# 426. *Some New Analogues of Pethidine. Part IV.*[1] *Substituents at the 1-Position incorporating Cyclic Ether Groups.**

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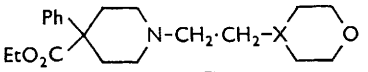
Several new derivatives of pethidine are described in which the *N*-methyl group is replaced by a substituent containing a tetrahydrofuran or tetrahydropyran ring. Some of the substances have high analgesic potency and consideration of structure–activity relationships indicates that an oxygen atom at the ε-carbon atom greatly enhances potency and acts by a different mechanism from one at the β-carbon atom.

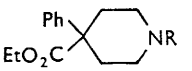
It was shown [2] that, whilst 2′-morpholinoethylnorpethidine (Morpheridine) (I; X = N) is a useful analgesic, the corresponding piperidino-analogue has little analgesic potency. The ether group of the morpholino-ring constitutes the only obvious difference between these




(I)

two substances, but it is far removed from the part of the molecule thought to give rise to the pharmacological action. This finding has led us to synthesise the substance (I) where X = CH, and other derivatives of norpethidine (ethyl 4-phenylpiperidine-4-carboxylate) in which the alkyl substituent at the 1-position carries an ether grouping in a saturated ring. The introduction of such substituents into the pethidine molecule has not previously been reported.

The substances prepared are listed in the Table. They were made by alkylation of norpethidine with the respective chloride, the accessibility of which varied considerably. Generally, the starting materials were tetrahydrofurfuryl alcohol, furylacraldehyde, tetrahydro-2-hydroxymethylpyran or 2,3-dihydropyran. For substance No. 1, tetrahydrofurfuryl alcohol was converted into the chloride by the method of Eglington, Jones, and Whiting,[3] which was used also for final step in the preparations of the other chlorides as it minimised the loss of the cyclic ether. For substance No. 2, tetrahydro-2-furylacetic acid [4]

*New pethidine analogues* 


| No. | R * | Found (%) C | H | N | Formula | Required (%) C | H | N | Approx. analgesic potency [10] † |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $CH_2$·Fur | 71·85 | 8·7 | 4·2 | $C_{19}H_{27}O_3N$ | 71·9 | 8·55 | 4·4 | 1 |
| 2 | $[CH_2]_2$·Fur | 72·9 | 8·8 | 4·4 | $C_{20}H_{29}O_3N$ | 72·5 | 8·8 | 4·2 | 3 |
| 3 | $[CH_2]_3$·Fur | 72·3 | 9·0 | 4·1 | $C_{21}H_{31}O_3N$ | 73·0 | 9·05 | 4·05 | 33 |
| 4 | $[CH_2]_4$·Fur | 73·75 | 9·05 | 3·7 | $C_{22}H_{33}O_3N$ | 73·5 | 9·25 | 3·9 | 33 |
| 5 | $[CH_2]_5$·Fur | 73·45 | 8·95 | 3·8 | $C_{23}H_{35}O_3N$ | 73·95 | 9·4 | 3·75 | 3 |
| 6 | $[CH_2]_2$·Pyr-4 | 72·5 | 8·8 | 4·0 | $C_{21}H_{31}O_3N$ | 73·0 | 9·05 | 4·05 | 5 |
| 7 | $[CH_2]_2$·O·$CH_2$·Fur | 69·45 | 8·9 | 3·6 | $C_{21}H_{31}O_4N$ | 69·75 | 8·65 | 3·9 | 25 |
| 8 | $[CH_2]_2$·O·$CH_2$·Pyr | 69·55 | 8·7 | 3·8 | $C_{22}H_{33}O_4N$ | 70·35 | 8·85 | 3·75 | 10 |
| 9 | $[CH_2]_3$·O·$CH_2$·Fur | 71·0 | 9·1 | 4·0 | $C_{22}H_{33}O_4N$ | 70·35 | 8·85 | 3·75 | 1·5 |
| 10 | $[CH_2]_4$·O·$CH_2$·Fur | 70·3 | 9·1 | 3·3 | $C_{23}H_{35}O_4N$ | 70·9 | 9·05 | 3·6 | 6 |
| 11 | $[CH_2]_2$·O·Pyr | 69·25 | 9·0 | 3·45 | $C_{21}H_{31}O_4N$ | 69·75 | 8·65 | 3·9 | 1 |
| 12 | $[CH_2]_4$·O·Pyr | 70·8 | 8·9 | 3·4 | $C_{23}H_{35}O_4N$ | 70·9 | 9·05 | 3·6 | 1·5 |
| 13 | $[CH_2]_2$·O·$[CH_2]_2$·O·$CH_2$·Fur | 68·6 | 8·9 | 3·4 | $C_{23}H_{35}O_5N$ | 68·1 | 8·7 | 3·45 | 3 |

* Fur = tetrahydro-2-furyl; Pyr = tetrahydro-2-pyranyl; Pyr-4 = tetrahydro-4-pyranyl.
† Relative to pethidine = 1.

* Some of this work forms part of B.P. 797,448.

[1] Part III, *J.*, 1958, 3065.
[2] Anderson, Frearson, and Stern, *J.*, 1956, 4088.
[3] Eglington, Jones, and Whiting, *J.*, 1952, 287.
[4] Barger, Robinson, and Smith, *J.*, 1937, 718.

(three steps from tetrahydrofurfuryl alcohol) was esterified and reduced with lithium aluminium hydride; chlorination then gave 2-(tetrahydro-2-furyl)ethyl chloride. The corresponding 3-(tetrahydro-2-furyl)propyl chloride was known [5] and used for substance No. 3; chain-elongation *via* the cyanide, acid, ester, and alcohol gave the new 4-(tetrahydro-2-furyl)butyl chloride (for substance No. 4). Tetrahydrofurylpropyl chloride did not react readily with magnesium and the known 5-(tetrahydro-2-furyl)pentyl chloride [6] (for substance No. 5) was therefore obtained from 3-(tetrahydro-2-furyl)propylmagnesium bromide by action of ethylene oxide and subsequent chlorination. 2-(Tetrahydro-4′-pyranyl)ethyl chloride (for No. 6) was made in acceptable yield from tetrahydropyran-4-carbonyl chloride,[7] by Arndt–Eistert reaction, Bouveault–Blanc reduction of the resulting ethyl tetrahydro-4-pyranylacetate,[8] and chlorination. The chloro-ethers required for the preparation of substances No. 7 and 13 were prepared by condensation of tetrahydrofurfuryl alcohol with ethylene oxide in presence of little sodium, and subsequent chlorination: with 0·33 mol. of ethylene oxide, the monoadduct was obtained in 55—60% yield, accompanied by some diadduct (12—15%). 3-Tetrahydrofurfuryloxypropyl chloride (for substance No. 9) was made by reaction of sodium tetrahydrofurfuryl oxide and trimethylene chlorohydrin, and subsequent chlorination. 2-(Tetrahydro-2-pyranyl)methoxyethyl chloride (for No. 8) was prepared analogously. The intermediate for substance No. 10, however, was prepared by action of 2-4′-chlorobutoxytetrahydropyran [9] on sodium tetrahydrofurfuryl oxide, removal of the protecting group by acidic hydrolysis, and chlorination of the 4-tetrahydrofurfuryloxybutanol. Addition of dihydropyran to ethylene or tetramethylene chlorohydrin in the usual manner gave the intermediates for substances No. 11 and 12.

Alkylation of norpethidine proceeded smoothly in a high-boiling solvent over sodium carbonate. The new bases were high-boiling oils (some crystallised on prolonged storage), readily soluble in dilute aqueous acids. The salts of the bases with mineral acids were, in general, excessively water-soluble and the bases were best characterised as the picrates.

Since some of these substances had very high analgesic potency [10] (cf. Table), two open-chain diethers were prepared for comparison, namely, *N*-2-2′-ethoxyethoxyethyl- and *N*-2-2′-phenoxyethoxyethyl-norpethidine; these were less potent. The former has since been described; [11] the latter, like the simple aryloxyalkylnorpethidines,[1] was readily isolated as the crystalline hydrobromide.

*Structure–Activity Relations.*—Full details of the pharmacological work are being published elsewhere,[10] but certain effects of changes in structure on activity may be summarised. First, substances Nos. 3, 4, and 7 have very high analgesic potency, 25—40 times that of pethidine, and of the same order as that of the 1-cinnamyl analogue.[12]

Substance No. 8 has less than one-half and ethoxyethoxyethylnorpethidine about one-twentieth of potency of that of No. 7 (Furethidine). Thus the analgesic potency of the pethidine analogues is greatly influenced, not only by the position of the ether-oxygen atom in relation to the piperidine ring,[9] but also by its environment. The open-chain ethoxyethoxyethyl-compound, for instance, differs from Furethidine only in minor respects: that the potencies are, in fact, in a ratio of 1 : 20 implies that an additional effect operates with regard to the ε-oxygen atom. A similar relation (though a potency ratio of 1 : 7) exists between ethoxybutylnorpethidine [9] and substance No. 4. Such an effect might well be the ability to form hydrogen bonds: thus it is known [13] that the ability of an oxygen atom to

[5] Gilman and Hewlett, *Rec. Trav. chim.*, 1932, **51**, 93; see also ref. 4.
[6] Onesta, Ferreti, and Notari, *Gazzetta*, 1956, **86**, 178.
[7] Gibson and Johnson, *J.*, 1930, 2552.
[8] Prelog, Kohlbach, Cerkovnikov, Rezek, and Piatanida, *Annalen*, 1937, **532**, 69.
[9] Cf. Part II, *J.*, 1958, 3062.
[10] Blair and Stephenson, *Brit. J. Pharmacol.*, in the press.
[11] Morren and Strubbe, *Ind. chim. belge*, 1957, **22**, 795.
[12] Elpern, Gardner, and Grumbach, *J. Amer. Chem. Soc.*, 1957, **79**, 1951.
[13] Cf. Searles and Tamres, *J. Amer. Chem. Soc.*, 1951, **73**, 3604.

form hydrogen bonds with a solvent decreases in the order tetrahydrofuran, tetrahydropyran, open-chain ether, and this order appears to be followed by the analgesic potency of the substances described. Whereas this principle may hold for the ε-oxygen atom, it is clearly not in operation at the β-oxygen atom since the open-chain ether, ethoxyethyl norpethidine,[7] is much more potent than the tetrahydrofurfuryl analogue (No. 1) although the difference in structure is the same as between the open-chain ethoxyethoxyethyl-norpethidine and Furethidine. Moreover, omission or replacement by $CH_2$ of the β-oxygen atom, as in substances Nos. 3 and 4, does not reduce the potency, but in fact increases it. Clearly the physiological functions of the ε- and β-oxygen atoms are different and the effect of the former is much more important: this effect may well be to provide electrons for hydrogen-bonding at a distance equivalent to between four and five carbon atoms from the nitrogen.

## Experimental

Analyses for the new esters are recorded in the Table (p. 2013).

*Ethyl 4-Phenyl-1-(tetrahydrofurfuryl)piperidine-4-carboxylate* (No. 1 *in Table*).—Tetrahydrofurfuryl chloride (3·5 g.),[3] b. p. 41—42°/1 mm., $n_D^{20}$ 1·4553, with norpethidine (5 g.) in boiling pentyl alcohol (50 ml.) containing sodium carbonate (3 g.) gave the desired *ethyl 4-phenyl-1-(tetrahydrofurfuryl)piperidine-4-carboxylate* (5 g.), b. p. 170—180°/0·7 mm., $n_D^{20}$ 1·5276, isolated by filtration and fractional distillation of the filtrate.

*Ethyl 4-Phenyl-1-[2-(tetrahydro-2-furyl)ethyl]piperidine-4-carboxylate* (Substance No. 2).—Tetrahydrofurfuryl bromide [14] was converted through the cyanide into tetrahydro-2-furylacetic acid, b. p. 140—145°/11 mm., $n_D^{20}$ 1·4589 (Barger *et al.*[4] give b. p. 114°/11 mm.), the *ethyl ester* of which had b. p. 98°/13 mm., $n_D^{20}$ 1·4369 (Found: C, 61·2; H, 8·7. $C_8H_{14}O_3$ requires C, 60·75; H, 8·9%). This ester (17 g.) on reduction with lithium aluminium hydride in anhydrous ether gave 2-*(tetrahydro-2-furyl)ethanol* (9 g.), b. p. 94°/10 mm., $n_D^{20}$ 1·4525 (Found: C, 62·35; H, 10·4. $C_6H_{12}O_2$ requires C, 62·0; H, 10·4%). Treatment as described by Eglington *et al.*[3] yielded 2-*(tetrahydro-2-furyl)ethyl chloride* (6 g.), b. p. 70°/15 mm., $n_D^{20}$ 1·4540 (Found: C, 53·65; H, 8·3. $C_6H_{11}ClO$ requires C, 53·55; H, 8·25%), which alkylated norpethidine, as above, giving *ethyl 4-phenyl-1-[2-(tetrahydro-2-furyl)ethyl]piperidine-4-carboxylate*, b. p. 180°/0·2 mm., $n_D^{20}$ 1·5220.

*Ethyl 4-Phenyl-1-[3-(tetrahydro-2-furyl)propyl]piperidine-4-carboxylate* (No. 3).—Hydrogenation of 2-furylacraldehyde and subsequent treatment as described by Eglington *et al.*[3] gave 3-(tetrahydro-2-furyl)propyl chloride, b. p. 90—95°/20 mm., $n_D^{20}$ 1·4578 (Gilman and Hewlett [5] give b. p. 75°/4 mm., $n_D^{25}$ 1·4540). This (2 g.) with norpethidine (2 g.), as above, gave the *ester* No. 3 (3 g.), b. p. 180—185°/0·2 mm., $n_D^{20}$ 1·5188.

*Ethyl 4-Phenyl-1-[4-(tetrahydro-2-furyl)butyl]piperidine-4-carboxylate* (No. 4).—3-(Tetrahydro-2-furyl)propyl chloride (15 g.), which failed to react with magnesium in dry ether, was refluxed for 24 hr. with potassium cyanide (8·2 g.) in 1 : 4 v/v aqueous ethanol (50 ml.). Water (10 ml.) was then added. Chloroform-extraction and distillation gave 3-(tetrahydrofuryl)propyl cyanide (11 g.), b. p. 85—90°/2 mm., $n_D^{20}$ 1·4548 (Arh-Lipovac and Seiwerth [15] give b. p. 115—116°/10 mm.). Hydrolysis with boiling aqueous-alcoholic potassium hydroxide until no further ammonia was evolved gave ω-(tetrahydro-2-furyl)butyric acid (7 g.), b. p. 110°/3 mm., $n_D^{20}$ 1·4635 (Gilman and Hewlett [4] give b. p. 145°/5 mm., $n_D^{25}$ 1·4572; Hornberger *et al.*[16] give b. p. 160°/1 mm., $n_D^{25}$ 1·457; Holmquist *et al.*[17] give b. p. 104—106°/2·5 mm., $n_D^{25}$ 1·4590), converted into the ethyl ester (7 g.), b. p. 80—82°/1·5 mm., $n_D^{20}$ 1·4452 (Arh-Lipovac and Seiwerth [15] give b. p. 118—120°/10 mm.; Holmquist *et al.*[17] give b. p. 66—70°/0·9 mm., $n_D^{25}$ 1·4438). Reduction of this with lithium aluminium hydride (2 equiv.) afforded 4-(tetrahydro-2-furyl)butanol (4 g.), b. p. 87°/1·5 mm., $n_D^{20}$ 1·4588 (Found: C, 65·95; H, 10·9. Calc. for $C_8H_{16}O_2$: C, 66·6; H, 11·15%) (Arh-Lipovac and Seiwerth [15] give b. p. 124°/10 mm. for impure material and Holmquist *et al.*[17] give b. p. 84—86°/1·8 mm.). This afforded [3] the *chloride* (2·5 g.), b. p. 105°/20 mm., $n_D^{20}$

[14] Smith, *Org. Synth.*, Coll. Vol. III, p. 793, John Wiley, New York, 1955 (there is an error on line 3 of this recipe; 0·36 mole of $PBr_3$ is 98 g. or 35 ml. at 15°).
[15] Arh-Lipovac and Seiwerth, *Monatsh.*, 1953, **87**, 992.
[16] Hornberger, Heitmiller, Gunsalus, Schnakenberg, and Reed, *J. Amer. Chem. Soc.*, 1953, **75**, 1273.
[17] Holmquist, Marsh, Sauer, and Engelhardt, *J. Amer. Chem. Soc.*, 1959, **81**, 3681.

1·4564 (Found: C, 58·75; H, 9·55. $C_8H_{15}ClO$ requires C, 59·05; H, 9·3%) which with norpethidine gave the desired *ester* No. 4, b. p. 200°/0·1 mm., $n_D^{20}$ 1·5178.

*Ethyl 4-Phenyl-1-[5-(tetrahydro-2-furyl)pentyl]piperidine-4-carboxylate* (No. 5).—3-(Tetrahydro-2-furyl)propyl bromide, b. p. 115°/20 mm., $n_D^{20}$ 1·4880, was submitted to Grignard reaction with ethylene oxide. The resulting pentyl alcohol (60% yield), b. p. 98—100°/0·6 mm., $n_D^{20}$ 1·4608 (Vranjican *et al.*[18] give b. p. 136—142°/10 mm.) was converted into the chloride, b. p. 115°/10 mm., $n_D^{20}$ 1·4615 (Onesta *et al.*[6] give b. p. 103—104°/8 mm., $n_D^{20}$ 1·4580), which was added to norpethidine to yield *ester* No. 5, b. p. 175°/0·1 mm., $n_D^{20}$ 1·5150.

*Ethyl 4-Phenyl-1-[2-(tetrahydrofurfuryloxy)ethyl]piperidine-4-carboxylate* (No. 7).—Tetrahydrofurfuryl alcohol (306 g.) containing sodium (3 g.) and ethylene oxide (44 g.) were kept in a closed vessel at 70—80° for 3 hr. The cool mixture was then neutralised and fractionated. Besides starting material, there were obtained 2-*(tetrahydrofurfuryloxy)ethanol* (55—60% based on ethylene oxide), b. p. 114—116°/20 mm., $n_D^{20}$ 1·4578 (Found: C, 57·4; H, 9·7. $C_7H_{14}O_3$ requires C, 57·5; H, 9·65%), and 2-[2-*(tetrahydrofurfuryloxy)ethoxy]ethanol* (12—15%), b. p. 130°/0·6 mm., $n_D^{20}$ 1·4618 (Found: C, 56·4; H, 9·75. $C_9H_{18}O_4$ requires C, 56·8; H, 9·55%).

The lower-boiling alcohol was converted in the usual manner into 2-*(tetrahydrofurfuryloxy)-ethyl chloride*, b. p. 95—96°/18 mm., $n_D^{20}$ 1·4628 (Found: C, 50·95; H, 7·95; Cl, 21·1. $C_7H_{13}ClO_2$ requires C, 51·05; H, 7·95; Cl, 21·55%). This chloride with norpethidine, in the usual manner, gave *ester* No. 7, b. p. 175—183°/0·3 mm., m. p. *ca.* 28°, $n_D^{20}$ 1·5219, p$K_a$ 7·48. The *methiodide*, recrystallised from ethyl acetate, had m. p. 174° (Found: C, 52·35; H, 6·9; N, 2·9. $C_{22}H_{34}INO_4$ requires C, 52·3; H, 6·85; N, 2·8%). The picrate, recrystallised from ethanol, had m. p. 104—105°.

*Ethyl 4-Phenyl-1-2′-[2″-(tetrahydrofurfuryloxy)ethoxy]ethylpiperidine-4-carboxylate* (No. 13).—2-[2-(Tetrahydrofurfuryloxy)ethoxy]ethanol (cf. above) in the usual manner gave the *chloride*, b. p. 135°/5 mm., $n_D^{20}$ 1·4635 (Found: C, 52·15; H, 8·4. $C_9H_{17}ClO_3$ requires C, 51·75; H, 8·2%), which on condensation with norpethidine yielded *ester* No. 13, b. p. 170°/0·2 mm., $n_D^{20}$ 1·5122.

*Ethyl 4-Phenyl-1-[3-(tetrahydrofurfuryloxy)propyl]piperidine-4-carboxylate* (No. 9).—Condensation of sodium tetrahydrofurfuryl oxide (from 11·5 g. of sodium) and trimethylene chlorohydrin (47 g.) in excess of the alcohol gave 3-*(tetrahydrofurfuryloxy)propanol* (45 g.), b. p. 135°/16 mm., $n_D^{20}$ 1·4565 (Found: C, 59·25; H, 10·15. $C_8H_{16}O_3$ requires C, 60·0; H, 10·5%); the derived *chloride*, b. p. 120°/16 mm., $n_D^{20}$ 1·4580 (Found: C, 53·35; H, 8·25; Cl, 20·7. $C_8H_{15}ClO_2$ requires C, 53·8; H, 8·45; Cl, 19·85%), alkylated norpethidine, giving *ester* No. 9, b. p. 225°/0·5 mm., $n_D^{20}$ 1·5110.

*Ethyl 4-Phenyl-1-[4-(tetrahydrofurfuryloxy)butyl]piperidine-4-carboxylate* (No. 10).—4-(Tetrahydro-2-pyranyloxy)butyl chloride[9] with a solution of sodium (1 equiv.) in tetrahydrofurfuryl alcohol (excess) gave 1-*(tetrahydrofurfuryloxy)-4-(tetrahydro-2-pyranyloxy)butane*, b. p. 135°/0·25 mm., $n_D^{20}$ 1·4640 (Found: C, 65·4; H, 10·2. $C_{14}H_{26}O_4$ requires C, 65·1; H, 10·15%), which was hydrolysed by boiling 2N-hydrochloric acid in 8 hr. to 4-*(tetrahydrofurfuryloxy)-butanol*, b. p. 140—150°/19 mm., $n_D^{20}$ 1·4618 (Found: C, 61·5; H, 10·2. $C_9H_{18}O_3$ requires C, 62·05; H, 10·4%). This alcohol (5·5 g.) with thionyl chloride (5·6 g.) in chloroform containing pyridine (2·5 g.) yielded the *chloride* (4·5 g.), b. p. 120°/20 mm., $n_D^{20}$ 1·4617 (Found: C, 56·0; H, 8·95. $C_9H_{17}ClO_2$ requires C, 56·1; H, 8·9%), which with norpethidine in the usual manner gave the desired *ester* No. 10, b. p. 196°/1·5 mm., m. p. *ca.* 30°, $n_D^{20}$ 1·5140.

*Ethyl 4-Phenyl-1-[2-(tetrahydro-2-pyranylmethoxy)ethyl]piperidine-4-carboxylate* (No. 8).—Tetrahydro-2-hydroxymethylpyran (11·6 g.) was treated with sodium (1 equiv.) in benzene and then with ethylene chlorohydrin (1 equiv.), the mixture was refluxed for some hours and then filtered, and the filtrate distilled: 2-*(tetrahydro-2-pyranylmethoxy)ethanol* (5·6 g.) had b. p. 138—140°/30 mm., $n_D^{20}$ 1·4610 (Found: C, 59·65; H, 10·0. $C_8H_{16}O_3$ requires C, 60·0; H, 10·05%). With thionyl chloride in boiling chloroform it gave the *chloride* (3·5 g.), b. p. 95—96°/18 mm., $n_D^{20}$ 1·4628 (Found: C, 53·75; H, 8·6; Cl, 19·5. $C_8H_{15}ClO_2$ requires C, 53·8; H, 8·45; Cl, 19·85%), which with norpethidine in the usual manner gave *ester* No. 8, b. p. 190—220°/0·6 mm., $n_D^{20}$ 1·5182.

*Ethyl 4-Phenyl-1-[2-(tetrahydro-4-pyranyl)ethyl]piperidine-4-carboxylate* (No. 6).—Tetrahydropyran-4-carbonyl chloride (15 g.), b. p. 80°/17 mm., $n_D^{15}$ 1·4659 (Gibson and Johnson[7] give b. p. 85—86°/18 mm.), with diazomethane in ether gave the solid diazoketone, which was not isolated but was converted by silver oxide in alcohol into ethyl tetrahydro-4-pyranylacetate (10·5 g.),

[18] Vranjican, Pavlović, and Seiwerth, *Arhiv Kem.*, 1953, **25**, 81 (*Chem. Abs.*, 1955, **49**, 2419d).

b. p. 106—110°/18 mm., $n_D^{20}$ 1·4465 (Prelog *et al.*[8] give b. p. 113°/15 mm.). Bouveault–Blanc reduction of this ester (10·3 g.) yielded tetrahydro-4-2′-hydroxyethylpyran (6 g.), b. p. 110°/14 mm., $n_D^{20}$ 1·4590 (Prelog *et al.*[8] give b. p. 119—120°/14 mm.), also obtained in 15% yield from the ester (15 g.) by reduction with lithium aluminium hydride (2 g.) in ether (50 ml.). Finally, action of thionyl chloride in chloroform converted the hydroxy-compound (6 g.) into the *2′-chloroethyl compound* (4·5 g.), b. p. 89°/16 mm., $n_D^{20}$ 1·4680 (Found: C, 56·7; H, 8·6; Cl, 23·3. $C_7H_{13}ClO$ requires C, 56·6; H, 8·8; Cl, 23·85%). This halide (3 g.) with norpethidine (4 g.) in the usual manner gave *ester* No. 6 (3·5 g.), b. p. 183°/0·4 mm., m. p. 28—32°, $n_D^{20}$ 1·5245. The *picrate*, recrystallised from ethanol, had m. p. 126° (Found: C, 56·65; H, 6·2; N, 9·7. $C_{21}H_{31}NO_3,C_6H_3N_3O_7$ requires C, 56·3; H, 6·0; N, 9·75%).

*Ethyl 4-Phenyl-1-[4-(tetrahydro-2-pyranyloxy)butyl]piperidine-4-carboxylate* (No. 12).—4-(Tetrahydro-2-pyranyloxy)butyl chloride [9] (5 g.), b. p. 93—94°/3 mm., $n_D^{20}$ 1·4608, and norpethidine (6 g.), refluxed in pentyl alcohol for 24 hr. over sodium carbonate and then distilled, gave the desired *ester* No. 12 (6 g.), b. p. 200°/1 mm., $n_D^{20}$ 1·5135.

*Ethyl 4-Phenyl-1-[2-(tetrahydro-2-pyranyloxy)ethyl]piperidine-4-carboxylate* (No. 11).—Keeping a mixture of ethylene chlorohydrin (80·5 g.) and $\Delta^2$-dihydropyran (84 g.) containing hydrochloric acid (3 drops) overnight, neutralisation, and distillation gave 2-(tetrahydro-2-pyranyloxy)-ethyl chloride (134 g.), b. p. 93°/20 mm., $n_D^{20}$ 1·4580. This chloride with norpethidine in the usual manner afforded the desired *product*, b. p. 200°/2·5 mm., $n_D^{20}$ 1·5178.

*Ethyl 1-[2-(2-Phenoxyethoxy)ethyl]-4-phenylpiperidine-4-carboxylate.*—Di-(2-chloroethyl) ether (144 g.) and phenol (94 g.) were added to a cold solution of sodium (23 g.) in ethanol; the mixture was refluxed for 8 hr. and filtered, and the filtrate evaporated. The residue was dissolved in ether, washed with aqueous alkali, recovered, and distilled. 2-2′-Phenoxyethoxyethyl chloride (120 g.) had b. p. 160°/19 mm., $n_D^{20}$ 1·5230 (Bruson [19] gives b. p. 113—120°/1 mm.), and it (10 g.) readily condensed with norpethidine (5 g.) in the usual manner giving ethyl 1-[2-(2-phenoxyethoxy)ethyl]-4-phenylpiperidine-4-carboxylate (7·5 g.), isolated as the *hydrobromide* which, recrystallised from ethanol, had m. p. 172—173° (Found: C, 60·5; H, 6·65; N, 2·95. $C_{24}H_{31}NO_4$,HBr requires C, 60·25; H, 6·75; N, 2·95%).

*Ethyl 1-[2-(2-Ethoxyethoxy)ethyl]-4-phenylpiperidine-4-carboxylate.*—2-2′-Ethoxyethyloxyethyl chloride, b. p. 68—71°/18 mm., $n_D^{20}$ 1·4330 (Blicke and Zienty [20] give b. p. 89—90°/28 mm.), was prepared from commercial diethylene glycol monoethyl ether. With norpethidine (5 g.) it (3 g.) gave *ethyl 1-[2-(2-ethoxyethoxy)ethyl]-4-phenylpiperidine-4-carboxylate* (5 g.), b. p. 175—185°/1 mm., $n_D^{20}$ 1·5122 (Found: C, 67·85; H, 8·9; N, 3·8. $C_{20}H_{31}NO_4$ requires C, 68·75; H, 8·95; N, 4·0%).

*4-[2-(Tetrahydrofurfuryloxy)ethyl]morpholine.*—This substance was prepared as a " model " carrying two groups which, in the 1-position of norpethidine, confer high potency on the molecule. 2-Tetrahydrofurfuryloxyethyl chloride (2 g.) (see above) was heated with morpholine (6 g.). The morpholine hydrochloride which crystallised on cooling was filtered off, and the filtrate fractionally distilled: *4-[2-(tetrahydrofurfuryloxy)ethyl]morpholine* had b. p. 100°/0·5 mm., $n_D^{20}$ 1·4781 (Found: C, 61·8; H, 10·05; N, 6·5. $C_{10}H_{21}NO_3$ requires C, 61·35; H, 9·85; N, 6·5%), and gave a picrate, m. p. 128—129° (from ethyl acetate–light petroleum). It had no analgesic action.

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