621. *Some New Analogues of Pethidine. Part II.*[1] *Alkoxyalkylnorpethidines.**

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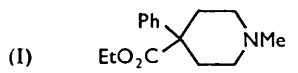
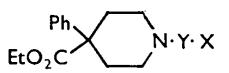
Alkylation of ethyl 4-phenylpiperidine-4-carboxylate with ω-chloroalkyl alkyl ethers has given a new series of substances related to pethidine, some of which are potent analgesics. Structure–activity relations within this series of alkoxyalkylnorpethidines have been examined and alkylthio-analogues prepared for comparison.

In Part I,[1] a series of analogues (II) of pethidine (I) was reported, where Y represented an alkyl chain and X a nitrogenous heterocyclic residue. Of the substances tested, only those carrying a morpholino- (or tetrahydro-1 : 4-thiazin-4-yl) ring (for X in Formula II) had



(I)



(II)

marked analgesic potency;[2] the close analogues in which the oxygen (or sulphur) atom of this residue was replaced by carbon or nitrogen were almost inactive. Clearly, the presence of this oxygen atom was desirable in this series of pethidine analogues, although it is chemically inert and at some distance from the part of the molecule normally considered to be active.

These findings and deductions led to the synthesis of further analogues of pethidine, again formulated as (II) and derived from norpethidine (ethyl 4-phenylpiperidine-4-carboxylate), Y representing an alkyl chain and X an alkyl group bearing an oxygenated function. When this work started (1955), only one such substance had been reported,[3] namely, 2-hydroxyethylnorpethidine[4] (II; Y = CH_2·CH_2, X = OH), which was rather less active than pethidine (I). Recently, two further oxygenated derivatives of norpethidine, namely, (II; Y = CH_2·CHPh, X = OH and OAc, respectively) were synthesised and tested,[5] and the secondary alcohol (II; Y = CH_2·CHPh, X = OH) was shown to be about three times as potent as pethidine; its acetate ester, surprisingly, was almost inactive.

The present paper deals with aliphatic ethers (II; Y = alkyl, X = alkoxy) derived from norpethidine. It was found that some of these ethers exceeded pethidine in analgesic potency, and an attempt was then made—by varying the alkyl and alkoxy groupings—to establish the optimum position of the oxygen atom with respect to the heterocyclic residue.

Norpethidine was readily alkylated by ω-chloroalkyl alkyl ethers in, *e.g.*, ethyl or pentyl alcohol. The intermediate chloroalkyl alkyl ethers were generally prepared from the alkyl hydroxyalkyl ethers (alkylene glycol monoethers) some of which were commercially available. In the preparation of ω-chlorobutyl ethyl ether the attempted conversion of tetramethylene chlorohydrin into ethyl hydroxybutyl ether resulted in cyclisation to tetrahydrofuran; it was necessary, therefore, to protect the hydroxyl group of the chlorohydrin: this was accomplished by addition of 2 : 3-dihydropyran before etherification, and similar work has since been published.[6]

The alkoxyalkylnorpethidines prepared are listed in Tables 1 and 2; they were high-boiling, fairly viscous bases, some of which began to crystallise on prolonged storage. They dissolved very readily in mineral acids, but the salts were very soluble in water and alcohol, and hygroscopic when precipitated from solution by ether or light petroleum. Only

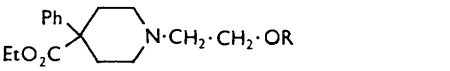
* Some of the work reported forms part of B.P. Applns. 34,051/55 and 4965/57.

[1] Part I, Anderson, Frearson, and Stern, *J.*, 1956, 4088.
[2] Millar and Stephenson, *Brit. J. Pharmacol.*, 1956, **11**, 27.
[3] Cf. Braenden, Eddy, and Halbach, *Bull. World Health Organisation*, 1955, **13**, 937.
[4] Schaumann, *Arch. Path. Pharmakol.*, 1940, **196**, 127.
[5] Perrine and Eddy, *J. Org. Chem.*, 1956, **21**, 125.
[6] Crisan, *Ann. Chim.* (*France*), 1956, **1**, 436.

ethoxypropylnorpethidine (No. 6) afforded a well-crystallised hydrobromide suitable for characterisation; the alkoxyalkylnorpethidines (Table 1), however, gave readily crystallisable picrates. For characterisation of ethoxybutyl- and ethoxypentyl-norpethidine (Nos. 7 and 8) the methiodides were prepared.

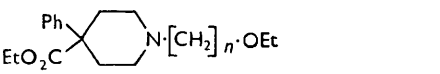
For comparison with these oxygenated substances, methylthio- and ethylthio-ethylnorpethidine (II; Y = CH_2·CH_2, X = SMe and SEt, respectively) were prepared. These were readily distillable oils which differed from the oxygen analogues in giving highly crystalline hydrobromides, very suitable for characterisation.

TABLE 1. *Alkoxyethylnorpethidines*



					Found (%)			Required (%)		
No.	R	B. p./mm.	n_D^{20}	Formula	C	H	N	C	H	N
1	Me	135—140°/1	1·5152	$C_{17}H_{25}O_3N$	69·9	8·9	4·35	70·05	8·6	4·8
2	Et	166—168°/1—1·5	1·5111	$C_{18}H_{27}O_3N$	71·2	9·0	4·35	70·8	8·9	4·6
3	Pr^n	170—180°/0·8	1·5079	$C_{19}H_{29}O_3N$	71·55	9·0	4·25	71·45	9·15	4·4
4	Pr^i	170—180°/1	1·5050	$C_{19}H_{29}O_3N$	71·65	9·15	4·3	71·45	9·15	4·4
5	Bu^n	185—190°/1	1·5050	$C_{20}H_{31}O_3N$	71·95	9·45	3·95	72·05	9·35	4·2

Table 2. *Ethoxyalkylnorpethidines*



					Found (%)			Required (%)		
No.	*n*	B. p./mm.	n_D^{20}	Formula	C	H	N	C	H	N
2	2	See Table 1								
6	3	185°/2	1·5083	$C_{19}H_{29}O_3N$	72·0	9·25	3·95	71·45	9·15	4·4
7	4	180°/1	1·5068	$C_{20}H_{31}O_3N$	72·2	9·35	4·25	72·05	9·35	4·2
8	5	195°/0·6	1·5072	$C_{21}H_{33}O_3N$	72·25	9·5	4·35	72·55	9·55	4·05
9	6	185°/0·5	1·5052	$C_{22}H_{35}O_3N$	73·2	9·6	4·4	73·1	9·75	3·9

Pharmacological tests are being reported in detail elsewhere [7]: they established that the ethoxyalkylnorpethidines (II; Y = $[CH_2]_n$, X = OEt; cf. Table 2) have high analgesic potency: the potency of the 4-aminobutanol derivative (substance No. 7, when *n* is 4) is approximately ten times that of pethidine and that of the ethanolamine derivative (substance No. 2, when *n* is 2) is approximately 5 times that of pethidine. Analgesic potency is lower (about equal to that of pethidine) when *n* is 3, 5, or 6 (substances No. 6, 8, and 9). It is remarkable, though not necessarily significant, that certain other simple derivatives of 4-aminobutanol and of ethanolamine have interesting pharmacological properties.[8]

In the series of alkoxyethylnorpethidines (II; Y = CH_2·CH_2; X = OR; cf. Table 1) analgesic acitivity was greatest for the ethoxyethyl compound (No. 2); the *iso*propoxy-compound (No. 4) had about half and the other ethers one-third of this activity. Methylthio- and ethylthio-ethylnorpethidine were considerably less active.

EXPERIMENTAL

Intermediates.—2-Chloroethyl ethyl ether had b. p. 109—110°, n_D^{20} 1·4122 (Heilbron and Bunbury [9] quote b. p. 107—108°, n_D^{20} 1·4113). 3-Chloropropyl ethyl ether had b. p. 129—130°, n_D^{20} 1·4162 (Smith and Sprung [10] give b. p. 125—128°; Pishnamazzade [11] gives b. p. 128—136°, n_D^{20} 1·4119). 4-Chlorobutyl ethyl ether was prepared from tetramethylene chlorohydrin. Action of dihydropyran (Copelin's method [12]) gave 4-chlorobutyl tetrahydropyran-2-yl ether, b. p. 93—94°/3 mm., n_D^{20} 1·4608 (Copelin gives b. p. 105°/10 mm.; Crisan [6] gives b. p. 114°/12 mm., n_D^{22} 1·4596), which with sodium ethoxide (1 equiv.) in ethanol gave 4-ethoxybutyl tetrahydropyran-2-yl ether,

[7] Blair and Stephenson, *Brit. J. Pharmacol.*, in the press.

[8] Cf. Lunsford, Murphey, and Rose, *J. Org. Chem.*, 1957, **22**, 1225; Kuehl, Jacob, Ganley, Ormond, and Meisinger, *J. Amer. Chem. Soc.*, 1957, **79**, 5577.

[9] Heilbron and Bunbury's " Dictionary of Organic Compounds," Eyre and Spottiswoode, London, 1943.

[10] Smith and Sprung, *J. Amer. Chem. Soc.*, 1943, **65**, 1276.

[11] Pishnamazzade, *Trudy Inst. khim. Akad. Nauk Azerbaidzhan*, 1954, **13**, 49; *Chem. Abs.*, 1955, **49**, 9481.

[12] Copelin, U.S.P. 2,541,747.

b. p. 125—130°/20 mm., n_D^{20} 1·4440 (Found: C, 64·7; H, 10·7. Calc. for $C_{11}H_{22}O_3$: C, 65·3; H, 10·95%) (Crisan [6] gives b. p. 118°/12 mm., n_D^{22} 1·4400). This ether was hydrolysed by boiling 2N-hydrochloric acid to 4-ethoxybutanol, b. p. 76—80°/14 mm., n_D^{20} 1·4242 (Crisan [6] gives b. p. 83°/16 mm., n_D^{20} 1·4229; Palomaa and Jansson [13] give b. p. 72°/8 mm., n_D^{20} 1·4229), converted by thionyl chloride into the desired 4-*chlorobutyl ethyl ether*, b. p. 142°, n_D^{20} 1·4244 (Found: C, 52·85; H, 9·35. $C_6H_{13}OCl$ requires C, 52·75; H, 9·6%). 5-*Chloropentyl ethyl ether*, prepared by action of thionyl chloride on 5-ethoxypentanol,[13] had b. p. 72°/17 mm., n_D^{20} 1·4300 (Found : C, 55·55; H, 10·05; Cl, 23·3. $C_7H_{15}OCl$ requires C, 55·8; H, 10·05; Cl, 23·55%). 6-Bromohexyl ethyl ether, prepared by action of sodium ethoxide on hexamethylene dibromide, had b. p. 64°/1 mm., n_D^{20} 1·444 (Dionneau [14] gives b. p. 121—123°/35 mm.). 2-Chloroethyl methyl ether had b. p. 88·5—89°, n_D^{20} 1·4112 (Karvonen [15] gives b. p. 89·4—89·7°/763 mm., n_D^{20} 1·4111). 2-Chloroethyl *n*-propyl ether had b. p. 131—134°, n_D^{20} 1·4188 (Karvonen [15] gives b. p. 130°/756 mm., n_D^{20} 1·4176). 2-*Chloroethyl* iso*propyl ether* had b. p. 118—120°/754 mm., n_D^{20} 1·4125 (Found: C, 49·05; H, 9·0. $C_5H_{11}OCl$ requires C, 49·0; H, 9·05%). *n*-Butyl 2-chloroethyl ether had b. p. 148—152°, n_D^{20} 1·4235 (Chalmers [16] gives b. p. 153—154°, but Sklyarov [17] gives b. p. 139—141°, n_D^{20} 1·4310). 2-Chloroethyl methyl sulphide had b. p. *ca.* 55°/30 mm., n_D^{20} 1·4970 (Kirner [18] gives b. p. 55—56°/30 mm., n_D^{30} 1·4902). 2-Chloroethyl ethyl sulphide had b. p. 80—84°/82 mm., n_D^{20} 1·4890 (Thompson *et al.*[19] give b. p. 55—58°/22 mm.).

Preparation and Characterisation of Tertiary Bases.—In a typical experiment, norpethidine (5 g.), m. p. *ca.* 33°, and 2-chloroethyl methyl ether (5·5 g.) were refluxed in pentyl alcohol (20 ml.) over sodium carbonate (2 g.) for about 30 hr. The solution was filtered and the filtrate distilled, giving, as high-boiling fraction, ethyl 1-2′-methoxyethyl-4-phenylpiperidine-4-carboxylate (No. 1 in Table 1) (*ca.* 4·5 g.).

Ethyl 1-2′-*methylthioethyl*-4-*phenylpiperidine*-4-*carboxylate*, prepared from norpethidine and chloroethyl methyl sulphide, had b. p. 174—175°/0·5—1 mm., n_D^{20} 1·5402 (Found: C, 66·7; H, 7·6; N, 4·15. $C_{17}H_{25}O_2NS$ requires C, 66·4; H, 8·2; N, 4·55%). The *hydrobromide*, recrystallised from aqueous alcohol, had m. p. 197° (Found: C, 52·45; H, 6·65; N, 3·5. $C_{17}H_{25}O_2NS$,HBr requires C, 52·6; H, 6·75; N, 3·6%).

Ethyl 1-2′-*ethylthioethyl*-4-*phenylpiperidine*-4-*carboxylate* had b. p. 180—185°/0·5—1 mm., n_D^{20} 1·5370 (Found: C, 67·15; H, 8·3; N, 4·15. $C_{18}H_{27}O_2NS$ requires C, 67·25; H, 8·45; N, 4·35%). The *hydrobromide* had m. p. 183° (Found: C, 54·3; H, 6·85; N, 3·4. $C_{18}H_{27}O_2NS$,HBr requires C, 53·75; H, 7·0; N, 3·5%).

The bases described in Tables 1 and 2 were characterised as follows: *Ethyl* 1-2′-*ethoxyethyl*-4-*phenylpiperidine*-4-*carboxylate* (No. 2) had pK_a 7·45 and gave a *picrate* which, crystallised from ethanol, had m. p. 86° (Found: C, 53·4; H, 5·6; N, 10·2. $C_{18}H_{27}O_3N,C_6H_3O_7N_3$ requires C, 53·95; H, 5·65; N, 10·45%). Ethyl 1-3′-ethoxypropyl-4-phenylpiperidine-4-carboxylate (No. 6) gave the *hydrobromide*, m. p. 130—131° (from ethanol) (Found: C, 56·85; H, 7·45; N, 3·3; Br, 20·05. $C_{19}H_{29}O_3N$,HBr requires C, 56·9; H, 7·55; N, 3·5; Br, 19·95%). Ethyl 1-4′-ethoxybutyl-4-phenylpiperidine-4-carboxylate (No. 7) had pK_a 7·7 and gave a *methiodide*, m. p. 120—122° (from ethyl acetate) (Found: C, 52·9; H, 7·0; N, 2·8. $C_{21}H_{34}O_2NI$ requires C, 53·05; H, 7·2; N, 2·95%). Ethyl 1-5′-ethoxypentyl-4-phenylpiperidine-4-carboxylate (No. 8) gave the *methiodide* (from ethyl acetate), m. p. 152—154° (Found: C, 53·65; H, 7·2; N, 2·5. $C_{22}H_{36}O_3NI$ requires C, 54·0; H, 7·4; N, 2·85%). Ethyl 2-methoxyethyl-4-phenylpiperidine-4-carboxylate (No. 1) was characterised as *picrate*, m. p. 70—71° (from ethanol–light petroleum (Found: N, 11·05. $C_{17}H_{25}O_3N,C_6H_3O_7N$ requires N, 10·75%); ethyl (2-*n*-propoxyethyl)- and ethyl (2-*iso*propoxyethyl)-4-phenylpiperidine-4-carboxylate (Nos. 3 and 4 respectively) as *picrates* (from ethyl acetate–light petroleum) of m. p. 124° (Found: N, 10·1. $C_{19}H_{29}O_3N,C_6H_3O_7N$ requires N, 10·2%) and m. p. 108° (Found: N, 10·4%), respectively; and ethyl (2-*n*-butoxyethyl-4-phenylpiperidine-4-carboxylate (No. 5) as *picrate*, m. p. 125° (from ethyl acetate–light petroleum) (Found: N, 9·9. $C_{20}H_{31}O_3N,C_6H_3O_7N_3$ requires N, 9·9%).

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[15] Karvonen, *Ann. Acad. Sci. Fennicae*, 1912, **3**, *A*, No. 7, p. 1, *Chem. Zentr.*, 1912, II, 1270.
[16] Chalmers, *Canad. J. Res.*, 1932, **7**, 464.
[17] Sklyarov, *J. Gen. Chem. U.S.S.R.*, 1939, **9**, 2121.
[18] Kirner, *J. Amer. Chem. Soc.*, 1928, **50**, 2446.
[19] Thompson, Chenicek, and Symon, *Ind. Eng. Chem.*, 1952, **44**, 1659.