potent analgesics carrying a large substituent at the " piperidine " nitrogen, though one further closely related example, phenethylnorpethidine, has lately been reported.[6]

It was particularly striking that the four highly active pethidine analogues of this series contained the morpholine or tetrahydro-1 : 4-thiazine ring system. This led to the synthesis, by simple new routes (cf. Experimental section), of two known morpholine derivatives, 1 : 2-dimorpholinoethane and 2-morpholinoethyl*cyclo*hexane, and of the new *N*-(2-4′-hydroxypiperidinoethyl)morpholine; these substances were devoid of analgesic activity. The conclusion was reached, therefore, that whilst analgesic activity did not reside in the morpholine moiety of the molecule itself, the morpholine ring system had an important bearing on analgesic potency in this series of pethidine analogues. Further work is in progress.

Experimental

Intermediates.—The intermediate alkyl halides were prepared by recorded methods. 2-Pyrrolidinoethyl chloride hydrochloride had m. p. 172—173° (Wright *et al.*[7] give m. p. 173·5—174°); 2-piperidinoethyl chloride hydrochloride had m. p. 228° (Dunlop [8] gives m. p. 231°, but Marckwald and Frobenius [9] give m. p. 208°); 2-morpholinoethyl chloride hydrochloride had

[4] Millar and Stephenson, *Brit. J. Pharmacol.*, 1956, **11**, 27; Green and Ward, *ibid.*, p. 32.
[5] Cf. Burger, " Medicinal Chemistry," p. 174 Interscience, New York, 1951; Braenden, Eddy, and Halbach, *Bull. Wld. Hlth. Org.*, 1955, **13**, 937.
[6] Perrine and Eddy, *J. Org. Chem.*, 1956, **21**, 125.
[7] Wright, Kolloff, and Hunter, *J. Amer. Chem. Soc.*, 1948, **70**, 3098.
[8] Dunlop, *J.*, 1912, **101**, 1998.
[9] Marckwald and Frobenius, *Ber.*, 1901, **34**, 3556.

m. p. 182° (Mason and Block [10] give m. p. 182—182·5°); 2-(tetrahydro-1 : 4-thiazin-1-yl)ethyl chloride hydrochloride had m. p. 208° (Gilman and Woods [11] give m. p. 206—208°); 3-morpholinopropyl chloride hydrochloride had m. p. 168° (Adams and Whitmore [12] give m. p. 168—170°); and 1-methyl-2-morpholinoethyl chloride hydrochloride had m. p. 176—177° (Attenburrow *et al.*[13] give m. p. 176—178°).

Ethyl 1-2′-*Chloroethyl*-4-*phenylpiperidine*-4-*carboxylate* (I; R = ·CH_2·CH_2·Cl).—Ethyl 4-phenylpiperidine-4-carboxylate (20 g.), m. p. *ca.* 33°, b. p. 150°/1·8 mm. (cf. Eisleb [2]) [*hydrobromide*, m. p. 165—166° (Found: N, 4·55; Br, 25·4. $C_{14}H_{20}O_2NBr$ requires N, 4·45; Br, 25·45%)], and ethylene chlorohydrin (6 ml.) were refluxed in ethyl acetate for 2·5 hr. For isolation of the intermediate (II; YX = ·CH_2·CH_2·OH), the ethyl acetate was removed and the liquid remaining distilled. Ethyl 1-2′-hydroxyethyl-4-phenylpiperidine-4-carboxylate (mentioned, but not described by Schaumann [1]) has b. p. 125—128°/1—1·5 mm., n_D^{19} 1·5215 (Found: C, 70·1; H, 8·6; N, 4·75. Calc. for $C_{16}H_{23}O_3N$: C, 69·3; H, 8·35; N, 5·05%).

To prepare the product (II; YX = ·CH_2·CH_2Cl), the stirred cool mixture was slowly treated with thionyl chloride (8 ml.) and, when addition was complete, the solution was boiled for a short time until crystallisation started. The *hydrochloride* of 1-2′-chloroethyl-4-phenylpiperidine-4-carboxylate was collected, and recrystallised from aqueous alcohol. When pure it (*ca.* 8·5 g.) had m. p. 219—220° (decomp.) (Found: C, 58·4; H, 6·9; N, 4·05; Cl, 21·4. $C_{16}H_{22}O_2NCl$,HCl requires C, 57·8; H, 6·9; N, 4·2; Cl, 21·4%).

Preparation of Tertiary Bases.—(A) *Ethyl* 1-2′-*morpholinoethyl*-4-*phenylpiperidine*-4-*carboxylate*. Ethyl 4-phenylpiperidine-4-carboxylate (7 g.), 2-morpholinoethyl chloride (4·5 g.), and anhydrous sodium carbonate (1·8 g.) were boiled in alcohol (50 ml.) for several hours. The suspension was filtered and the filtrate concentrated under reduced pressure. Ethanolic hydrogen chloride was then added to precipitate the crude product; recrystallisation from aqueous ethanol gave the pure dihydrochloride (cf. Table) (9·8 g.), m. p. 264—266° (decomp.). *Ethyl* 1-2′-*morpholinoethyl*-4-*phenylpiperidine*-4-*carboxylate*, regenerated from the dihydrochloride, had b. p. 188—192°/0·5 mm., n_D^{18} 1·5276 (Found: C, 69·4; H, 8·85; N, 8·45. $C_{20}H_{30}O_3N_2$ requires C, 69·3; H, 8·75; N, 8·1%), and gave a *picrate*, m. p. 247—248° (decomp.) (Found: N, 14·25. $C_{20}H_{30}O_3N_2,2C_6H_3O_7N_3$ requires N, 13·9%).

(B) *Ethyl* 1-2′-*piperazinoethyl*-4-*phenylpiperidine*-4-*carboxylate*. Ethyl 1-2′-chloroethyl-4-phenylpiperidine-4-carboxylate hydrochloride (5·5 g.) (see above) in alcohol was neutralised with alcoholic sodium ethoxide (1 equiv.); piperazine (3·6 g.) was added and the mixture boiled for 4 hr. After concentration under reduced pressure, addition of alcoholic hydrogen chloride gave the desired trihydrochloride, which was recrystallised from aqueous alcohol and then had m. p. 244—246° (decomp.).

1 : 2-*Dimorpholinoethane*.—Morpholine (10 g.) and 2-morpholinoethyl chloride (17 g.) were boiled for 1 hr.; two layers were formed. To the mixture was added an excess of aqueous ammonia, and the organic bases were extracted into chloroform. Vacuum-distillation gave, besides unchanged morpholinoethyl chloride (4·5 g.), b. p. 90°/12 mm., the desired 1 : 2-dimorpholinoethane (12 g.), b. p. 140—150°/12 mm., m. p. 70—72° (Knorr and Brownsden [14] give m. p. 74°, b. p. 153—154°/9 mm.).

2′-*Morpholinoethyl*cyclo*hexane*.—The decarboxylated condensation product (76 g.), b. p. 97—99°/15 mm. (cf. Cope *et al.*[15]), of cyanoacetic acid and *cyclo*hexanone on hydrogenation over Raney nickel in alcoholic ammonia at 55—60°/100 atm. for 24 hr. gave 2′-aminoethyl*cyclo*hexane (63 g.), b. p. 70°/15 mm., 188°/1 atm., n_D^{17} 1·4720 (Wallach [16] gives b. p. 188—189°, n_D^{19} 1·4647). This amine (30 g.) and di-(2-chloroethyl) ether (34 g.) in boiling ethanol (100 ml.) over sodium carbonate (25 g.) for 8 hr. yielded, besides much unchanged starting material, 2′-morpholinoethyl*cyclo*hexane (12 g.), b. p. 130°/12 mm., which gave a hydrochloride, m. p. 253—254° (Blicke and Zienty [17] give b. p. 132—134°/12 mm.; hydrochloride, m. p. 260—261°).

4-(2-4′-*Hydroxypiperidinoethyl*)*morpholine*.—4-Hydroxypiperidine (24·7 g.), b. p. 110—125°/10—15 mm. (Bowden and Green [18] give b. p. 110—115°/10 mm.), and 2-morpholinoethyl chloride (37 g.) were boiled in alcohol (150 ml.) over sodium carbonate (13 g.) for several hours.

[10] Mason and Block, *J. Amer. Chem. Soc.*, 1940, **62**, 1443.
[11] Gilman and Woods, *ibid.*, 1945, **67**, 1843.
[12] Adams and Whitmore, *ibid.*, p. 735.
[13] Attenburrow, Elks, Hems, and Speyer, *J.*, 1949, 510.
[14] Knorr and Brownsden, *Ber.*, 1902, **35**, 4472.
[15] Cope, D'Addieco, Whyte, and Glickman, *Org. Synth.*, 1951, **31**, 25.
[16] Wallach, *Annalen*, 1907, **353**, 284; 1908, **359**, 311.
[17] Blicke and Zienty, *J. Amer. Chem. Soc.*, 1939, **61**, 771.
[18] Bowden and Green, *J.*, 1952, 1164.

The suspension was filtered, the filtrate concentrated, and 20% alcoholic hydrogen chloride added: 4-(2-4'-*hydroxypiperidinoethyl*)*morpholine dihydrochloride* separated; on crystallisation from aqueous alcohol it (50 g.) had m. p. 295° (decomp.) (Found: C, 46·35; H, 8·45; N, 9·55; Cl, 24·3. $C_{11}H_{22}O_2N_2$,2HCl requires C, 46·0; H, 8·4; N, 9·75; Cl, 24·7%). Regeneration with aqueous alkali, extraction into chloroform, and distillation gave the *base*, b. p. 155—158°/2—3 mm., which crystallised rapidly on cooling and, after recrystallisation from ether–light petroleum, had m. p. 65—66° (Found: C, 61·6; H, 10·1; N, 13·1. $C_{11}H_{22}O_2N_2$ requires C, 61·65; H, 10·35; and N, 13·05%).

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