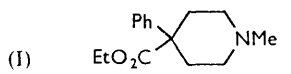
622. *Some New Analogues of Pethidine. Part III.*[1] *1-Aryloxyalkylnorpethidines, and Close Analogues.**

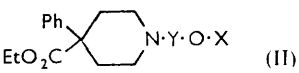
By P. M. Frearson and E. S. Stern.

The preparation of further pethidine derivatives, by alkylation of norpethidine with aryl chloroethyl ethers, is described. The phenylthioethyl, *cyclo*hexyloxyethyl, benzyloxyethyl, and phenoxybutyl analogues were prepared for comparison. Some of the substances have high analgesic potency.

The present paper describes the preparation of analogues of pethidine (I) with the general formula (II), in which Y represents $[CH_2]_2$ or $[CH_2]_4$ and X is an aryl or an aralkyl group, linked to Y by an oxygen atom. Such analogues of pethidine have not been reported before, but the preparation of and tests on phenethyl-[2] and *p*-aminophenethyl-norpethidine,[3] closely related to the present series of compounds but lacking the ether grouping, were reported while the present work was in progress.



(I)



(II)

Ethyl 1-2′-phenoxyethyl-4-phenylpiperidine-4-carboxylate was readily obtained on alkylation of norpethidine (II; Y·O·X = H) with 2-phenoxyethyl chloride in, *e.g.*, ethanol or pentyl alcohol. The product was isolated as the hydrobromide from the reaction mixture after removal of solvent; the hydrobromide was sparingly soluble in water, but more soluble in alcohol. For comparison with this phenyl ether, the phenylthio-compound and the *cyclo*hexyl ether were also prepared. The aryl-substituted phenoxyethyl analogues listed in the Table were similarly prepared for pharmacological evaluation of substituent effects.

No unexpected difficulties were encountered in the preparations but *o*-substitution made condensation and isolation of the products more difficult; the *o*-chlorophenoxyethyl analogue, for instance, could not be obtained pure, and the *o*-methoxyphenoxyethyl analogue was obtainable in poor yield only.

The intermediate aryl chloroethyl ethers were prepared by one of three methods: (*a*) the phenol in form of its sodio-derivative was treated with ethylene dichloride: yields by this method were not very good; (*b*) the phenol in form of its sodio-derivative was treated with ethylene chlorohydrin and the glycol monoether then converted into the desired intermediate by means of thionyl chloride; (*c*) the phenol was treated with aqueous sodium hydroxide and with 2-chloroethyl benzenesulphonate—this method[4] was particularly useful in the preparation of naphthyloxyethyl chloride.

Pharmacological tests are being reported in detail elsewhere.[5] The tests showed that the phenoxyethyl- (II; Y = CH_2·CH_2, X = Ph), phenoxybutyl- (II; Y = $[CH_2]_4$, X = Ph), and benzyloxyethyl-norpethidines (II; Y = CH_2·CH_2, X = CH_2Ph) were highly active as analgesics; they were about 5—10 times as potent as pethidine. Further substitution in the aromatic ring reduced, or in some cases abolished, the analgesic potency. Ethyl 1-2′-phenylthioethyl- and ethyl 1-2′-*cyclo*hexyloxyethyl-4-phenylpiperidine-4-carboxylate were both much less active than the phenoxyethyl analogue, although their potency appeared to be somewhat greater than that of pethidine; the 2-naphthyloxyethyl compound had little analgesic potency.

The final stages of these investigations will be reported later.

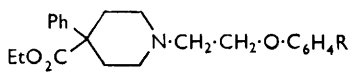
* Some of this work forms part of B.P. Applns. 34,051/55 and 4965/57.

[1] Part II, preceding paper.
[2] Perrine and Eddy, *J. Org. Chem.*, 1956, **21**, 125.
[3] Weijlard, Orahovats, Sullivan, Purdue, Heath, and Pfister, *J. Amer. Chem. Soc.*, 1956, **78**, 2342.
[4] Herbst and Johnson, *J. Org. Chem.*, 1952, **17**, 693.
[5] Blair and Stephenson, *Brit. J. Pharmacol.*, in the press.

Experimental

Intermediates.—2-Phenoxyethyl chloride had m. p. >25°, b. p. 108—110°/16 mm. (Bentley *et al.*[6] give m. p. 28°, b. p. 220°). 2-cyclo*Hexyloxyethyl chloride*, prepared from 2-*cyclo*hexyloxyethanol,[7] b. p. 105°/20 mm., n_D^{20} 1·4648, had b. p. 82—84°/16 mm., n_D^{20} 1·4636 (Found: C, 59·5; H, 9·2. $C_8H_{15}OCl$ requires C, 59·1; H, 9·3%). 2-Phenylthioethyl chloride had b. p. 140—141°/30 mm., n_D^{20} 1·5845 (Price and Morita [8] give b. p. 114—115°/1 mm.). 2-*o*-Tolyloxyethyl chloride had b. p. 118—120°/120 mm., n_D^{20} 1·5292 (Harris and Stewart [9] give b. p. 230—231°); 2-*m*- and 2-*p*-tolyloxyethyl chloride had b. p. 125—126°/20 mm., n_D^{20} 1·5294, and m. p. 35—36°, b. p. 127—128°/20 mm., respectively (Harris and Stewart [9] give b. p. 235—236° and 236—237°, respectively). 2-m-*Chlorophenoxyethyl chloride* had b. p. 128—130°/18 mm., n_D^{20} 1·5478 (Found: C, 49·9; H, 4·25. $C_8H_8OCl_2$ requires C, 50·3; H, 4·25%), and the 2-p-*chloro-isomer* had m. p. 34—35°, b. p. 135°/20 mm. (Found: C, 50·25; H, 4·65%); these were prepared from the corresponding 2-chlorophenoxyethanol.[10] 2-o-*Nitrophenoxyethyl chloride* had m. p. 35·5—36·5° (Found: C, 47·15; H, 4·0; N, 6·85. $C_8H_8O_3NCl$ requires C, 47·65; H, 4·0; N, 6·95%); the *m*- and *p*-isomers had, respectively, m. p. 59—60° (Found: C, 47·6; H, 4·0; N, 7·4%), and m. p. 47—48°, b. p. 204—206°/25 mm. (Katrak [11] gives m. p. 67—68° for the *p*-nitro-isomer). 2-*o*-Methoxyphenoxyethyl chloride had m. p. 40°, b. p. 138°/30 mm. (Harris and Stewart [9] give b. p. 254—255°); 2-*m*- and 2-*p*-methoxyphenoxyethyl chloride had b. p. 146—147°/15 mm., n_D^{20} 1·5380 (Motwani and Wheeler [12] give b. p. 130°/5 mm.), and m. p. 44—45° (Harris and Stewart [9] give b. p. 286—287°), respectively. 2-*p*-Acetamidophenoxyethyl chloride had m. p. 119° (Harris and Stewart [9] give b. p. 230—231°). 2-p-*Ethoxycarbonylphenoxyethyl chloride* (prepared from the alcohol [13]) had m. p. 68—70° (Found: C, 57·55; H, 5·7. $C_{11}H_{13}O_3Cl$ requires C, 57·75; H, 5·75%). p-*Diphenylyloxyethyl chloride*, crystallised from alcohol, had

Hydrobromides of substituted phenoxyethylnorpethidines



R	M. p.	Found (%) C	H	N	Br	Formula	Required (%) C	H	N	Br
H [a]	156·5—157·5°	60·4	6·35	3·2	18·7	$C_{22}H_{27}O_2N,HBr$	60·8	6·5	3·25	18·4
o-Me [b]	168—170°	61·65	6·8	3·2	—	$C_{23}H_{29}O_2N,HBr$	61·6	6·75	3·1	—
m-Me	168—169°	61·85	6·8	2·75	—	$C_{23}H_{29}O_2N,HBr$	61·6	6·75	3·1	—
p-Me [c]	145—146°	61·9	6·4	3·2	—	$C_{23}H_{29}O_2N,HBr$	61·6	6·75	3·1	—
m-Cl	170—171°	56·25	5·95	2·65	—	$C_{22}H_{26}O_2NCl,HBr$	56·35	5·8	3·0	—
p-Cl [d]	180°	56·7	5·9	2·75	—	$C_{22}H_{26}O_2NCl,HBr$	56·35	5·8	3·0	—
o-NO_2	171—172°	55·1	5·7	5·7	—	$C_{22}H_{26}O_5N_2,HBr$	55·1	5·7	5·85	—
m-NO_2	194—195°	55·45	5·75	5·3	—	$C_{22}H_{26}O_5N_2,HBr$	55·1	5·7	5·85	—
p-NO_2 [e]	186—187°	55·05	5·65	5·25	—	$C_{22}H_{26}O_5N_2,HBr$	55·1	5·7	5·85	—
m-MeO	171—172°	59·8	6·8	3·2	16·7	$C_{23}H_{29}O_4N,HBr$	59·5	6·5	3·0	17·2
p-MeO	180—182°	59·6	6·45	3·2	—	$C_{23}H_{29}O_4N,HBr$	59·5	6·5	3·0	—
p-NHAc	220—221°	58·75	6·55	5·25	16·75	$C_{24}H_{30}O_4N_2,HBr$	58·65	6·35	5·7	16·25
p-CO_2Et	190—191°	59·7	6·2	2·75	—	$C_{25}H_{31}O_5N,HBr$	59·3	6·35	2·75	—
p-Ph	170°	65·55	6·4	2·9	—	$C_{28}H_{31}O_3N,HBr$	65·85	6·4	2·75	—

[a] Hydrochloride, m. p. 156° (from alcohol). [b] Hydrochloride, m. p. 130°. [c] Hydrochloride, m. p. 167°. [d] Hydrochloride, m. p. 178°. [e] Base, m. p. 89° (from light petroleum–ethyl acetate).

m. p. 103—104° (Found: C, 72·35; H, 5·75. $C_{14}H_{13}OCl$ requires C, 72·25; H, 5·65); it was prepared from the alcohol.[14] 2-2′-Naphthyloxyethyl chloride had m. p. 81—82° (Herbst and Johnson [4] give m. p. 79—80°). 2-Benzyloxyethyl chloride had b. p. 112°/10 mm., n_D^{20} 1·5225 (Bennett [15] gives b. p. 124°/20 mm.). 4-Phenoxybutyl chloride had b. p. 144°/20 mm., n_D^{20} 1·5230 (Kharash *et al.*[16] give b. p. 133—134°/9 mm.), and was obtained in high yield from

[6] Bentley, Haworth, and Perkin, *J.*, 1896, **69**, 161.
[7] Mousseron, Jacquier, Mousseron-Canet, and Zagdoun, *Bull. Soc. chim. France*, 1952, 1042.
[8] Price and Morita, *J. Amer. Chem. Soc.*, 1953, **75**, 4747.
[9] Harris and Stewart, *Canad. J. Res.*, 1949, **27***B*, 739.
[10] Cf. Boyd and Marle, *J.*, 1914, **105**, 2117.
[11] Katrak, *J. Indian Chem. Soc.*, 1936, **13**, 334.
[12] Motwani and Wheeler, *J.*, 1935, 1098.
[13] Sugiyama, Washizu, and Jinno, *J. Chem. Soc. Japan*, 1954, **75**, 545.
[14] Vernon, U.S.P. 2,140,824.
[15] Bennett, *J.*, 1925, **127**, 1277.
[16] Kharasch, Stampa, and Nudenberg, *J. Org. Chem.*, 1953, **18**, 575.

4-chlorobutanol by action of dihydropyran and etherification of the 2-4′-chlorobutoxytetrahydropyran with sodium phenoxide in alcohol to 2-4′-*phenoxybutoxytetrahydropyran*, b. p. 185°/25 mm., n_D^{20} 1·5080 (Found: C, 71·55; H, 8·45. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%); this was hydrolysed to 4-phenoxybutanol which was treated with thionyl chloride in chloroform.

Tertiary Bases.—Ethyl 4-*phenyl*-1-2′-*phenylthioethylpiperidine*-4-*carboxylate.* In a typical experiment, norpethidine (5 g.) and 2-phenylthioethyl chloride (3·7 g.) were dissolved in pentyl alcohol (25 ml.) and sodium carbonate (1 g.) was added. The mixture was boiled under reflux for 30 hr. and then filtered, and the filtrate was concentrated under reduced pressure. On acidification with 40% aqueous hydrobromic acid, *ethyl* 4-*phenyl*-1-2′-*phenylthioethylpiperidine*-4-*carboxylate hydrobromide* (5·5 g.) crystallised; recrystallised from ethyl acetate–ethanol it had m. p. 178—180° (Found: C, 58·35; H, 6·15; N, 3·4. $C_{22}H_{28}O_2NBrS$ requires C, 58·65; H, 6·30; N, 3·1%). Analogously prepared, and not listed in the Table, were: *ethyl* 1-2′-cyclo*hexyloxyethyl*-4-*phenylpiperidine*-4-*carboxylate hydrobromide*, m. p. 123—124° (Found: C, 60·15; H, 7·6; N, 3·2. $C_{22}H_{34}O_3NBr$ requires C, 60·0; H, 7·8; N, 3·2%); *ethyl* 1-(2′-2″-*naphthyloxyethyl*)-4-*phenylpiperidine*-4-*carboxylate hydrobromide*, m. p. 164° (Found: C, 64·45; H, 6·25; N, 2·9. $C_{26}H_{29}O_3N$,HBr requires C, 63·85; H, 6·25; N, 2·9%); *ethyl* 1-2′-*benzyloxyethyl*-4-*phenylpiperidine*-4-*carboxylate hydrobromide*, m. p. 138—139° (Found: C, 61·4; H, 6·6; N, 3·05; Br, 18·3. $C_{23}H_{29}O_3N$,HBr requires C, 61·6; H, 6·75; N, 3·1; Br, 17·85%) (hydrochloride, m. p. 105°); and *ethyl* 1-(4′-*phenoxybutyl*)-4-*phenylpiperidine*-4-*carboxylate hydrobromide*, m. p. 161—162° (Found: C, 61·75; H, 6·85; N, 2·85. $C_{24}H_{32}O_3NBr$ requires C, 62·3; H, 7·0; N, 3·05%).

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