Bis(3-trimethylammoniumpropyl) Diselenide Diiodide (Homocholine Diselenide Diiodide).—A solution of bis(3-dimethylaminopropyl) diselenide [from 10.0 g. (0.025 mole) of the dihydrochloride by extraction from alkaline solution] in dry ether (100 ml.) was mixed with methyl iodide (5 ml.). The reaction was allowed to proceed overnight at room temperature and the yellow precipitate (15.4 g., 100%) was recrystallized from methanol, m.p. 211–213° dec.

Anal. Calcd. for $C_{12}H_{30}I_2N_2Se_2$: C, 23.47; H, 4.92; N, 4.56; Se, 25.72. Found: C, 23.73; H, 4.75; N, 4.75; Se, 26.01.

3-Trimethylammoniumpropylselenol Iodide (homocholineselenol iodide) was obtained by a reduction procedure similar to the one described for cholineselenol iodide. The homocholine diselenide diiodide (3.0 g., 0.005 mole) in absolute ethanol (25 ml), reduced with hypophosphorous acid (2 ml.) at the boiling point of the solvent, yielded colorless needles of the desired selenol iodide (2.8 g., 93%), m.p. 169–170°.

Anal. Calcd. for $C_6H_{16}INSe$: C, 23.39; H, 5.23; N, 4.55; Se, 25.63. Found: C, 23.48; H, 5.23; N, 4.79; Se, 25.26.

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Structure–Activity Relationship of Some New Analogs of Pethidine

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The synthesis and analgesic activity are described for 32 N-substituted analogs of pethidine, which may be grouped in seven series with the structure 1-R$(CH_2)_n$-4-C_6H_5-piperidine-4-$CO_2C_2H_5$: series A (n = 4–7, R = Me); B (n = 1–5, R = CH_2OH); C (n = 1–5, R = CH_2OEt); D [n = 1, R = $CH_2O(CH_2)_{0,2-5}CH_3$]; E (n = 1–3, R = CH_2OCH_2-2-furyl); F (n = 0–4, R = CH_2-2-furyl); G (n = 0–4, R = cyclopentyl). A comparison of the structure–activity relationship within and between these series is made. Analgesic activities range from less than one-tenth to twenty-eight times that of pethidine and increase regularly with increasing chain length of the N-substituent to a maximum, after which activity falls off at a similar rate. Maximum analgesic activity is found when the N-substituent skeleton consists of six or seven atoms, with a chain length of 7–9 Å. Possible explanations for these findings are discussed.

Many N-substituted derivatives of norpethidine (ethyl 4-phenyl-4-piperidinecarboxylate) have been synthesized in recent years,[2–7] and several of these substances were found to be more potent than the parent substance pethidine. Thus morpheridine, first synthesized in these laboratories in 1953,[4] was twice as potent (on a weight basis) as pethidine.[8] Subsequently, derivatives in which the N-substituent contained an open chain[9] or a cyclic ether linkage[10] were described. Systematic modifications in the chain length of the substituent attached to the nitrogen atom have now been made in seven series of derivatives (see Table I). The effect of these modifications upon analgesic potency within each series indicates that a definite relationship exists between chain length of the N-substituent and analgesic potency.

Chemistry.—The compounds of series C–F have been described previously[9,10]; the other substances were prepared by alkylation of norpethidine with the appropriate halide. Some n-alkylnorpethidines (series A) were described[11] while this work was in progress. The ω-chloroalkanols required for the preparation of the compounds of series B were synthesized from the respective glycols or from tetrahydrofuran (*cf.* Experimental Section). The cyclopentylalkyl bromides (for series G) were all made from cyclopentyl bromide, the chain being lengthened by the action of formaldehyde or of ethylene oxide on the appropriate Grignard reagent.

Pharmacology.—Analgesic activity was measured in weanling male rats of the Wister strain weighing 50–60 g. by a method[12] based on that of Green and Young.[13] This method uses pressure on the tip of the tail as the pain stimulus, and this is the major difference between the method we have adopted and the hot-plate method used by Janssen and Eddy.[14] Five groups of 8 or 10 rats were used for each evaluation, and each animal was used as its own control. The mean pressure required to produce a pain response before and after drug administration was determined; if the postdrug threshold pressure were equal to or greater than twice the predrug threshold, the drug was judged to be producing an analgesic effect. The ED_{50} and 95% confidence limit for analgesia were determined using the standard probit analysis. All compounds were injected subcutaneously and the analgesic activity was determined 30 min. after injection. All ED_{50} values were expressed as μmoles of base/kilogram of body weight and the potency ratios were compared on an equimolar basis, with pethidine taken as unity. This method permits a direct comparison with the figures obtained by Janssen and Eddy.

The analgesic activities of the seven series of norpethidine derivatives investigated are shown in Table I. Figures 1 and 2 show plots of molar potency (relative to pethidine taken as unity) on a log scale against chain length of N-substituent. The number of side-chain

(1) Biological Research Laboratories, Reckitt & Sons Ltd., Hull, Yorkshire, England.

(2) T. D. Perrine and N. B. Eddy, *J. Org. Chem.*, **21**, 125 (1956).

(3) J. Weijlard, P. D. Orahovats, A. P. Sullivan, G. Purdue, F. K. Heath, and K. Pfister, *J. Am. Chem. Soc.*, **78**, 2342 (1956).

(4) R. J. Anderson, P. M. Frearson, and E. S. Stern, *J. Chem. Soc.*, 4088 (1956).

(5) B. Elpern, L. N. Gardner, and L. Grumbach, *J. Am. Chem. Soc.*, **79**, 1951 (1957).

(6) P. A. J. Janssen, A. Jageneau, E. G. Van Proosdij-Hartzema, and D. K. de Jongh, *Acta Physiol. Pharmacol. Neerl.*, **7**, 373 (1958).

(7) H. Morren and H. Strubbe, *Ind. Chim. Belge*, **22**, 795 (1957).

(8) A. F. Green and N. B. Ward, *Brit. J. Pharmacol.*, **11**, 32 (1956).

(9) P. M. Frearson and E. S. Stern, *J. Chem. Soc.*, 3062 (1958).

(10) P. M. Frearson, D. G. Hardy, and E. S. Stern, *ibid.*, 2103 (1960).

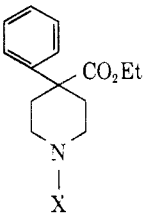
(11) B. Elpern, U. S. Patent 2,901,487 (1959).

(12) R. E. Lister, *Brit. J. Pharmacol.*, **15**, 254 (1960).

(13) A. F. Green and P. A. Young, *ibid.*, **6**, 578 (1951).

(14) P. A. J. Janssen and N. B. Eddy, *J. Med. Pharm. Chem.*, **2**, 31 (1960).

TABLE I
SUBSTITUENT CHAIN LENGTH AND ANALGESIC ACTIVITY OF N-SUBSTITUTED NORPETHIDINES



No.	X	No. of atoms in side-chain skeleton	Chain length, Å.[a]	ED_{50} (rat), μmoles/kg. s.c.[b]	Molar potency ratio[c]
Series A					
1	$(CH_2)_4CH_3$	5	6.5	16.8 (13.9–19.1)	1.5
2	$(CH_2)_5CH_3$	6	7.7	4.4 (3.5–5.4)	5.8 (4.7–7.3)
3	$(CH_2)_6CH_3$	7	8.9	15.5 (13.1–18.5)	1.6 (1.4–1.9)
4	$(CH_2)_7CH_3$	8	10.1	350	0.1
Series B					
5	$(CH_2)_2OH$	3	3.8	350	0.1
6	$(CH_2)_3OH$	4	3.0	350	0.1
7	$(CH_2)_4OH$	5	6.2	65.6 (25.5–120)	0.4 (0.2–0.6)
8	$(CH_2)_5OH$	6	7.4	5.8 (3.6–7.3)	4.3 (3.5–7.1)
9	$(CH_2)_6OH$	7	8.6	14.4 (11.7–17.7)	1.8 (1.3–2.2)
Series C					
10	$(CH_2)_2OC_2H_5$	5	6.2	6.0 (5.3–5.9)	4.2 (3.7–4.8)
11	$(CH_2)_3OC_2H_5$	6	7.4	11.0 (8.8–12.5)	2.3 (2.0–2.9)
12	$(CH_2)_4OC_2H_5$	7	8.6	2.7 (2.1–3.5)	9.4 (7.2–12.4)
13	$(CH_2)_5OC_2H_5$	8	9.8	8.6 (7.2–10.4)	2.9 (2.4–3.5)
14	$(CH_2)_6OC_2H_5$	9	11.2	14.4 (12.2–16.9)	1.8 (1.5–2.1)
Series D					
15	$C_2H_4OCH_3$	4	4.9	56.8 (46.5–69.5)	0.4 (0.3–0.5)
16	$C_2H_4O(CH_2)_2CH_3$	6	7.4	17.0 (15.1–19.2)	1.5 (1.3–1.7)
17	$C_2H_4O(CH_2)_3CH_3$	7	8.6	13.2 (10.5–16.5)	1.9 (1.5–2.4)
18	$C_2H_4O(CH_2)_4CH_3$	8	9.8	18.4 (16.1–21.0)	1.4 (1.2–1.6)
19	$C_2H_4O(CH_2)_5CH_3$	9	11.2	63.8 (41.3–98.0)	0.4 (0.2–0.6)
Series E					
20	$(CH_2)_2OCH_2$-Fur[d,e]	7	8.5	1.2 (0.7–1.8)	21.2 (14.1–36.4)
21	$(CH_2)_3OCH_2$-Fur	8	9.7	8.5 (8.5–10.7)	3.0 (2.4–3.8)
22	$(CH_2)_4OCH_2$-Fur	9	11.1	7.8 (5.8–10.6)	3.3 (2.4–4.4)
Series F					
23	CH_2-Fur	4	4.6	82.0	0.34 (0.27–0.44)
24	$(CH_2)_2$-Fur	5	5.8	10.8 (9.9–11.2)	2.4 (2.3–2.6)
25	$(CH_2)_3$-Fur	6	7.0	0.89 (0.43–2.08)	28.4 (12.2–58.5)
26	$(CH_2)_4$-Fur	7	8.2	0.97 (0.42–1.22)	26.2 (11.6–60.5)
27	$(CH_2)_5$-Fur	8	9.4	4.5 (3.3–6.4)	5.6 (4.0–7.7)
Series G					
28	Pent[f]	3	3.6	115	0.2
29	CH_2-Pent	4	5.0	198	0.13
30	$(CH_2)_2$-Pent	5	6.2	72.8	0.35
31	$(CH_2)_3$-Pent	6	7.4	61.5	0.41
32	$(CH_2)_4$-Pent	7	8.6	4.20	0.6

[a] Measured on Dreiding stereomodels. Where kinking of the chain was possible, the distance from the nitrogen atom to the terminal carbon was taken with the model fully extended upon a flat surface. In series E and F, C_5, and in series G, C_3, was taken as terminal. [b] 95% confidence limits in brackets. [c] Relative to pethidine = 1.0. [d] Furethidine. [e] Fur = tetrahydro-2-furyl. [f] Pent = cyclopentyl.

atoms is also indicated. In the *n*-alkyl series (A), maximum activity occurred when the side-chain skeleton contained six atoms; introduction of a terminal hydroxyl (series B), although leading to an over-all decrease in potency, left the side-chain skeleton for maximum activity unaltered at six atoms (Figure 1). Series E–G showed the effects on analgesic potency of the introduction of a terminal heterocyclic or alicyclic group into the side chain. Series F contained the most active compounds of all those studied; an ethereal oxygen atom in the aliphatic portion of the side chain (series E) was slightly detrimental to potency (Figure 2). Removal of all oxygen atoms gave series G, isosteric with series E and F but showing a marked decrease in potency.

In four of the series (A, B, C, and F; Figure 1) the plots showed no significant deviation from parallelism in the neighborhood of their maxima ($P < 0.05$). A change of side-chain skeleton by one atom from the optimum number led to an approximate fivefold decrease in activity. These relationships did not hold for series D and G.

Experimental Section

Ethyl 1-*n*-Alkyl-4-phenyl-4-piperidinecarboxylate (Series A).—Norpethidine (4.7 g.), the appropriate *n*-alkyl bromide (1.1

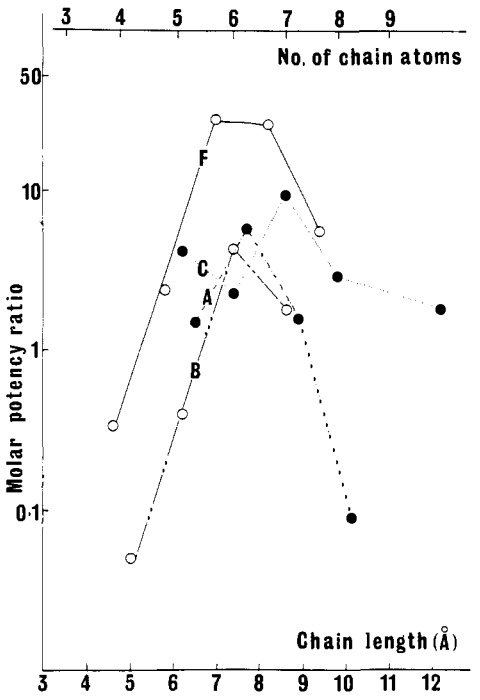


Figure 1.—Molar potency ratio (pethidine = 1.0) on log scale against chain length of nitrogen substituent in *n*-alkyl- (series A), ω-hydroxyalkyl- (series B), ethoxyalkyl- (series C), and tetrahydro-2-furylalkylnorpethidines (series F).

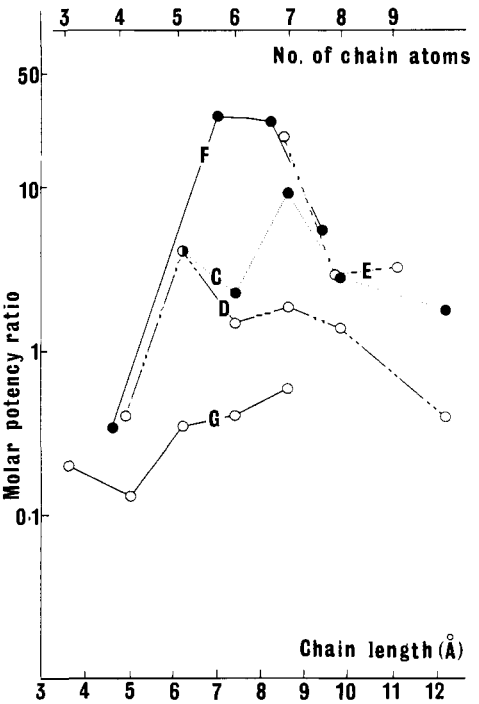


Figure 2.—Molar potency ratio (pethidine = 1.0) on log scale against chain length of nitrogen substituent in ethoxyalkyl- (series C), alkoxyethyl- (series D), tetrahydrofurfuryloxyalkyl- (series E), tetrahydro-2-furylalkyl- (series F), and cyclopentylalkyl-norpethidines (series G).

equiv.), anhydrous Na_2CO_3 (3 g.), and pentyl alcohol (50 ml.) were refluxed for 36 hr. and filtered. Removal of solvent gave the desired ester which was characterized as the hydrochloride or hydrobromide (from alcohol–ether). The following 1-*n*-alkyl derivatives were prepared.

1-Pentyl Hydrochloride (1, Table I), m.p. 130–131°.

Anal. Calcd. for $C_{19}H_{30}ClNO_2$: C, 67.1; H, 8.9; N, 4.1. Found: C, 66.7; H, 8.5; N, 3.9.

1-Hexyl Hydrochloride (**2**), m.p. 158°.

Anal. Calcd. for $C_{20}H_{32}ClNO_2$: C, 67.9; H, 9.1; N, 4.0. Found: C, 68.1; H, 9.2; N, 3.8.

1-Heptyl Hydrochloride (**3**), m.p. 148–149°.

Anal. Calcd. for $C_{21}H_{34}ClNO_2$: C, 68.5; H, 9.3; N, 3.8. Found: C, 68.2; H, 8.9; N, 4.0.

1-Octyl Hydrobromide (**4**).

Anal. Calcd. for $C_{22}H_{36}BrNO_2$: C, 62.0; H, 8.5; N, 3.3. Found: C, 62.0; H, 8.5; N, 3.4.

Ethyl 1-(2-Hydroxyethyl)-4-phenyl-4-piperidinecarboxylate (5) Hydrobromide.—Norpethidine (4.7 g.) was condensed with 2-chloroethanol (1.2 g.) as described above to give the desired ester characterized as the hydrobromide (4.7 g.) from ethyl acetate–methanol; m.p. 140–142°.

Anal. Calcd. for $C_{16}H_{23}NO_3 \cdot HBr$: C, 53.6; H, 6.9; N, 3.9. Found: C, 53.5; H, 6.7; N, 3.9.

Ethyl 1-(3-Hydroxypropyl)-4-phenyl-4-piperidinecarboxylate (**6**).—Condensation of norpethidine with 3-chloropropanol gave the ester **6**, which crystallized spontaneously when the solvent was removed. On recrystallization from ethyl acetate–petroleum ether (b.p. 40–60°), it had m.p. 60–61°.

Anal. Calcd. for $C_{17}H_{25}NO_3$: C, 70.2; H, 8.7; N, 4.8. Found: C, 70.0; H, 8.5; N, 4.7.

Ethyl 1-(4-Hydroxybutyl)-4-phenyl-4-piperidinecarboxylate (**7**).—4-Chlorobutanol, prepared by the action of hydrogen chloride on tetrahydrofuran, had b.p. 99–100° (15 mm.), $n^{20}D$ 1.4505 [lit.[15] b.p. 87° (10 mm.), $n^{20}D$ 1.4502]. It condensed with norpethidine to yield the ester **7**, b.p. 160° (1 mm.), which crystallized from ethyl acetate; m.p. 74–76°.

Anal. Calcd. for $C_{18}H_{27}NO_3$: C, 70.8; H, 8.9; N, 4.6. Found: C, 70.8; H, 9.1; N, 4.8.

Ethyl 1-(5-Hydroxypentyl)-4-phenyl-4-piperidinecarboxylate (**8**).—5-Chloropentanol was prepared from pentane-1,5-diol in pyridine solution with thionyl chloride, as described by Kirner and Richter[16] for the monochlorination of butane-1,4-diol. It had b.p. 108° (11 mm.), $n^{20}D$ 1.4540 [lit.[15] b.p. 103° (8 mm.), $n^{20}D$ 1.4518]. Condensation with norpethidine gave the desired ester which crystallized from ethyl acetate–petroleum ether; m.p. 63–64°.

Anal. Calcd. for $C_{19}H_{29}NO_3$: C, 71.4; H, 9.2; N, 4.4. Found: C, 71.0; H, 9.0; N, 4.3.

Ethyl 1-(6-Hydroxyhexyl)-4-phenyl-4-piperidinecarboxylate (**9**).—6-Chlorohexanol was prepared from hexane-1,6-diol as described above; it had b.p. 130° (15 mm.), $n^{20}D$ 1.4560 [lit.[15] b.p. 112° (12 mm.), $n^{20}D$ 1.4541]. Condensation with norpethidine gave the ester **9**, which crystallized from ethyl acetate; m.p. 74–75°.

Anal. Calcd. for $C_{20}H_{31}NO_3$: C, 72.0; H, 9.4; N, 4.2. Found: C, 72.2; H, 9.4; N, 4.4.

Ethyl 1-Cyclopentyl-4-phenyl-4-piperidinecarboxylate (**28**).—Cyclopentyl bromide was condensed with norpethidine to give the ester **28**, characterized as the **hydrobromide** (from alcohol–ether), m.p. 216–218°.

Anal. Calcd. for $C_{19}H_{27}NO_2 \cdot HBr$: C, 59.7; H, 7.4; N, 3.7. Found: C, 60.0; H, 7.5; N, 3.5.

Ethyl 1-(Cyclopentylmethyl)-4-phenyl-4-piperidinecarboxylate (**29**).—Cyclopentylmagnesium bromide (from 74.5 g. of the halide) in dry ether solution was treated with gaseous formaldehyde (from 30 g. of paraformaldehyde) to give cyclopentylcarbinol (21 g.), b.p. 90° (24 mm.), $n^{20}D$ 1.4582 (lit.[17] b.p. 162–162.5°, $n^{20}D$ 1.4579). This (13 g.) was brominated by the dropwise addition of phosphorus tribromide (13 g.) below −5°; subsequent treatment as described by Noller and Adams[17] gave cyclopentylmethyl bromide (12 g.), b.p. 56° (3 mm.), $n^{20}D$ 1.4812 [lit.[17] b.p. 56–57° (17 mm.)]. This halide with norpethidine gave the ester **29** isolated as the **hydrochloride** (from ethanol–ether), m.p. 189–190°.

Anal. Calcd. for $C_{20}H_{29}NO_2 \cdot HCl$: C, 68.3; H, 8.6; N, 4.0. Found: C, 68.2; H, 8.6; N, 3.9.

Ethyl 1-(2-Cyclopentylethyl)-4-phenyl-4-piperidinecarboxylate (**30**).—Cyclopentylmagnesium bromide was treated with ethylene oxide in ethereal solution to give 2-cyclopentylethanol, b.p. 72–76° (5 mm.), $n^{20}D$ 1.4587 [lit.[18] b.p. 80–81° (13 mm.), $n^{19}D$ 1.4572]. Bromination of this (19 g.) at 0° with phosphorus

(15) S. M. McElvain and T. P. Carney, *J. Am. Chem. Soc.*, **68**, 2596 (1946).

(16) W. R. Kirner and G. H. Richter, *ibid.*, **51**, 2503 (1929).

(17) C. R. Noller and R. Adams, *ibid.*, **48**, 1080 (1926).

(18) K. Birschkies and J. Scholl, *Arch. Pharm.*, **281**, 328 (1943).

tribromide (17 g.) followed by steam distillation gave 2-cyclopentylethyl bromide, (20 g.), b.p. 80° (750 mm.), $n^{20}D$ 1.4808 (lit.[18] 78–79°, $n^{20}D$ 1.4866), which with norpethidine gave the ester **30**, isolated as the **hydrobromide** (from acetone–ether), m.p. 194–195°.

Anal. Calcd. for $C_{21}H_{31}NO_2 \cdot HBr$: C, 61.5; H, 7.9; N, 3.4. Found: C, 61.3; H, 7.5; N, 3.6.

Ethyl 1-(3-Cyclopentylpropyl)-4-phenyl-4-piperidinecarboxylate (31).—The Grignard reagent from 2-cyclopentylethyl bromide (20 g.) in ethereal solution was treated with gaseous formaldehyde (from 7 g. of paraformaldehyde) to give 3-cyclopentylpropanol (5.8 g.), b.p. 110–115° (6 mm.), $n^{20}D$ 1.4603. This with phosphorus tribromide yielded cyclopentylpropyl bromide (5.3 g.), b.p. 90–95° (15 mm.), $n^{20}D$ 1.4740 [lit.[19] b.p. 99–100° (22 mm.), $n^{25}D$ 1.4819]. Condensation of the bromide with norpethidine gave the ester **31**, characterized as the **hydrobromide** (from ethanol–ether), m.p. 168–170° dec.

Anal. Calcd. for $C_{22}H_{33}NO_2 \cdot HBr$: N, 3.3. Found: N, 3.3.

Ethyl 1-(4-Cyclopentylbutyl)-4-phenyl-4-piperidinecarboxylate (32).—The Grignard reagent from 2-cyclopentylethyl bromide (33 g.) was treated with an ice-cold solution of ethylene oxide (8.6 g.) in ether (30 ml.) to yield 4-cyclopentylbutanol (18 g.), b.p. 100–105° (8 mm.), $n^{20}D$ 1.4616 [lit.[20] b.p. 88–92° (2 mm.), $n^{20}D$ 1.4613]. This (12 g.) in toluene (21 ml.) was treated with phosphorus tribromide (7.6 g.) below 0°. The mixture was then heated at 70° for 30 min. After dilution with petroleum ether, the solution was washed with dilute alkali and then with water; 4-cyclopentylbutyl bromide had b.p. 80–85° (5 mm.), $n^{20}D$ 1.4792 [lit.[18] b.p. 107° (15 mm.), $n^{20}D$ 1.4815]. This bromide was condensed with norpethidine to yield the ester **32**, characterized as the **hydrochloride** (from ethyl acetate–petroleum ether), m.p. 123–125°.

Anal. Calcd. for $C_{23}H_{35}NO_2 \cdot HCl$: C, 70.1; H, 9.2; N, 3.6. Found: C, 69.8; H, 8.8; N, 3.6.

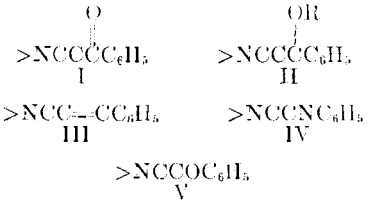
Discussion

Until 1955, all known potent analgesics possessed a relatively small substituent on the nitrogen atom. The generalization[21] that a small nitrogen substituent, such as methyl, appeared to be optimal for analgesic activity, however, no longer holds.[22]

A remarkable feature of our findings is the constant relationship between structure and activity in the four series A, B, C, and F (Figure 1). In each of these series, an increase of the chain length of the nitrogen substituent by one carbon atom led to an approximate fivefold increase in activity, until a peak was reached, when activity fell off at a similar rate. In series E only the decrease in activity was shown (Figure 2). For peak activity *in each series* the side-chain skeleton contained six or seven atoms, *i.e.*, it had an over-all length of from 7–9 Å.

The importance of an ether linkage in the side chain of a series of N-substituted norpethidine derivatives with marked analgesic activity has been stressed recently, and the suggestion has been made that optimum activity is obtained when this electron-donating substituent is situated at a distance of six carbon atoms from the nitrogen of the piperidine ring.[23] Our results have shown that the over-all chain length is of great importance in the production of maximum analgesic potency irrespective of the presence or absence of an electron-donating substituent. Thus N-*n*-hexylnorpethidine (**2**) is six times as active as pethidine, and twice as active as N-ethoxypentylnorpethidine (**13**, which has an oxygen atom at a distance of six atoms from the nitrogen), although it is less potent than N-ethoxybutylnorpethidine (**12**), the most active compound in series C.

Janssen and Eddy[14] have discussed a number of N-aralkyl norpethidine derivatives. The most active compounds in these series have the nitrogen substituents shown (I–III), in each of which there is an electron-rich area at a distance of approximately 7 Å. from the piperidine nitrogen.



Other derivatives of norpethidine (IV and V) with high analgesic activity have also been described[23,24]; these compounds have similar over-all chain lengths and electron-rich areas.

Our results do present three anomalies. First, in view of the greatly increased potency of compounds with an electron-donating group in the nitrogen substituent, the slightly reduced potency of the ω-hydroxyalkyl compounds, *vis-a-vis*, the *n*-alkyl analogs, requires explanation. This reduction in potency may be due, apart from possible changes in partition coefficient, to conjugate attack *in vivo* on the terminal hydroxyl group; such attack could reduce the number of molecules penetrating to the site of action. Secondly, the *n*-alkyl compounds (A) are very much more potent then the corresponding cyclopentylalkyl derivatives (G). This difference in activity is particularly marked in comparison with the corresponding oxygenated series C and F. Figure 2 shows that series G differs markedly from these other series which give similar plots of chain length against log potency ratio. This difference may be due to the fact that the bulky cyclopentyl ring, unlike the tetrahydrofuryl ring, may have no specific receptor orientation. A third anomaly is shown by comparison of the ethoxyalkyl series (C) with the alkoxyethyl series (D). When the oxygen atom is at a distance of two carbon atoms from the nitrogen, potency is higher than might be expected. Possibly there is some bonding of the oxygen atom at this point with the receptor surface, and the chain beyond this atom, in the compounds of series D, may be distorted.

Our results indicate that the effect on analgesic potency of increasing chain length in the nitrogen substituent is similar within different series of compounds. This may be due to equivalent effects upon rate of transport to the site of action or to similar changes in affinity for that site.

A possible arrangement of the analgesic receptor surface has been suggested by Beckett.[25] In the analogs of pethidine that we have prepared, attention centers on the nitrogen substituent, since in each case the norpethidine part of the molecule is presumably associated

(19) G. H. Coleman, J. E. Caller, and C. A. Dornfeld, *J. Am. Chem. Soc.*, **68**, 1101 (1946).

(20) G. R. Yoke and R. Adams, *ibid.*, **50**, 1506 (1928).

(21) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organ.*, **13**, 937 (1955).

(22) N. B. Eddy, *Chem. Ind.* (London), 1462 (1959).

(23) A. M. J. N. Blair and R. P. Stephenson, *Brit. J. Pharmacol.*, **15**, 217 (1960).

(24) C. Berry, A. Burkhalter, L. W. Davis, E. G. Gross, and H. H. Keasling, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 365 (1959).

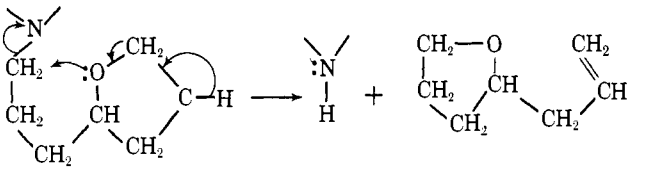
(25) A. H. Beckett, *J. Pharm. Pharmacol.*, **8**, 848 (1956).

with the receptor surface in the same way as pethidine itself. Consideration of the role of the nitrogen substituent leads to two hypotheses: (a) that the chain is fully extended, and (b) that it simulates a ring.

If the side chain is fully extended, then any interaction between it and the receptor surface will be distinct from the norpethidine–receptor interaction, *i.e.*, it seems likely that two different areas of the receptor are involved with the two different portions of the molecule. Further, the attraction at the second site, due mainly to the electron-donating portion of the side chain, may be further enhanced by Van der Waals' forces involving a flat ring system such as phenyl or tetrahydrofuryl.

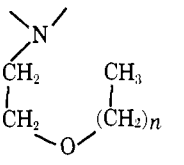
Alternatively, if the electron-donating portion of the side chain is attracted by the piperidino-nitrogen atom, which will carry some positive charge *in vivo*, then the side chain will be held in the form of a ring. In this case the side-chain "ring" might afford a wider area of interaction with that region of the receptor surface occupied by the methyl group of pethidine. In addition, the effect of the side chain upon the charge carried by the nitrogen atom may increase the lipid solubility of the molecule and so facilitate transfer across the aqueous–lipid barrier.

It has been suggested that analgesic action in compounds of this type is due to the secondary base produced by oxidative dealkylation *in vivo*.[26] There is little evidence for this hypothesis[27]; normorphine and norpethidine are considerably less active than the N-methyl homologs when given by any but the intracisternal route, and the validity of the results of drug administration by this route has been questioned.[28] If the side chain in our compounds does simulate a ring, however, it is possible that N-dealkylaiion may occur by a process of the type VI → VII (**25**, series F). Similar



VI VII

schemes may be written for other N-substituents, and such an hypothesis would predict that in series D (VIII) there would be no wide-spread activity.[29]



VIII

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(26) A. H. Beckett, A. F. Casy, and N. J. Harper, *J. Pharm. Pharmacol.*, **8**, 874 (1956).
(27) C. Elison, H. W. Elliott, M. Look, and H. Rapoport, *J. Med. Chem.*, **6**, 237 (1963).
(28) J. Dobbing, *Physiol. Rev.*, **41**, 130 (1961).
(29) Suggested by a referee.

4-Substituted Piperidines. II. Reaction of 1-Benzyl-4-cyano-4-*t*-aminopiperidines with Organometallic Compounds

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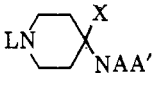
The reaction of 1-benzyl-4-cyano-4-*t*-aminopiperidines with organomagnesium and organolithium compounds is described. Reaction of these α-aminonitriles with Grignard reagents results in replacement of the nitrile group, whereas with the organolithium compounds normal ketone formation takes place. The resulting products are debenzylated, whereafter other substituents are introduced. Some of the obtained products show CNS-depressant activity.

Continuing our program on 4-substituted piperidines of possible therapeutic interest we prepared piperidines of the general formula I. As in the preceding paper,[1]



I

NAA′ represents a dialkylamino group or a saturated heterocyclic moiety; X stands for alkyl, aryl, alkanoyl, or aroyl; and L can represent any substituent retaining the basic character of the piperidine ring system.

Chemistry.—In the preceding paper[1] the peculiar properties of α-aminonitriles were pointed out.[2] This behavior is also demonstrated by their reaction with Grignard reagents. Several authors have investigated the reaction of α-aminonitriles with Grignard reagents and found that "normal" ketone formation takes place infrequently and that in most cases nitrile replacement occurs. Welvart[3] explained these anomalies by suggesting that the α-aminonitriles react in the form of the immonium ion II. In this ion the chemical bond between α-C and CN is electrovalent as well as covalent, allowing both C atoms to react with a nucleophilic reagent as RMgX.

(1) C. van de Westeringh, P. Van Daele, B. Hermans, C. Van der Eycken, J. Boey, and P. A. J. Janssen, *J. Med. Chem.*, **7**, 619 (1964).
(2) For a more detailed discussion of this class of compounds, see V. Migrdichian in "The Chemistry of Organic Cyanogen Compounds," Reinhold Publishing Corp., New York, N. Y., 1947, covering the literature up to 1947, and a review by P. Van Daele, *Mededel. Vlaam. Chem. Ver.*, **23**, 163 (1961), covering more recent literature.
(3) Z. Welvart, *Compt. rend.*, **238**, 2536 (1954).