8: Uv max 229.5 (ε 14,600), 246 (ε 12,200); 251 (ε 11,050), 335 (ε 6160), 340 (ε 6270), 388 mμ (ε 2520); ir 1660, 1630 cm^{-1} (C=N); mass spectrum *m/e* 170 (M^+); nmr [$(CD_3)_2SO$] δ 8.91 (s, 1, H-7).

9: Uv max 228 (ε 16,800), 321 (ε 6350), inflection 356 mμ (ε 2450); ir 1635 cm^{-1} (C=N).

10: Uv max 215 (ε 30,050), 298 (ε 11,200), 308 (ε 11,150), inflections 222 (ε 27,900); 236 (ε 2400), 253 (ε 6400), 285 mμ (ε 8500); ir 1680 cm^{-1} (C=O).

12: Uv max 233 (ε 27,900), 314 (ε 3900), inflection 263 mμ (ε 4700); ir 1675, 1650 cm^{-1} (C=O).

14: Uv max 228 (ε 21,200), 356 (ε 4850), inflection 260 mμ (ε 5700); ir 1635 cm^{-1} (C=O).

16: Uv max 232 (ε 21,950), 316 mμ (ε 7400); ir 1640 cm^{-1} (C=O).

18: Uv max 252 (ε 12,300), 267 (ε 11,100), 355 (ε 4200), 401 (ε 8050), inflection 224 mμ (ε 18,900); mass spectrum *m/e* 246 (M^+).

20: Uv max 226 (ε 22,800), 250 (ε 7700), 299 mμ (ε 2350).

22: Uv max 227 (ε 35,500), 352 (ε 6200), inflection 263 mμ (ε 7100); ir 1650 cm^{-1} (C=N).

29: Uv max 211 (ε 24,000), 250 (ε 6950), 293 mμ (ε 2300).

31: Uv max 262 (ε 16,150), 464 (ε 6800), inflections 224 (ε 12,000), 244 (ε 11,400), 295 mμ (ε 10,000).

36: Uv max 244 (ε 17,350), 342 mμ (ε 2650).

37: Uv max 222 (ε 32,350), 246 (ε 8070), 299 mμ (ε 2220).

38: Uv max 219 (ε 28,300), 256 (ε 33,200), 336 (ε 7200), inflection 285 mμ (ε 10,150); ir 1675 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.23 (t, 2, *J* = 8 Hz, H-2), δ 3.57 (s, 2, H-5), δ 3.14 (t, 2, *J* = 8 Hz, H-1); mass spectrum *m/e* 296, 298 (M^+).

40: Uv max 208 (ε 33,800), 215 (ε 33,200), 272 (ε 32,500), 282 (ε 32,400), 313 (ε 1310), 426 (ε 1150), inflections 235 (ε 26,500), 262 (ε 24,600), 322 (ε 1195), 340 mμ (ε 514); ir 3300 (NH), 1650 cm^{-1} (C=O); nmr [$(CD_3)_2SO$] δ 4.09 (d, 1, *J* = 2 Hz, H-5), δ 8.75 (s, 1, H-7); mass spectrum *m/e* 296, 298 (M^+).

41: Uv max 234.5 (ε 31,050), 272 (ε 8600), 281 (ε 7800), 333 mμ (ε 3900); ir 3300 (NH), 1655 cm^{-1} (C=O).

42: Uv max 220 (ε 28,600), 236 (ε 20,850), 262 (ε 20,350), 272 (ε 27,150), 282 (ε 27,150), 314 (ε 1800), 425 (ε 1050), inflection 324 mμ (ε 1650); ir 1690 (C=O), 1620 cm^{-1} (C=N).

46: Uv max 243 (ε 24,800), 313 mμ (ε 2350); ir 1670 cm^{-1} (C=O).

48:[37] Uv max 343 (ε 11,500), inflections 225 (ε 18,300), 232 mμ (ε 17,950);

54: Uv max 236 (ε 29,950), 325 mμ (ε 3150); ir 1670 cm^{-1} (C=O).

57: Uv max 258 (ε 16,650); 308 (ε 7250), inflection 318 mμ (ε 6400); ir 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.68 (s, 2, H-5); mass spectrum *m/e* 260 (M^+).

60: Uv max 246 (ε 20,410), 296 (ε 5330), 304 (ε 6030), inflection 284 mμ (ε 3290); ir 3340 (NH), 1690 cm^{-1} (C=O); nmr [$(CD_3)_2SO$] δ 5.49 (s, 1, H-7), 3.83 (s, 2, H-5).

62: Uv max 244 (ε 18,950), 437 (ε 6250), inflection 275 mμ (ε 5700).

64:[38] Uv max 225 (ε 19,800), 252 (12,850), 276 (9800), 356 (4420), 401 mμ (ε 5850); ir 1615 cm^{-1} (C=N); mass spectrum *m/e* 280, 282 (M^+).

Acknowledgment.—The authors are indebted to Dr. E. C. Olson and his associates for physical and analytical data and to Mr. J. Robert Greene for laboratory assistance.

(37) The nmr spectrum [$(CD_3)_2SO$] of **52** had peaks at δ 8.17 (d, *J* = 2 Hz) and 7.99 (broad singlet) for H-6 and H-4 which thus estblished the location of the NO_2.

(38) The nmr spectrum [$(CD_3)_2SO$] of **64** was essentially the same as that of **18** except that in **64** H-1 (δ 6.89, d, *J* = 3 Hz) was absent and H-2 was represented by a singlet at 8.01.

4-Substituted Piperidines. V.[1] Local Anesthetic 4-Aminoalkoxy-4-arylpiperidines

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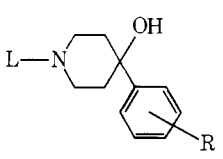
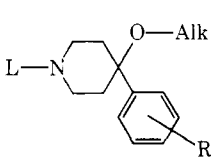
The synthesis of a new series of 4,4-disubstituted piperidines is described. These 4-aminoalkoxy-4-arylpiperidines are obtained by performing successively a Grignard reaction on *N*-carbethoxy-4-piperidone, transformation of the tertiary alcohol in an ether, decarbethoxylation, and finally reaction of the secondary amine with a halide. The compounds are good local conduction anesthetics in laboratory animals.

In previous publications[1] of this series the synthesis and pharmacological activity of several 4,4-disubstituted and 4-monosubstituted piperidines were described. One of the most important series was that of the well-known 4-aryl-4-hydroxypiperidine compounds[2] (I), of which haloperidol, moperone, and trifluperidol are the most important drugs.

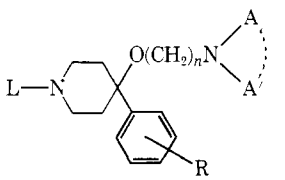


I

In a first trial to change the chemical structure of these compounds, a series of 4-lower alkoxy-4-arylpiperidines (II) with anticonvulsant properties[3] was synthesized and a further variant was the introduction of an amine function in this 4-alkoxy group, giving a new series of 4-aminoalkoxy-4-arylpiperidines (III) in which *n* = 2 or 3, $-\overset{\frown}{NAA'}$ stands for lower dialkylamino, piperidino, or hexamethyleneimino, R represents H, Cl, CH_3, or CF_3, and, as in all our series, L can be any substituent retaining the basic character of the piperidine nucleus.



II



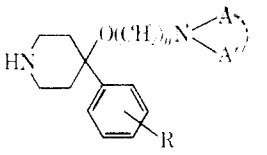
III

(1) B. Hermans, P. Van Daele, C. van de Westeringh, C. Van der Eycken, J. Boey, J. Dockx, and P. Janssen, *J. Med. Chem.*, **11**, 797 (1968).

(2) P. Janssen, C. van de Westeringh, A. Jageneau, P. Demoen, B. Hermans, P. Van Daele, K. Schellekens, C. Van der Eycken, and C. Niemegeers, *ibid.*, **1**, 281 (1959).

(3) P. Janssen, Belgian Patent 615,350 (1962); *Chem. Abstr.*, **59**, 1602*h* (1963).

TABLE I

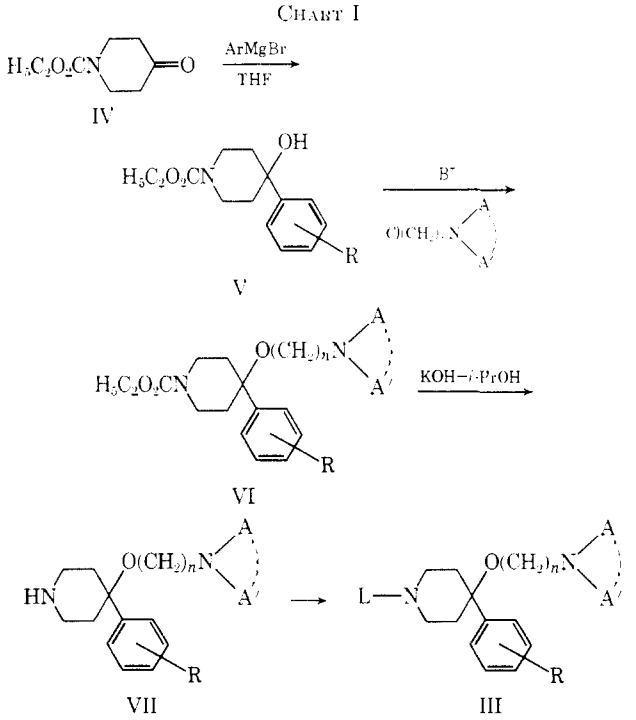


Compd	R	n	$-N\overset{A}{\underset{A'}{<}}$	Yield[a] %	Bp, °C (mm)	Formula[b]
1	H	2	$N(CH_3)_2$	51	134–137 (0.9)	$C_{15}H_{24}N_2O$
2	H	2	$N(C_2H_5)_2$	60	153–158 (1.0)	$C_{17}H_{28}N_2O$
3	H	2	$N(i\text{-}C_3H_7)_2$	76	173–177 (1.5)	$C_{19}H_{32}N_2O$
4	H	2	$N(n\text{-}C_4H_9)_2$	69	166–170 (0.4)	$C_{21}H_{36}N_2O$
5	H	2	$N(i\text{-}C_4H_9)_2$	45	163–165 (0.6)	$C_{21}H_{36}N_2O$
6	H	2	$C_5H_{10}N$[c]	80	158–161 (0.4)	$C_{18}H_{28}N_2O$
7	H	3	$N(C_2H_5)_2$	63	148–153 (0.3)	$C_{18}H_{30}N_2O$
8	H	3	$C_5H_{10}N$[c]	60	170–174 (0.5)	$C_{19}H_{30}N_2O$
9	4-CH_3	2	$N(i\text{-}C_3H_7)_2$	67	153–158 (0.4)	$C_{20}H_{34}N_2O$
10	4-Cl	2	$N(CH_3)_2$	60	170–173 (1.7)	$C_{15}H_{23}ClN_2O$[f]
11	4-Cl	2	$N(C_2H_5)_2$	52[d]	157–161 (0.3)	$C_{17}H_{27}ClN_2O$[f]
12	4-Cl	2	$C_5H_{10}N$[c]	57	162–167 (0.1)	$C_{18}H_{27}ClN_2O$[f]
13	4-Cl	2	$C_6H_{12}N$[e]	33	175–178 (0.3)	$C_{19}H_{29}ClN_2O$[f]
14	4-Cl	3	$C_5H_{10}N$[c]	60	170–175 (0.2)	$C_{18}H_{29}ClN_2O$[f]
15	3-CF_3	2	$N(i\text{-}C_3H_7)_2$	70	135–138 (0.2)	$C_{20}H_{31}F_3N_2O$[g]
16	3-CF_3	2	$C_5H_{10}N$[c]	73	162–165 (0.7)	$C_{19}H_{27}F_3N_2O$[g]
17	3-CF_3	2	$C_6H_{12}N$[e]	64	154–155 (0.3)	$C_{20}H_{29}F_3N_2O$[g]
18	3-CF_3	3	$N(C_2H_5)_2$	66	142–144 (0.4)	$C_{19}H_{29}F_3N_2O$[g]

[a] Yield based on the appropriate *N*-carbethoxy-4-aryl-4-hydroxypiperidine. [b] All equivalent weights were determined and all compounds were analyzed for N. [c] Piperidino. [d] By condensation with sodium amide and distillation of the intermediate, the yield was only 19%. [e] Hexamethyleneimino. [f] Cl analysis. [g] F analysis.

Chemistry.—The total synthesis of these new compounds is outlined in Chart I. The first step consists of a Grignard reaction on *N*-carbethoxy-4-piperidone (IV) with ArMgX in THF; the Grignard complexes formed were decomposed with dilute AcOH to prevent dehydration of the tertiary alcohols V. Yields of at least 75% were achieved without difficulty in all 4 cases (R = H, *p*-CH_3, *p*-Cl, and *m*-CF_3). These products can also be obtained by reaction of a 4-aryl-4-hydroxypiperidine with ethyl chloroformate.

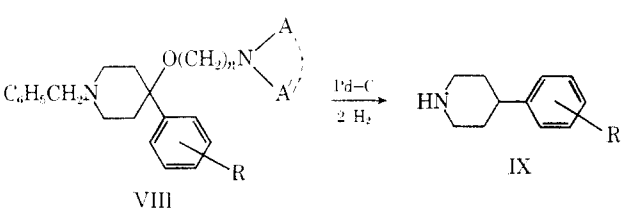
CHART I



By treatment with a strong base and an appropriate aminoalkyl chloride·HCl, these tertiary alcohols were converted into the corresponding aminoethers VI. As condensing agent $NaNH_2$ in PhMe was used initially, as adopted by several authors for analogous cyclohexyl derivatives.[4] The yields were rather low (about 25%) and therefore $LiNH_2$ was used subsequently. This amide was much easier to use and the yields of the condensation reaction were much higher (about 75%). From all 18 4-aminoalkoxy-4-aryl-*N*-carbethoxypiperidines (VI) only one [n = 2; $-N\overset{A}{\underset{A'}{<}}$ = $-N(C_2H_5)_2$; R = *p*-Cl] was purified by distillation but the high boiling point [bp about 200° (0.5 mm)] led us to use all other analogs in their crude form.

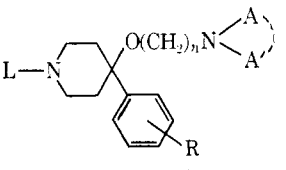
The third step of this reaction consisted of the decarbethoxylation of compounds VI to give the secondary amines VII; the decarbethoxylation was carried out by treatment of the carbethoxypiperidine with a boiling solution of KOH in *i*-PrOH (Table I).

In contrast to all our other series the starting material in this case was *N*-carbethoxy-4-piperidone instead of *N*-benzyl-4-piperidone; indeed, upon debenzylation of the tertiary amines VIII 2 equiv of H_2 were taken up and debenzylation took place on the benzylamine part of the molecule and simultaneously at the α,α-



(4) (a) C. F. Boehringer & Söhne G.m.b.H. (W. Winter and K. Stach), German Patent 1,096,347; *Chem. Abstr.*, **57**, 10,984 (1962); (b) K. Bolzo and H. Dell, *Arch. Pharm.* (Weinheim), **301**, 386 (1968).

Table II



Compd	L	R	n	N(A,A')	Mp, °C	Formula[a]
19	$C_6H_5(CH_2)_2$	H	2	$N(C_2H_5)_2$	184–185	$C_{25}H_{36}N_2O \cdot 2(COOH)_2$
20				$C_5H_{10}N$[b]	164–184 dec	$C_{26}H_{36}N_2O \cdot 2(COOH)_2$
21			3	$C_5H_{10}N$[b]	216–223	$C_{27}H_{38}N_2O \cdot 2C_6H_{13}NO_3S$[c]
22		4-Cl	2	$N(C_2H_5)_2$	228–229	$C_{25}H_{35}ClN_2O \cdot 2HBr$
23				$C_5H_{10}N$[b]	250–251	$C_{26}H_{35}ClN_2O \cdot 2HBr$
24				$C_6H_{12}N$[d]	179–181	$C_{27}H_{37}ClN_2O \cdot 2(COOH)_2$
25		3-CF_3		$C_5H_{10}N$[b]	192–194	$C_{27}H_{35}F_3N_2O \cdot 2(COOH)_2$
26				$C_6H_{12}N$[d]	156–172 dec	$C_{28}H_{37}F_3N_2O \cdot 2(COOH)_2$
27			3	$N(C_2H_5)_2$	182–184	$C_{27}H_{37}F_3N_2O \cdot 2C_6H_{13}NO_3S$[c]
28	4-$FC_6H_4(CH_2)_2$	4-Cl	2	$C_5H_{10}N$[b]	200–213.5	$C_{26}H_{34}ClFN_2O \cdot 2HBr$
29		3-CF_3		$C_5H_{10}N$[b]	181–183	$C_{27}H_{34}F_4N_2O \cdot 2(COOH)_2$
30	4-$CH_3C_6H_4(CH_2)_2$	4-Cl		$C_5H_{19}N$[b]	205–207	$C_{27}H_{37}ClN_2O \cdot 2HBr$
31	$C_6H_5(CH_2)_3$	H	3	$C_5H_{10}N$[b]	156–193 dec	$C_{28}H_{40}N_2O \cdot 3C_6H_{13}NO_3S$[c]
32		4-CH_3	2	$N(i\text{-}C_3H_7)_2$	134–136	$C_{29}H_{44}N_2O \cdot 2C_6H_{13}NO_3S$[c]
33		4-Cl		$C_5H_{10}N$[b]	150–164 dec	$C_{27}H_{37}ClN_2O \cdot 2(COOH)_2$
34	$C_6H_5NH(CH_2)_2$	H		$N(CH_3)_2$	156–195 dec	$C_{23}H_{33}N_3O \cdot 2C_6H_{13}NO_3S$[c]
35				$N(C_2H_5)_2$	110–121	$C_{25}H_{37}N_3O \cdot 2C_6H_{13}NO_3S$[c]
36			3	$N(C_2H_5)_2$	127–130	$C_{26}H_{39}N_3O \cdot 2C_6H_{13}NO_3S$[c]
37				$C_5H_{10}N$[b]	164–167	$C_{27}H_{39}N_3O \cdot 2C_6H_{13}NO_3S$[c]
38		4-CH_3	2	$N(i\text{-}C_3H_7)_2$	159–163	$C_{28}H_{43}N_3O \cdot 2C_6H_{13}NO_3S$[c]
39		4-Cl		$C_5H_{10}N$[b]	178–182	$C_{26}H_{36}ClN_3O \cdot 2HBr$
40			3	$C_5H_{10}N$[b]	146–179 dec	$C_{27}H_{38}ClN_3O \cdot 3C_6H_{13}NO_3S$[c]
41		3-CF_3	2	$C_6H_{12}N$[d]	159–191	$C_{28}H_{38}F_3N_3O \cdot 2(COOH)_2$
42	4-$FC_6H_4NH(CH_2)_2$	H		$N(CH_3)_2$	153–200 dec	$C_{23}H_{32}FN_3O \cdot 2C_6H_{13}NO_3S$[c]
43	2-$ClC_6H_4NH(CH_2)_2$			$N(CH_3)_2$	185–190	$C_{23}H_{32}ClN_3O \cdot 2C_6H_{13}NO_3S$[c]
44	3-$ClC_6H_4NH(CH_2)_2$			$N(CH_3)_2$	164–190 dec	$C_{23}H_{32}ClN_3O \cdot 2C_6H_{13}NO_3S$[c]
45	4-$ClC_6H_4NH(CH_2)_2$			$N(C_2H_5)_2$	148–150	$C_{25}H_{36}ClN_3O \cdot 2C_6H_{13}NO_3S$[c]
46	2,5-$Cl_2C_6H_3NH(CH_2)_2$			$N(CH_3)_2$	188–189	$C_{23}H_{31}Cl_2N_3O \cdot 2C_6H_{13}NO_3S$[c]
47	2-$CH_3C_6H_4NH(CH_2)_2$			$N(CH_3)_2$	168–215 dec	$C_{24}H_{35}N_3O \cdot 2C_6H_{13}NO_3S$[c]
48	4-$CH_3C_6H_4NH(CH_2)_2$			$N(n\text{-}C_4H_9)_2$	100–106	$C_{30}H_{47}N_3O \cdot 2C_6H_{13}NO_3S$[c]
49	$C_6H_5NH(CH_2)_3$[e]			$N(n\text{-}C_4H_9)_2$	121–132	$C_{30}H_{47}N_3O \cdot 2C_6H_{13}NO_3S$[c]
50	2-Cl-6-$CH_3C_6H_3NHCOCH_2$			$N(i\text{-}C_3H_7)_2$	133–136	$C_{28}H_{40}ClN_3O_2 \cdot 2C_6H_{13}NO_3S$[c]
51	2,6-$(CH_3)_2C_6H_3NHCOCH_2$			$N(i\text{-}C_3H_7)_2$	92–93	$C_{29}H_{43}N_3O_2$
52		4-Cl		$N(C_2H_5)_2$	120–122	$C_{27}H_{38}ClN_3O_2$
53			3	$C_5H_{10}N$[b]	161–181 dec	$C_{29}H_{40}ClN_3O_2 \cdot 2(COOH)_2$
54		3-CF_3	2	$C_6H_{12}N$[d]	154–160	$C_{30}H_{40}F_3N_3O_4 \cdot 2(COOH)_2$
55	$C_6H_5NHCO(CH_2)_2$	H		$N(n\text{-}C_4H_9)_2$	168–170	$C_{30}H_{41}N_3O_2 \cdot 2C_6H_{13}NO_3S$[c]

[a] All compounds were analyzed for C,H,N. [b] Piperidino. [c] Cyclohexylsulfamic acid. [d] Hexamethyleneimino. [e] Obtained by reduction of **55**.

disubstituted benzyl ether formed by the two substituents in the 4 position of the piperidine nucleus; in this way a 4-arylpiperidine IX was obtained.

Finally, all but one of the desired final products were synthesized by reaction of a halide with the secondary amine VII in the presence of Na_2CO_3 and in MeCO-*i*-Bu as solvent. Table II presents data on a representative sample of the 150 tertiary amines synthesized; three types of L are particularly indicated, namely aralkyl, anilinoalkyl, and anilinocarbonyl.

As we could not obtain anilinopropyl bromide satisfactorily, **49** was not synthesized in the usual way, but by LAH reduction of **55** in THF.

Pharmacology.—Pharmacologically the new compounds are potent local anesthetics. The experimental data are summarized in Table III, in which the known conduction anesthetics procaine, lidocaine, mepivacaine and tetracaine are included as reference drugs. All tests were conducted on male Wistar rats.

The anesthetic activity of each compound was assessed by measuring the rapidity of response to a noxious stimulus (H_2O at 55°) applied to the hind 5 cm of the tail.

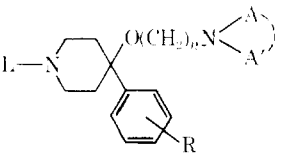
The irritancy was assessed by measuring the swelling of the hindpaw after local injection of the compound.

The toxicity and side-effects liability were assessed in the same rats 8 hr after the initial injections. A single dose of 0.4 ml of a solution of the compound was injected iv into the tail and mortality and side-effects during the next 24 hr were recorded.

The results show that, in general, the new compounds were more potent conduction anesthetics than procaine, lidocaine, and mepivacaine, but approximately equipotent with tetracaine. However, tetracaine induced more side-effects and had a lower margin of safety than the new compounds. Owing to these screening results, **35** (Diamocaine ®) has been selected for further investigation.

TABLE III

PHARMACOLOGICAL PROPERTIES OF



Compd	L	R	n	NA_2	ED_{50} values in mg/rat			
					Anesthesia	Side effects	Mortality	Irritancy
19	$C_6H_5(CH_2)_2$	H	2	$N(C_2H_5)_2$	0.5	<1.0	1.5	−
20				$C_5H_{10}N$	0.5	1.0	4.0	−
22		4-Cl		$N(C_2H_5)_2$	0.5	1.5	4.0	−
23				$C_5H_{10}N$	0.4	2.2	3.2	−
24				$C_6H_{12}N$	0.4	3.0	3.0	±
25		3-CF_3		$C_5H_{10}N$	0.5	3.0	3.0	−
26				$C_6H_{12}N$	≥0.1	<4.0	<4.0	±
27			3	$N(C_2H_5)_2$	0.5	2.0	4.0	±
28	4-$FC_6H_4(CH_2)_2$	4-Cl	2	$C_5H_{10}N$	0.7	2.8	2.8	−
33	$C_6H_5(CH_2)_3$			$C_5H_{10}N$	0.5	2.5	3.5	+
35	$C_4H_3NH(CH_2)_2$	H		$N(C_2H_5)_2$	0.6	3.6	6.0	−
41		3-CF_3		$C_6H_{12}N$	≤0.5	3.0	3.0	+
50	2-Cl-6-$CH_3C_6H_3NHCOCH_2$	H		$N(i\text{-}C_3H_7)_2$	0.5	5.0	5.0	−
55	$C_6H_5NHCO(CH_2)_2$			$N(n\text{-}C_3H_7)_2$	0.7	>4.0	>4.0	
56	Procaine				4.0	5.0	12.0	−
57	Lidocaine				2.0	2.5	6.0	±
58	Mepivacaine				1.8	3.2	7.2	−
59	Tetracaine				0.7	0.4	1.4	±

Experimental Section[5,6]

1-(Ethoxycarbonyl)-4-hydroxy-4-(3-trifluoromethylphenyl)-piperidine.—A solution of 3-$F_3CC_6H_4MgBr$ was prepared in the usual manner starting from 19.4 g of Mg and 180 g of 3-$BrC_6H_4CF_3$ in 500 ml of THF. To this solution was added dropwise a solution of 90.4 g of 1-(ethoxycarbonyl)-4-oxopiperidine in 100 ml of THF (exothermic reaction; reflux temperature was maintained). After the addition was complete, the reaction mixture was cooled to room temperature and stirred overnight. The mixture was poured onto a mixture of 200 g of crushed ice and 60 ml of glacial AcOH. The aq phase was separated and extracted twice with 200 ml of C_6H_6. The combined extracts were stirred with activated charcoal and filtered over Hyflo and the filtrate was evaporated to dryness. The oily residue was poured onto toluene and after cooling to 0°, the precipitated solid product was filtered off and dried *in vacuo*, yielding 128 g of material, mp 142–145.6°. *Anal.* ($C_{15}H_{18}F_3NO_3$)F, N.

1-(Ethoxycarbonyl)-4-hydroxy-4-(4-tolyl)piperidine.—A mixture of 155 g of 4-hydroxy-4-(4-tolyl)piperidine, 101 g of Et_3N, and 1500 ml of $CHCl_3$ was stirred at room temperature until all solid went into solution. Then there was added dropwise 108.5 ml of ethyl chloroformate (slightly exothermic reaction). After the addition was complete, the whole was stirred for 2 days at room temperature. The reaction mixture was washed with 2000 ml of H_2O. The organic layer was separated, dried, filtered, and evaporated *in vacuo*. The oily residue solidified on triturating in *i*-Pr_2O. The solid was filtered off and dried, yielding 158 g of product mp 116–117°. *Anal.* ($C_{15}H_{21}NO_3$)C, H, N.

4-(4-Chlorophenyl)-4-(3-piperidinopropoxy)piperidine (14).—To a hot mixture of 62.2 g of 1-(ethoxycarbonyl)-4-hydroxy-4-(4-chlorophenyl)piperidine and 600 ml of PhMe was added, portionwise, 11.5 g of $LiNH_2$. After the addition was complete, the whole was stirred and refluxed for 5 hr. The mixture was cooled to 50° and there was added slowly 44 g of 1-(3-chloropropyl)-piperidine·HCl. The whole was further stirred at this temperature for 30 min, followed by stirring and refluxing for 15 hr. After cooling, 300 ml of H_2O was added to the reaction mixture. The aq layer was separated and extracted with PhMe. The combined PhMe layers were dried (K_2CO_3), filtered, and evaporated, yielding 84 g of 1-(ethoxycarbonyl)-4-(4-chlorophenyl)-4-(3-piperidinopropoxy)piperidine. This crop was stirred and refluxed for 40 hr together with 84 g of KOH in 800 ml of *i*-PrOH. This mixture was cooled and evaporated *in vacuo*. The residue was poured onto H_2O; after extraction (PhMe) the extract was dried, filtered, and evaporated. The residue was distilled *in vacuo*, yielding 44 g of oily **14**; bp 170–175° (0.2 mm).

1-(2-Anilinoethyl)-4-(2-diethylaminoethoxy)-4-phenylpiperidine (35).—A mixture of 8.4 g of 2-anilinoethyl bromide·HBr, 6.9 g of 4-(2-diethylaminoethoxy)-4-phenylpiperidine, 8.48 g of Na_2CO_3, a few crystals of KI in 250 ml of 4-methyl-2-pentanone was stirred and refluxed for 2 days. After cooling there was added 50 ml of H_2O. The organic layer was separated, dried, filtered, and evaporated. The oily residue was dissolved in 100 ml of Me_2CO. To this solution was added a solution of 7.2 g of *N*-cyclohexylsulfamic acid in 100 ml of Me_2CO. The whole was boiled for a few minutes and filtered hot and, after cooling the filtrate to room temperature, the solid salt was precipitated, yielding 10.5 g of **35** dicyclohexylsulfamate, mp 110.5–122°.

1-(3-Anilinopropyl)-4-(2-dibutylaminoethoxy)-4-phenylpiperidine (49).—To a suspension of 2.3 g of LAH in 80 ml of THF was added dropwise a solution of 15.5 g of 3-[4-(2-dibutylaminoethoxy)-4-phenylpiperidino]propionanilide in 50 ml of THF and the whole was further stirred and refluxed for 12 hr. The reaction mixture was cooled and treated with successive additions of 2.3 ml of H_2O, 2.3 ml of 15% aq NaOH, and 9.6 ml of H_2O. The formed precipitate was filtered off and washed on the filter with THF and the filtrate was evaporated. From the oily free base the dicyclohexylsulfamate salt was prepared in the usual manner, yielding, after recrystallization of the crude salt from Me_2CO, 9 g of **49** dicyclohexylsulfamate; mp 121–132°.

(5) Analytical data are given in Tables I and II.

(6) All melting points were taken on a Tottoli melting point apparatus and are corrected.

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