was soluble in acid and contained no halogen (Beilstein test). It evidently was 6,6′-dimethoxy-8,8′-biquinolyl.

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10. Found: C, 76.05; H, 5.10.

8-p-Aminophenyl-6-methoxyquinoline.—To 27.2 g. (0.097 mole) of crude tan-colored 6-methoxy-8-nitrophenylquinolines was added 145 ml. of 6 N hydrochloric acid and 88 g. (0.389 mole) of stannous chloride dihydrate. This mixture was heated under reflux on a steam-bath for forty minutes and the clear red solution which formed was allowed to cool to room temperature. A brown precipitate, probably the stannic chloride salt of the higher melting amine, formed in the solution. This salt was filtered and decomposed with an excess of 40% sodium hydroxide to give a tan, alkali-insoluble solid. After this solid was filtered and washed free of sodium hydroxide, it was recrystallized from 400 ml. of 95% ethanol, the boiling solution being treated with Darco. On cooling the amine crystallized in light yellow prisms, m. p. 181–182°. The filtrates were evaporated and the solids obtained fractionally recrystallized. The total weight of amine so obtained was 6.6 g. (27.2%). Recrystallized for analysis, the aminophenylmethoxyquinoline melted at 180–182°.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.20. Found: C, 76.66; H, 5.84; N, 11.41.

It was found that when the purified sample of 6-methoxy-8-p-nitrophenylquinoline melting at 206° was reduced it gave a product identical with this amine, establishing its structure as 8-p-aminophenyl-6-methoxyquinoline.

The filtrate from removal of the tin salt was made alkaline with excess 40% sodium hydroxide to give a red-brown solid. This solid was washed with water and then dissolved in 100 ml. of 95% ethanol. Cooling in an ice-bath for an hour gave only a trace of brown crystals. An equal volume of water was added to the filtrate and the milky solution so produced was again cooled. A dark brown precipitate separated. This precipitate was again dissolved in ethanol, and the solution was diluted with water to cloudiness. The solution was heated, treated with Darco, filtered and cooled to give a white solid. This procedure was repeated until the solid fused at 130–132°, although the melt was not clear until 140°. The weight of dry material so obtained was 5.5 g. (23%).

A portion of this fraction was recrystallized repeatedly from 75% ethanol. After five recrystallizations, the product melted constantly at 148–149° and had the composition of an aminophenylmethoxyquinoline.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.20. Found: C, 76.55; H, 5.70; N, 11.36.

8-(p-3-Diethylaminopropylaminophenyl)-6-methoxyquinoline.—A mixture of 11.24 g. (0.045 mole) of 8-p-aminophenyl-6-methoxyquinoline and 7.0 g. (0.047 mole) of 3-diethylaminopropyl chloride was heated in an oil-bath at 130° for seven hours. The reaction mixture was cooled, the hard, glassy hydrochloride was treated with a solution of 6 g. of sodium hydroxide in 50 ml. of water and the mixture was extracted with ether. Quite a large amount of the reaction mixture was insoluble in ether and it was discarded. The ether solution was dried, the ether removed and the product distilled with a mercury vapor pump. The fraction boiling at 200–208°, a viscous, yellow liquid, was collected. It weighed 9.0 g. (0.0248 mole) representing a yield of 55%.

Anal.[11] Calcd. for $C_{23}H_{29}N_3O$: C, 76.00; H, 8.04. Found: C, 76.29; H, 8.20.

Attempts to isolate a crystalline hydrobromide were unsuccessful, since even very slight exposure to moist air caused it to turn into a red, semi-solid mass. The picrate was prepared in ethyl alcohol. It initially formed as a liquid but recrystallization gave a red solid, m. p. 157–158°.

Anal. Calcd. for $C_{35}H_{39}N_9O_{15}$: C, 51.16; H, 4.29. Found: C, 50.92; H, 4.34.

Summary

8-(3-Diethylaminopropylaminomethyl)-6-methoxyquinoline and 8-(p-3-diethylaminopropylaminophenyl)-6-methoxyquinoline have been synthesized and submitted for testing as potential antimalarial drugs.

(11) Analysis by Mr. H. L. Clark.

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Piperidine Derivatives. XVII. Local Anesthetics Derived from Substituted Piperidinoalcohols

By S. M. McElvain and Thomas P. Carney[1]

The favorable pharmacological properties of the hydrochloride of γ-(2-methylpiperidino)-propyl benzoate[2] (I) (Metycaine) have led to its rather extensive clinical adoption for both topical and infiltration local anesthesia. More recently it has been used and recommended for continuous caudal analgesia.[3] This compound has the additional clinical advantage of not showing the antagonism to the sulfa drugs that is characteristic

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(2) McElvain, This Journal, **49**, 2835 (1927).

(3) Edwards and Hingson, *Am. J. Surg.*, **57**, 459 (1942); Hingson and Southworth, *ibid.*, **58**, 93 (1943); Hingson and Edwards, *Anesthesia and Analgesia*, **21**, 301 (1942); *J. Am. Med. Assoc.*, **121**, 225 (1943); *ibid.*, **123**, 538 (1943); Southworth, Edwards and Hingson, *Ann. Surg.*, **117**, 321 (1943); Southworth and Hingson, *ibid.*, **118**, 945 (1943).

of such p-aminobenzoate esters as procaine.[4] The general usefulness of I as a local anesthetic suggested a systematic study of the effects of variations of its structure on the pharmacological properties of the resulting compounds, in the hope that even more satisfactory local anesthetics might be discovered.

I
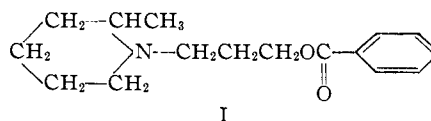
For the purposes of this work, the structure of I was considered as composed of three structural

(4) *Cf. inter alia*, Keltch, Baker, Krahl and Clowes, *Proc. Soc. Exp. Biol. Med.*, **47**, 533 (1941); Pfeiffer and Grant, *Anesthesiology*, **5**, 605 (1945); Peterson and Finland, *Am. J. Med. Sci.*, **207**, 166 (1944).

units: (1) a substituted piperidino radical, (2) an alkylene group connecting this radical to the remainder of the molecule, (3) which in most cases is an acyloxy group. Ninety compounds containing this basic structure have been prepared and are listed in Table I (no. 1 is the previously described compound I), together with the chemical and certain of the screening pharmacological data pertaining to them. The duration of topical anesthesia (T) was determined by application of a solution of the anesthetic in the per cent. shown to the rabbit's cornea; subcutaneous anesthesia (S) was determined on the guinea pig's skin. These pharmacological data were kindly furnished by Mr. Charles L. Rose of the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. A more complete report of his pharmacological evaluation of these piperidine derivatives will be published elsewhere.

The compounds listed in Table I may be conveniently divided into five groups. Those in the first group (nos. 2–54), with four exceptions, are various esters of γ-(2-methylpiperidino)-propyl alcohol; the exceptions, nos. 47–50, have an ether or ketonic residue instead of an acyloxy group attached to the alkylene radical. In the second group, nos. 55–62, are esters of substituted piperidinopropyl alcohols containing a single alkyl substituent (other than the 2-methyl) in the piperidine nucleus and having those acyloxy groups found to be most advantageous in the preceding group. The members of the third group, nos. 63–77, differ from those of the preceding groups by containing a dimethylpiperidino rather than a monoalkylpiperidino substituent. The compounds in the fourth group, nos. 78–79, contain the 2,4,6-trimethylpiperidino nucleus. The members of the fifth group, nos. 80–90, represent variations of the alkylene groups. The methods of preparations given in Table I refer to general procedures, which are described in the Experimental part.

Discussion of the Pharmacological Data.— A study of the pharmacological data for the groups of closely related compounds that appear in Table I leads to the conclusion that certain structural characteristics may be related fairly satisfactorily to one pharmacological property: the production of topical local anesthesia as measured by the application of a dilute solution of the compound to the rabbit's cornea. The other pharmacological properties, infiltration anesthesia and toxicities, depending as they do upon unknown rates of absorption, metabolic destruction and elimination of the tested compounds, do not appear amenable to even an approximate correlation with structure. This is particularly noticeable in the toxicities, where a group of compounds may have similar intravenous toxicities but show widely differently subcutaneous toxicities. Such deviations from regularity necessarily limit the discussion of these data to noting certain trends in the topical anesthesia values and pointing out

those few fortunate combinations of structural features that produce a generally favorable pharmacological behavior.

The introduction of methyl, isopropyl or halogen substituents (nos. 2, 3, 5–8) into the phenyl group of I causes no marked improvement in the pharmacological properties; however, a p-phenyl substituent (no. 4) causes a marked rise in the anesthetic action with a simultaneous lowering of the intravenous toxicity. The hydroxyl substituent causes an improvement in the pharmacological action only when it is in the o- or m-position (nos. 9 and 10). As a p-substituent (no. 11) this group causes the molecule to lose its topical anesthetic action as well as to become more toxic. This is particularly noticeable in no. 12, which has both o- and p-hydroxyl groups.

The alkoxy substituents show no advantage to the o-position, in fact the p-substituents appear to give superior pharmacological properties to the compounds (cf. nos. 13 and 14, 19 and 20, 12 and 33). The compounds (nos. 20–30) containing the higher p-alkoxy substituents in the benzoate portion of I produced such profound topical anesthesia that they had to be applied in more dilute solutions to obtain comparable values; 1% solutions of these compounds produce indefinite anesthesia of the rabbit's cornea. The toxicities of these compounds are interesting. While in general their intravenous toxicities are as low or lower than that of I, their subcutaneous toxicities are usually much higher. A particularly favorable combination of pharmacological properties, however, appears in the p-cyclohexyloxybenzoate, no. 27; it is very effective for anesthesia and also has surprisingly low intravenous and subcutaneous toxicities.

The separation of the phenyl group from the carbalkoxy group by one or more carbons (nos. 34–40) or by a carbon and an oxygen (no. 41) usually destroys the topical anesthesia, although infiltration anesthesia is retained; however, the p-butoxyphenyl acetate (no. 37) and the diphenylacetate (no. 40) do show some topical anesthesia. Of the three non-aromatic esters it is interesting to note that only those with cyclic structures (nos. 42 and 43) possess any anesthetic action and toxicity; the myristate (no. 44) is devoid of any anesthetic action and shows an extremely low toxicity. The carbamates (nos. 45 and 46) have no advantage over the benzoate I.

The non-ester compounds (nos. 47–50) are of interest because they show that the ester structure is not essential for local anesthetic action. Two of the ethers show some infiltration anesthesia, while the ketone (no. 50) produces topical anesthesia comparable to I. Each of these compounds has as high toxicity as do the more potent anesthetics with an ester structure.

The miscellaneous esters, nos. 51–54, have no noteworthy pharmacological properties except possibly the extremely low intravenous toxicity of the nicotinic ester, no. 52.

TABLE I
Hydrochlorides of Variously Substituted Piperidines, Their Local Anesthetic Actions and Toxicities

$CH_2CH_2CH_2CH_2CH(CH_3)N(CH_2)_3R \cdot HCl$

No.	R =	Molecular formula	M. p., °C.	Prep.[a]	% Ionic Cl Calcd.	Found	Anesthesia dur., min. T^b	% sol.	S^c	L. D.50 ± S. E. m.g/kg. in mice Intravenous	Subcutaneous
1	—OCOC₆H₅(I)			A			10	1		22 ± 1	589 ± 65
2	—OCOC₆H₄CH₃(p)	C₁₇H₂₆ClNO₂	182–184	A	11.37	11.35	9	1		25 ± 1	
3	—OCOC₆H₄CH(CH₃)₂(p)	C₁₉H₃₀ClNO₂	165–166	A	10.43	10.52	9	1		29 ± 1	
4	—OCOC₆H₄C₃H₅(p)	C₂₂H₂₅ClNO₂	185–187	B	9.48	9.51	80	0.5		35 ± 3	
5	—OCOC₆H₄Cl(p)	C₁₆H₂₃Cl₂NO₂	213–214	A	10.67	10.67	10	1		25 ± 2	
6	—OCOC₆H₄Br(p)	C₁₆H₂₃BrClNO₂	225–227	A	9.42	9.36	15	1		28 ± 2	
7	—OCOC₆H₄I(o)	C₁₆H₂₃ClINO₂	153–155	A	8.34	8.31	9	1		23 ± 1	
8	—OCOC₆H₄I(p)	C₁₆H₂₃ClINO₂	238–240	A	8.34	8.13	12	1		48 ± 1	
9	—OCOC₆H₄OH(o)	C₁₆H₂₄ClNO₃	145–146	A	11.30	11.29	21	1		34 ± 1	
10	—OCOC₆H₄OH(m)	C₁₆H₂₄ClNO₃	189–191	B	11.30	11.15	23	1		32 ± 2	
11	—OCOC₆H₄OH(p)	C₁₆H₂₄ClNO₃	130–132	B	11.30	10.92	0	1	40	18 ± 1	
12	—OCOC₆H₃(OH)₂(2.4)	C₁₆H₂₄ClNO₄	190–192	B	10.76	10.77	0	1	8	15 ± 2	
13	—OCOC₆H₄OCH₃(o)	C₁₇H₂₆ClNO₃	150–152	A	10.82	10.85	8	1		23 ± 1	
14	—OCOC₆H₄OCH₃(p)	C₁₇H₂₆ClNO₃	174–175	A	10.82	10.84	13	1		22 ± 1	
15	—OCOC₆H₄OC₂H₅(p)	C₁₈H₂₈ClNO₃	183–184	A	10.37	10.42	24	1		21 ± 1	120 ± 6
16	—OCOC₆H₄O(CH₂)₂CH₃(p)	C₁₉H₃₀ClNO₃	162–163	B	9.96	9.83	40	1		15 ± 1	115 ± 2
17	—OCOC₆H₄OCH(CH₃)₂(p)	C₁₉H₃₀ClNO₃	177–179	B	9.96	9.87	40	1		26 ± 2	217 ± 7
18	—OCOC₆H₄O(CH₂)₂CH=CH₂(p)	C₁₉H₂₈ClNO₃	155–156	B	10.02	9.95	30	1		27 ± 2	
19	—OCOC₆H₄O(CH₂)₃CH₃(o)	C₂₀H₃₂ClNO₃	103–105	B	9.59	9.54	30	0.5		12 ± 0	
20	—OCOC₆H₄O(CH₂)₃CH₃(p)	C₂₀H₃₂ClNO₃	147–149	A	9.59	9.61	39	0.5		22 ± 2	177 ± 11
21	—OCOC₆H₄OCH₂CH(CH₃)₂(p)	C₂₀H₃₂ClNO₃	175–176	B	9.59	9.55	80	0.5		32 ± 1	161 ± 23
22	—OCOC₆H₄OCH(CH₃)C₂H₅(p)	C₂₀H₃₂ClNO₃	153–155	B	9.59	9.51	50	0.5		22 ± 0	270 ± 21
23	—OCOC₆H₄O(CH₂)₄CH₃(p)	C₂₁H₃₄ClNO₃	154–155	B	9.24	9.24	50	0.25		24 ± 2	202 ± 26
24	—OCOC₆H₄O(CH₂)₂CH(CH₃)₂(p)	C₂₁H₃₄ClNO₃	145–146	B	9.24	9.24	50	0.25		31 ± 1	
25	—OCOC₆H₄O(CH₂)₅CH₃(p)	C₂₂H₃₆ClNO₃	160–162	B	8.91	8.86	85	0.25		23 ± 1	222 ± 17
26	—OCOC₆H₄OCH(CH₃)(CH₂)₃CH₃(p)	C₂₂H₃₆ClNO₃	136–139	B	8.91	8.97	55	0.1	37	27 ± 2	369 ± 48
27	—OCOC₆H₄OCH(CH₂)₄CH₂)(p)	C₂₂H₃₄ClNO₃	178–180	B	8.96	8.88	20	0.1	37	54 ± 4	447 ± 22
28	—OCOC₆H₄OC₆H₅(p)	C₂₂H₂₈ClNO₃	157–159	B	9.09	9.14	30	0.25		35 ± 2	156 ± 17
29	—OCOC₆H₄OCH₂C₆H₅(p)	C₂₃H₃₀ClNO₃	142–144	B	8.78	8.65	25	0.25		53 ± 2	187 ± 11
30	—OCOC₆H₄O(CH₂)₂C₆H₅(p)	C₂₄H₃₂ClNO₃	145–147	B	8.48	8.42	50	0.25		26 ± 2	272 ± 28
31	—OCOC₆H₄C₃H₄OCH₃(p,p')	C₂₃H₃₀ClNO₃	203–204	B	8.78	8.69	40	0.25		46 ± 2	235 ± 1
32	—OCOC₆H₄COC₆H₅(o)	C₂₃H₂₈ClNO₃	161–162	B	8.82	8.79	35	0.25		9 ± 1	155 ± 24
33	—OCOC₆H₃(OH)O(CH₂)₃CH₃(2.4)	C₂₀H₃₂ClNO₄	150–151	B	9.19	9.00	22	1		30 ± 2	
34	—OCOCH₂C₆H₅	C₁₇H₂₆ClNO₂	129–131	A	11.37	11.38	0	1	30	52 ± 2	800 ± 64
35	—OCOCH₂C₆H₄OH(p)	C₁₇H₂₆ClNO₃	146–149	A	10.82	10.92	0	1	28	74 ± 4	1550 ± 185
36	—OCOCH₂C₆H₄OCH₃(p)	C₁₈H₂₈ClNO₃	110–113	A	10.37	10.25	0	1	7	42 ± 4	235 ± 15
37	—OCOCH₂C₆H₄O(CH₂)₃CH₃(p)	C₂₁H₃₄ClNO₃	91–93	B	9.24	9.11	25	1		29 ± 5	275 ± 21
38	—OCOCH(C₂H₅)C₆H₅	C₁₉H₃₀ClNO₂	134–136	B	10.43	10.35	0	1	34	18 ± 1	305 ± 30
39	—OCO(CH₂)₂C₆H₅	C₁₈H₂₈ClNO₂	97–100	B	10.88	10.72	0	1	23	59 ± 2	690 ± 117
40	—OCOCH(C₆H₅)₂	C₂₃H₃₀ClNO₂	148–150	B	9.14	9.09	18	1		27 ± 1	
41	—OCOCH₂OC₆H₅	C₁₇H₂₆ClNO₃	110–112	A	10.82	10.84	0	1	22	36 ± 2	
42	—OCOCH(CH₂)₄CH₂	C₁₆H₃₀ClNO₂	121–123	B	11.67	11.62	0	1	25	40 ± 2	570 ± 56
43	—OCOCH₂CH(CH₂)₄CH₂	C₁₇H₃₂ClNO₂	103–105	B	11.12	11.34	0	1	50	31 ± 4	290 ± 39
44	—OCO(CH₂)₁₂CH₃	C₂₂H₄₆ClNO₂	107–109	A	8.78	8.65	0	1	0	117 ± 3	
45	—OCONHC₆H₅	C₁₆H₂₅ClN₂O₂	216–217	E	11.34	11.34	14	0.5		22 ± 2	177 ± 11
46	—OCONHC₁₀H₇(α)	C₂₀H₂₇ClN₂O₂	172–175	E	9.77	9.70	18	1		24 ± 1	109 ± 9
47	—O(CH₂)₃CH₃	C₁₃H₂₈ClNO	86–88	D	14.19	14.37	0	1	16	18 ± 0	
48	—OC₆H₅	C₁₅H₂₄ClNO	145–147	D	13.11	13.15	0	1	16	25 ± 1	
49	—OCH₂C₆H₅	C₁₆H₂₆ClNO	105–108	D	12.49	12.41	0	1		18 ± 2	
50	—COC₆H₅	C₁₆H₂₄ClNO	175–178	B	12.58	12.59	15	1		32 ± 5	
51	—OCOC₆H₄SH(o)	C₁₆H₂₄ClNO₂S	165–168	A	10.75	10.68	0	1	15	42 ± 3	230 ± 23
52	—OCOC=CHCH=CHN=CH	C₁₃H₂₂ClN₂O₂	171–172	A	11.88	11.70	0	1	8	100 ± 9	500 ± 11
53	—OCOC=CHCH=CHO	C₁₄H₂₂ClNO₃	126–128	A	12.32	12.16	0	1	5	36 ± 2	420 ± 19
54	—OCOC=CHCH=CHS	C₁₄H₂₂ClNO₂S	155–156	A	11.66	11.59	5	1		26 ± 1	730 ± 43

$R—C_5H_9N(CH_2)_3OCOR' \cdot HCl$

No.	R =	R' =	Molecular formula	M. p., °C.	Prep.[a]	% Ionic Cl Calcd.	Found	Anesthesia dur., min. T^b	% sol.	S^c	Intravenous	Subcutaneous
55	3-CH₃	—C₆H₄O(CH₂)₃CH₃(p)	C₂₀H₃₂ClNO₃	149–151	A	9.59	9.68	35	0.5		27 ± 2	
56	4-CH₃	—C₆H₄O(CH₂)₃CH₃(p)	C₂₀H₃₂ClNO₃	167–169	A	9.59	9.71	37	0.5		27 ± 1	
57	2-CH(CH₃)₂	—C₆H₅	C₁₈H₂₈ClNO₂	156–158	A	10.88	10.83	10	1		34 ± 1	
58	2-(CH₂)₃CH₃	—C₆H₅	C₂₀H₃₂ClNO₂	151–153	C	10.02	9.93	12	0.5		19 ± 1	
59	2-CH·C₄H₅)₂	—C₆H₄	C₂₀H₃₂ClNO₂	169–170	A	10.02	9.86	8	0.5		18 ± 1	
60	2-(CH₂)₅CH₃	—C₆H₅	C₂₁H₃₄ClNO₂	142–143	C	9.64	9.57	0	0.5		22 ± 2	
61	4-CH·CH₂)₂	—C₆H₅	C₁₈H₂₆ClNO₂	181–183	C	10.88	10.91	3	0.5		28 ± 1	
62	4-(CH₂)₃CH₃	—C₆H₅	C₂₀H₃₂ClNO₂	179–181	C	10.02	10.00	13	0.5		26 ± 1	

TABLE I   (*Concluded*)

(CH₃)₂C₅H₅N(CH₂)₃OCOR·HCl

No.	Position of CH₃	R =	Molecular formula	M. p., °C.	Prep.[a]	% Ionic Cl Calcd.	Found	T[b]	% Sol. S[c]		L. D.₅₀ ± S. E. m. g./kg. in mice Intravenous	Subcutaneous
63	2,3	—C₆H₅	C₁₇H₂₆ClNO₂	151–153	A	11.37	11.18	5	1		35 ± 2	1600 ± 69
64	2,3	—C₆H₄OH(o)	C₁₇H₂₆ClNO₃	144–146	B	10.82	10.68	15	1		18 ± 1	345 ± 29
65	2,4	—C₆H₅	C₁₇H₂₆ClNO₂	179–181	A	11.37	11.36	16	1		28 ± 1	
66	2,4	—C₆H₄OH(o)	C₁₇H₂₆ClNO₃	154–156	B	10.82	10.75	19	1	45	20 ± 1	410 ± 48
67	2,5	—C₆H₅	C₁₇H₂₆ClNO₂	144–147	A	11.37	11.24	12	1		23 ± 1	
68	2,5	—C₆H₄OH(o)	C₁₇H₂₆ClNO₃	154–156	B	10.82	10.89	15	1		21 ± 1	365 ± 21
69	2,6	—C₆H₅	C₁₇H₂₆ClNO₂	168–170	A	11.37	11.32	27	1	60	21 ± 1	
70	2,6	—C₆H₄OH(o)	C₁₇H₂₅ClNO₃	155–157	B	10.82	10.71	23	1	39	35 ± 1	386 ± 27
71	2,6	—C₇H₄O(CH₂)₄CH₃(p)	C₂₁H₃₄ClNO₃	155–156	A	9.24	9.02	30	0.5		24 ± 1	
72	2,6	—C₇H₄OC₆H₅(p)	C₂₂H₃₀ClNO₃	142–145	B	8.78	8.68	50	0.25		32 ± 2	160 ± 16
73	2,6	—C₇H₄O(CH₂)₅CH₃(p)	C₂₂H₃₆ClNO₃	149–151	B	8.65	8.75	60	0.25		33 ± 3	300 ± 20
74	2,6	—C₆H₄SH(o)	C₁₇H₂₆ClNO₂S	186–187	A	10.31	10.20	0	1	2	45 ± 3	250 ± 12
75	2,6	—CH₂C₆H₅	C₁₈H₂₈ClNO₂	117–119	A	10.88	10.79	0	1	11	28 ± 1	710 ± 55
76	2,6	—CH₂C₆H₄OCH₃(p)	C₁₉H₃₀ClNO₃	83–86	A	9.96	9.79	0	1	3	37 ± 3	630 ± 39
77	2,6	—C=CHCH=CHN=CH	C₁₅H₂₅ClN₂O₂	157–158	A	11.33	11.27	0	1	3	115 ± 6	330 ± 39

CH(CH₃)CH₂CH(CH₃)CH₂CH(CH₃)N(CH₂)₃OCOR·HCl

R =

78		—C₆H₅	C₁₈H₂₈ClNO₂	178–180	A	10.88	10.86	21	1	35	15 ± 1	
79		—C₆H₄OH(o)	C₁₈H₂₈ClNO₃	177–179	B	10.37	10.25	15	1		27 ± 1	510 ± 24

CH₃—C₅H₉N—X—OCOR·HCl

No.	Position of CH₃	X =	R =	Molecular formula	M. p., °C.[a]	Prep.[a]	% Ionic Cl Calcd.	Found	T[b]	% sol. S[c]		Pharmacological data L. D.₅₀ ± S. E. mg./kg. in mice Intravenous	Subcutaneous
80	2	—(CH₂)₄—	—C₆H₅	C₁₇H₂₆ClNO₂	135–137	A	11.37	11.43	7	1		20 ± 1	
81	2	—(CH₂)₅—	—C₆H₅	C₁₈H₂₈ClNO₂	117–119	A	10.88	10.79	17	1		17 ± 1	
82	2	—(CH₂)₆—	—C₆H₅	C₁₉H₃₀ClNO₂	112–114	A	10.43	10.37	15	1		28 ± 1	
83	2	—CH₂CH(CH₃)—	—C₆H₅	C₁₆H₂₄ClNO₂	174–176	A	11.91	11.70	3	1	0	36 ± 2	ca 1500
84	2	—CH₂CH(CH₃)—	—C₆H₄OC₄H₉(p)	C₂₀H₃₂ClNO₃	154–156	A	9.59	9.45	0	1	0	141 ± 2	ca 800
85	3	—CH(CH₃)CH₂CH₂—	—C₆H₄OC₄H₉(p)	C₂₁H₃₄ClNO₃	111–114	A	9.24	9.59	60	0.5		31 ± 2	
86	4	—CH(CH₃)CH₂CH₂—	—C₆H₅	C₁₇H₂₆ClNO₂	162–165	A	11.37	11.33	17	1		18 ± 2	
87	4	—CH₂CH(CH₃)CH(CH₃)—	—C₆H₅	C₁₈H₂₈ClNO₂	190–192	A	10.89	11.10	35	1		24 ± 1	
88	4	—CH₂C(CH₃)₂CH₂—	—C₆H₅	C₁₈H₂₈ClNO₂	197–200	A	10.89	10.89	8	1		27 ± 2	
89	4	—CH₂C(CH₃)₂CH₂—	—C₆H₄OC₄H₉(p)	C₂₂H₃₆ClNO₃	120–123	A	8.91	9.07	d	1		36 ± 3	
90	2	—(CH₂)₂O(CH₂)₂—	—C₆H₅	C₁₇H₂₆ClNO₃	118–120	D	10.82	10.71	30	1	15	20 ± 5	ca 1500

[a] Preparational procedure described in Experimental part.   [b] Topical anesthesia of the rabbit's cornea.   [c] Subcutaneous anesthesia of the guinea pig's skin.   [d] Eyes closed due to irritation; anesthesia value indefinite.

Among the other monoalkylpiperidino derivatives (nos. 55–62) it may be noted that the *p*-butoxybenzoates of the 3- and 4-methylpiperidinopropyl alcohols (nos. 55 and 56) are as potent as anesthetics as is the corresponding 2-methylpiperidino derivative (no. 20). However, the replacement of the methyl substituent of the piperidine nucleus of I by higher alkyl groups produces no marked improvement in pharmacological properties.

The dimethylpiperidino derivatives (nos. 63–77) show no advantage over the corresponding 2-methylpiperidino derivatives unless the dimethyl substituents are in the 2,6-position. Then the benzoates (*cf.* nos. 1 and 69), the *p*-phenoxybenzoates (nos. 28 and 72) and the *p*-amyloxybenzoates (nos. 23 and 73) show noticeably greater anesthetic action with approximately the same toxicities; however, the corresponding salicylates (nos. 9 and 70) and the *p*-butoxybenzoates (nos. 20 and 71) do not have very different pharmacological properties. Among these dimethylpiperidino derivatives, the very low subcutaneous toxicity of the 2,3-dimethylpiperidinopropyl benzoate (no. 63) should be noted. The trimethylpiperidino substituents in nos. 78 and 79 produce no improvement in pharmacological properties over the corresponding 2-methylpiperidino derivatives (nos. 1 and 9).

The variations of the alkylene radicals in compounds 80–90 show some striking effects. Lengthening of the carbon chain that joins the nitrogen to oxygen (nos. 80-82) causes no marked change in pharmacological action. However, shortening an alkylene group to a two carbon chain, which carries a methyl substituent, practically destroys the anesthetic action of the benzoate and *p*-butoxybenzoate (nos. 83-84). That this marked change in pharmacological properties is due to the shortening of the carbon chain of the alkylene group is shown by return of strong anesthetic action to compounds 85 and 86, which have a three carbon alkylene group similarly substituted by a methyl group. Indeed, unsymmetrical substitution of methyl groups in the alkylene chain appears to enhance anesthetic action (*cf.* nos. 87 to 1 and 86), while symmetrical substitution of the methyl groups lowers the activity (*cf.* nos. 88 to 1; 89 to 20 and 56). Finally, the interruption of a four carbon alkylene group by an oxygen appears to improve the anesthetic action as a comparison of the pharmacological properties of no. 90 with those of no. 80 will show.

Experimental

Alkylpiperidines.—2,3-Dimethylpiperidine was obtained from the Eastman Kodak Co.; 4-*n*-amylpiperidine was furnished by Reilly Tar and Chemical Corporation, Indianapolis, Indiana. The other alkylpiperidines were prepared by the hydrogenation of the corresponding alkylpyridines over Raney nickel according to the procedure described by Adkins.[5] Each hydrogenation product was fractionated through a 10-plate Fenske column packed with glass helices and a sample having a constant boiling point and index of refraction collected. These properties are listed in Table II; the yields of the alkylpiperidines with such properties varied from 45–66%.

Chlorohydrins.—The chlorohydrins used in this work were prepared from the corresponding glycols by the procedure described[6] for the preparation of trimethylene chlorohydrin. It was found desirable to employ somewhat higher reaction temperatures for the higher glycols. The properties, reaction temperatures used for the preparation, and the yields of the chlorohydrins are listed in Table III.

TABLE III

CHLOROHYDRINS

Chlorohydrin	B. p., °C. (mm.)	$n^{20}D$	Reaction temp., °C.	Yield, %
Tetramethylene	87 (10)	1.4502	165–170	16[a]
Pentamethylene[b]	103 (8)	1.4518	180–185	23
Hexamethylene	112 (12)	1.4541	195–200	31
2-Ethyl-3-chloro-hexanol[c]	121 (30)	1.4559	200–205	30

[a] The major product from the preparation of this chlorohydrin was tetrahydrofuran. [b] Calcd. for C_5H_{11}-ClO: Cl, 28.91. Found: Cl, 28.75. [c] Calcd. for C_8-H_{17}ClO: Cl, 21.53. Found: Cl, 21.33.

Methylpiperidinoaldehydes and Ketones by the Mannich Reaction.—For the preparation of the piperidinoaldehydes and ketones by means of the Mannich reaction two methods were used. In the first method the alkylpiperidine hydrochloride, paraformaldehyde, and the proper aldehyde or ketone were allowed to react in isoamyl alcohol. In the second method water was used as the solvent. The following examples illustrate both methods. In general, for the compounds prepared in this work, the aqueous medium gave the better results.

(1) **4-(3-Methylpiperidino)-butanone-2.**—Into a 500-ml. flask, equipped with a stirrer and dropping funnel and heated by means of an oil-bath, were placed 40 g. of β-

(5) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, pp. 64–67.

(6) "Organic Syntheses," Coll. Vol. I, 2nd ed., 533 (1941).

pipecoline hydrochloride, 12 g. of paraformaldehyde, and 200 ml. of isoamyl alcohol. The mixture was stirred and heated to 130° for one hour and then 40 g. of acetone was added over a period of thirty minutes. After two hours of heating, an additional 12 g. of paraformaldehyde was added. Stirring and heating were continued for an additional three hours after which the isoamyl alcohol was distilled off under diminished pressure. The solid residue was dissolved in water, and this solution extracted with ether. The separated aqueous layer then was made basic with sodium hydroxide, and the aminoketone extracted with ether. The ether layer was dried over sodium sulfate and distilled. A yield of 22.5 g. of the desired ketone was obtained.

(2) Into a 500-ml. flask, equipped as described in (1), were placed 40 g. of β-pipecoline, 39 ml. of concentrated hydrochloric acid, and 43 g. of 37% aqueous formaldehyde. The mixture was heated at 100° for one hour and then 40 g. of acetone was added over a period of thirty minutes. The mixture was stirred and heated for three hours more, after which an additional 20 g. of aqueous formaldehyde and 10 g. of acetone were added. Stirring and heating were continued for three additional hours. About 75 ml. of liquid was then distilled off to remove unreacted acetone and formaldehyde, after which water was added to the residue, and this solution extracted with ether. The water layer was then made basic with sodium hydroxide and extracted with ether. The ether layer was dried over sulfate, and distilled. A yield of 26 g. of the aminoketone was obtained.

The properties, method of preparation, yields, and analyses of the various methylpiperidinoaldehydes and ketones prepared in this work are listed in Table IV.

Substituted Piperidinoalcohols.—The substituted piperidinoalcohols were prepared by three general methods: (1) by the condensation of a chlorohydrin with a substituted piperidine, (2) by the reduction of an aldehyde or ketone obtained from the Mannich reaction, and (3) by the reaction of a substituted piperidine with propylene oxide. The following preparations illustrate these methods.

(1a) **3-(2,6-Dimethylpiperidino)-propyl Alcohol.**—In this method two moles of the piperidine per mole of chlorohydrin were used, the second mole of the base being used to take up the hydrogen chloride formed in the reaction: In a 100-ml. flask equipped with a stirrer and reflux condenser were placed 26 g. (0.23 mole) of 2,6-dimethylpiperidine and 10.8 g. (0.115 mole) of trimethylene chlorohydrin. An oil-bath surrounding the flask was heated to 150° for one hour, then to 175° for two hours, and finally the temperature was raised to 210° over a period of one hour. The reaction mixture on cooling set to a semi-solid mass. Ether was added and the insoluble 2,6-dimethylpiperidine hydrochloride filtered off. Distillation of the filtrate yielded 10 g. of 3-(2,6-dimethylpiperidino)-propyl alcohol.

(1b) **3-(2,4-Dimethylpiperidino)-propyl Alcohol.**—In this method the equimolecular proportions of the chlorohydrin and the piperidine are condensed in the presence of potassium carbonate: In a 100-ml. flask equipped as in (1a) were placed 13.2 g. (0.12 mole) of 2,4-dimethylpiperidine, 11.0 g. (0.12 mole) of trimethylene chlorohydrin, and 16 g. of anhydrous potassium carbonate. The oil-bath surrounding the flask was heated to 150–160° for seven hours. The reaction mixture then was cooled, and water added to dissolve the potassium chloride and excess potassium carbonate. The mixture was extracted with ether, and the ether layer dried and distilled. A yield of 10 g. of the desired alcohol was obtained.

(2a) **4-(4-Methylpiperidino)-butanol-2.**—In a 200-ml. flask equipped with a reflux condenser were placed 10 g. of 4-(4-methylpiperidino)-butanone-2, and 70 ml. of absolute ethyl alcohol. To this solution 10 g. of sodium was added over a period of fifteen minutes. The solution turned dark red on the first addition of sodium. An additional 30 ml. of alcohol was added and the reaction mixture heated until all the sodium dissolved; this usually required about twenty minutes. The mixture was cooled,

TABLE IV

METHYLPIPERIDINOALDEHYDES AND KETONES, $R—C_5H_9N—CH_2\overset{\displaystyle R_1}{\underset{\displaystyle R_2}{C}}COR_3$

R	R₁	R₂	R₃	B. p., °C. (mm.)	$n^{20}D$	Method of prep.	Yield, %	Formula	Analyses, % N Calcd.	Found
2-CH₃	H	H	CH₃	83 (6)	1.4660	1	28	$C_{10}H_{19}NO$	8.28	8.11
						2	29			
3-CH₃	H	H	CH₃	74 (2)	1.4621	1	45	$C_{10}H_{19}NO$	8.28	8.59
						2	38			
4-CH₃	H	H	CH₃	72 (2)	1.4613	1	52	$C_{10}H_{19}NO$	8.28	8.48
						2	38			
4-CH₃	CH₃	CH₃	H	64 (3)	1.4573	2	45	$C_{11}H_{21}NO$	7.64	7.73
4-CH₃	C₂H₅	H	H	86 (2)	1.4655	1	12	$C_{11}H_{21}NO$	7.64	7.70
4-CH₃	CH₃	H	CH₃	85 (2)	1.4623	2	26	$C_{11}H_{21}NO$	7.64	7.84

and 60 ml. of water slowly added. After saturation of the aqueous solution with sodium chloride, the reaction mixture was extracted with ether. The ether layer, after drying and distillation, yielded 3.3 g. of the desired alcohol; 3 g. of 4-methylpiperidine also was obtained.

(2b) **4-(4-Methylpiperidino)-3-methylbutanol-2.**—To a solution of 16 g. of the hydrochloride of 4-(4-methyl-piperidino)-3-methylbutanone-2 in 100 ml. of ethyl alcohol was added 0.7 g. of Adams platinum oxide catalyst. This mixture was shaken at room temperature under a pressure of two atmospheres of hydrogen for twenty-three hours. The catalyst then was filtered off, the alcohol evaporated, and the residue dissolved in water. The aqueous solution was made basic with sodium hydroxide and extracted with ether. The ether layer, after drying and distillation, yielded 4.5 g. of the desired aminoalcohol.

(2c) **2,2-Dimethyl-3-(4-methylpiperidino)-propanol-1.—** In a 200-ml. flask were placed 18 g. of 2,2-dimethyl-3-(4-

methylpiperidino)-propionaldehyde, 100 ml. of isopropanol, and 14 g. of aluminum isopropoxide. The flask was attached to a Fenske column and its contents heated to refluxing. The head temperature began to drop immediately, indicating the formation of acetone, which was removed as it formed. After two hours of refluxing the head temperature rose to 82°, the boiling point of isopropanol. Water then was added to the residue in the flask, and the mixture was extracted with ether. After drying, the ether layer was distilled and 10 g. of the desired aminoalcohol was obtained.

(3) **3-(2-Methylpiperidino)-propanol-2.**—To a solution of 125 ml. of methanol and 99 g. of α-pipecoline cooled to −5° was added, with stirring, 58 g. of propylene oxide over a period of thirty minutes. The reaction flask then was well packed in ice, and the mixture allowed to stand. As the ice melted, the temperature in the reaction mixture was allowed to come to room temperature over a period of

TABLE V

SUBSTITUTED PIPERIDINOALCOHOLS, $R_nC_5H_{(9-n)}N—R'$

R	R'	B. p., °C. (mm.)	$n^{20}D$	Method of prep.	Yield, %	Formula	Analyses, % N Calcd.	Found
2-CH₃	—CH₂CH₂CH₂OH	112 (15)	1.4780	1b	60	Ref. (2)		
3-CH₃	—CH₂CH₂CH₂OH	114 (16)	1.4708	1b	70	$C_9H_{19}NO$	8.91	8.84
4-CH₃	—CH₂CH₂CH₂OH	110 (13)	1.4699	1b	70	$C_9H_{19}NO$	8.91	9.01
2,3-(CH₃)₂	—CH₂CH₂CH₂OH	111 (8)	1.4754	1b	58	$C_{10}H_{21}NO$	8.18	8.02
2,4-(CH₃)₂	—CH₂CH₂CH₂OH	129 (16)	1.4729	1b	50	$C_{10}H_{21}NO$	8.18	8.21
2,5-(CH₃)₂	—CH₂CH₂CH₂OH	138 (24)	1.4719	1b	59	$C_{10}H_{21}NO$	8.18	8.15
2,6-(CH₃)₂	—CH₂CH₂CH₂OH	149 (30)	1.4839	1a	51	$C_{10}H_{21}NO$	8.18	8.04
				1b	57			
2,4,6-(CH₃)₃	—CH₂CH₂CH₂OH	131 (9)	1.4778	1b	41	$C_{11}H_{23}NO$	7.56	7.38
2-(CH₃)₂CH	—CH₂CH₂CH₂OH	134 (7)	1.4799	1b	57	$C_{11}H_{23}NO$	7.56	7.29
2-(C₂H₅)₂CH	—CH₂CH₂CH₂OH	148 (6)	1.4797	1b	57	$C_{13}H_{27}NO$	6.57	6.75
2-CH₃	—CH₂CH(CH₃)OH	115 (45)	1.4622	3	85	$C_9H_{19}NO$	8.91	8.78
2-CH₃	—CH₂(CH₂)₂CH₂OH	133 (8)	1.4792	1b	31	$C_{10}H_{21}NO$	8.18	8.39
2-CH₃	—CH₂CH₂CH(OH)CH₃	87 (4)	1.4630	2a	9	$C_{10}H_{21}NO$	8.18	8.24
				2c	0			
3-CH₃	—CH₂CH₂CH(OH)CH₃	111 (8)	1.4608	2a	36	$C_{10}H_{21}NO$	8.18	8.30
				2b	63			
				2c	0			
4-CH₃	—CH₂CH₂CH(OH)CH₃	98 (5)	1.4598	2a	32	$C_{10}H_{21}NO$	8.18	7.99
				2c	0			
2-CH₃	—CH₂(CH₂)₃CH₂OH	149 (10)	1.4800	1b	61	$C_{11}H_{23}NO$	7.56	7.34
4-CH₃	—CH₂CH(CH₃)CH(OH)CH₃	100 (3)	1.4590	2b	33	$C_{11}H_{23}NO$	7.56	7.37
4-CH₃	—CH₂CH(C₂H₅)CH₂OH	101 (2)	1.4700	2a	42	$C_{11}H_{23}NO$	7.56	7.49
				2c	0			
4-CH₃	—CH₂C(CH₃)₂CH₂OH	72 (2)	1.4600	2c	55	$C_{11}H_{23}NO$	7.56	7.58
2-CH₃	—CH₂(CH₂)₄CH₂OH	167 (13)	1.4780	1b	62	$C_{12}H_{25}NO$	7.03	7.12
2-CH₃	—CH(n-C₃H₇)CH(C₂H₅)CH₂OH	166 (24)	1.4667	1b	20	$C_{14}H_{29}NO$	6.16	6.40

Table VI

Substituted Piperidinoalkyl Chlorides, $R_nC_5H_{(10-n)}N$—X—Cl

R	X	B. p., °C. (mm.)	$n^{20}D$	Yield, %	Formula	Analyses, % Cl Calcd.	Found
2-Methyl	CH₂CH₂CH₂	100 (12)	1.4724	75	C₉H₁₈ClN	20.18	19.96
2-Methyl	CH₂CH(CH₃)	115 (40)	1.4665	90	C₉H₁₈ClN	20.18	19.97
2,3-Dimethyl	CH₂CH₂CH₂	99 (5)	1.4738	70	C₁₀H₂₀ClN	18.69	18.54
2,4-Dimethyl	CH₂CH₂CH₂	89 (3)	1.4684	78	C₁₀H₂₀ClN	18.69	18.60
2,5-Dimethyl	CH₂CH₂CH₂	99 (10)	1.4690	76	C₁₀H₂₀ClN	18.69	18.72
2,6-Dimethyl	CH₂CH₂CH₂	108 (8)	1.4770	75	C₁₀H₂₀ClN	18.69	18.55
2,4,6-Trimethyl	CH₂CH₂CH₂	106 (7)	Solid	75	C₁₁H₂₂ClN	17.42	17.61

about six hours, after which it was allowed to stand for twenty-four hours. Fractionation of the reaction mixture yielded the desired alcohol.

The properties, methods of preparation, yields, and analyses of the various piperidinoalcohols are summarized in Table V.

Substituted Piperidinopropyl Chlorides.—The substituted piperidinopropyl chlorides were prepared from the corresponding alcohols and thionyl chloride. The preparation of 3-(2-methylpiperidino)-propyl chloride illustrates the method: In a 500-ml. flask fitted with a dropping funnel, stirrer and reflux condenser was placed a solution of 30 g. of 3-(2-methylpiperidino)-propyl alcohol in 150 ml. of chloroform. To this solution was added, with stirring, a solution of 40 g. of thionyl chloride in 150 ml. of chloroform over a period of 45 minutes. The rate of addition was such that the temperature of the chloroform was maintained just below its boiling point. After the addition of the thionyl chloride was completed, the solution was refluxed on a steam-bath for three hours. The chloroform and excess thionyl chloride then was distilled off, the solid residue dissolved in water, and the aqueous solution extracted with ether. The water layer, after separation, was made basic with sodium hydroxide solution and the piperidinoalkyl halide extracted with ether. After drying over potassium carbonate, the ether was removed and the residue distilled; 25 g. of the piperidinopropyl chloride was obtained.

The structures, properties, yields and analyses of the piperidinoalkyl chlorides prepared in this work are given in Table VI.

Acids.—Those acids not listed in Table VII or mentioned below were purchased from the Eastman Kodak Company. The alkoxy acids in Table VII were prepared by two general methods: (1) the phenolic acid was alkylated with an alkyl bromide in an aqueous potassium hydroxide solution; (2) the methyl or ethyl ester of the phenolic acid was alkylated with the alkyl bromide in methanol in the presence of sodium methoxide. The following examples illustrate these procedures.

(1) *p*-(*n*-Butoxy)-benzoic Acid.—A mixture of 34.5 g. of *p*-hydroxybenzoic acid, 38 g. of butyl bromide and 28 g. of potassium hydroxide in 112 ml. of water was heated to refluxing for twelve hours. At the end of this time a large upper layer of the ester of the alkoxy acid was present. An additional 14 g. of potassium hydroxide in 140 ml. of water was added, and the mixture refluxed until a clear solution was obtained (one to three hours). The solution then was cooled and acidified. The precipitate was filtered off, washed with water, and recrystallized from glacial acetic acid. The recrystallized material was washed with water and dried; the *p*-butoxybenzoic acid obtained amounted to 28 g.

(2) *p*-Isoamyloxybenzoic Acid.—To a solution of 4.5 g. of sodium in 100 ml. of absolute methanol were added 30 g. of methyl-*p*-hydroxybenzoate and 42 g. of isoamyl iodide. The alcohol then was distilled off under vacuum, the residue made basic with 10% sodium hydroxide solution and this solution extracted with ether. The ether was removed and the residue refluxed with 10% sodium hydroxide until a clear solution resulted (one to three hours). The solution was acidified, filtered, and the resulting alkoxy acid recrystallized from glacial acetic acid.

The *n*-propoxy-, isopropoxy-, allyloxy-, isoamyloxy- and benzyloxybenzoic acids[7]; the *n*-butoxy-, isobutoxy-, *n*-amyloxy-, and *n*-hexyloxybenzoic acids,[8] and *s*-butoxybenzoic acid[9] have been reported in the literature. The 2-hydroxy-4-(*n*-butoxy)-, *p*-(2-pentyloxy)-, *p*-(2-hexyloxy)-, *p*-cyclohexyloxybenzoic acids and the *p*-(*n*-butoxy)-phenylacetic acid are new compounds, the analytical data for which are given in footnotes *a-e* of Table VII. The melting points, methods of preparation and yields of all the alkoxy acids prepared in this work are listed in this table.

Table VII

Alkoxy Benzoic and Phenylacetic Acids, R·COOH

R =	M. p., °C.	Method of prep.	Yield, %
p-CH₃(CH₂)₂OC₆H₄—	145–147	1	73
p-CH₂=CHCH₂OC₆H₄—	164–166	2	74
p-(CH₃)₂CHOC₆H₄—	167–168	2	45
p-CH₃(CH₂)₃OC₆H₄—	147–149	1	60
2-(OH)-4-(CH₃(CH₂)₃O)-C₆H₃—*ᵃ*	135–136	2	50
p-CH₃CH₂CH(CH₃)OC₆H₄—	121–122	2	45
p-(CH₃)₂CHCH₂OC₆H₄—	144–145	2*ᵍ*	27
p-CH₃(CH₂)₄OC₆H₄—	122–124	2	70
p-CH₃(CH₂)₂CH(CH₃)-OC₆H₄—*ᵇ*	Oil*ᶠ*	2	42
p-(CH₃)₂CH(CH₂)₂OC₆H₄—	141–143	2*ʰ*	64
p-CH₃(CH₂)₅OC₆H₄—	103–105	2	63
p-CH₃(CH₂)₃CH(CH₃)-OC₆H₄—*ᶜ*	Oil*ᶠ*	2	34
p-CH₂(CH₂)₄CHOC₆H₄—*ᵈ*	186–188	1*ʰ*	7*ᵏ*
p-C₆H₅CH₂OC₆H₄—	193–195	2*ⁱ*	76
p-CH₃OC₆H₄CH₂—	85–86	1*ʲ*	96
p-CH₃(CH₂)₃OC₆H₄CH₂—*ᵉ*	86–87	1	57

ᵃ Calcd. for C₁₁H₁₄O₄: C, 62.8; H, 6.7. Found: C, 62.8; H, 6.6. *ᵇ* Calcd. for C₁₂H₁₆O₃: C, 69.2; H, 7.7. Found: C, 69.3; H, 7.8. *ᶜ* Calcd. for C₁₃H₁₈O₃: C, 70.2; H, 8.2. Found: C, 70.0; H, 8.1. *ᵈ* Calcd. for C₁₃H₁₈O₃: C, 70.9; H, 7.3. Found: C, 70.7; H, 7.3. *ᵉ* Calcd. for C₁₂H₁₆O₃: C, 69.2; H, 7.7. Found: C, 69.0; H, 7.6. *ᶠ* Oil substantially pure as obtained. *ᵍ* Amyl alcohol instead of methyl alcohol used as solvent. *ʰ* Alkyl iodide instead of bromide used. *ⁱ* Benzyl chloride instead of the bromide used. *ʲ* Dimethyl sulfate used as methylating agent. *ᵏ* Twenty-two hours of heating required to produce this yield.

Miscellaneous Acids.—γ-Bromobutyric acid was prepared from γ-bromobutyronitrile[10]; α-thiophene-carboxylic acid and hexahydrobenzoic acid were obtained by

(7) Cohen and Dudley, *J. Chem. Soc.*, **97**, 1732 (1910).

(8) Bradfield and Jones, *ibid.*, **131**, 3073 (1928); **132**, 266 (1929); 1874 (1935).

(9) Lauer, *et al.*, This Journal, **61**, 3050 (1939).

(10) Prill and McElvain, *ibid.*, **55**, 1233 (1933).

the carbonation of α-thienylmagnesium bromide[11] and cyclohexylmagnesium bromide,[12] respectively; resorcylic acid was prepared from resorcinol[13]; cyclohexylacetic acid was prepared from cyclohexylmalonic ester, obtained from the reaction of cyclohexyl bromide with sodiomalonic ester[14]; p-isopropylbenzoic acid was obtained by oxidation of p-isopropylbenzaldehyde with an aqueous solution of potassium permanganate; p-phenylbenzoic acid, p-phenoxybenzoic acid, and p-(4-methoxyphenyl)-benzoic acid were prepared by the oxidation of p-phenylaceto-phenone,[15] p-phenoxyacetophenone[16] and p-(4-methoxyphenyl)-acetophenone,[17] respectively, by the procedure of Johnson, Gutsche and Offenhauer.[18]

Acyl Chlorides.—All of the acyl chlorides used in this work were prepared by the action of thionyl chloride on the acids. An excess of the reagent was employed and the reaction mixture heated on the steam-bath for two to three hours, after which time the excess thionyl chloride was distilled off and the acyl chloride distilled. p-Iodobenzoyl chloride was used without purification, as it decomposed at the temperature required for its distillation.

The boiling points and yields of these acyl chlorides are listed in Table VIII.

TABLE VIII

ACYL CHLORIDES

Acyl group	B. p., °C. (mm.)	Yield, %
γ-Bromobutyryl[a]	101 (37)	60
Myristoyl[b]	166 (15)	96
p-Methylbenzoyl[c]	106 (12)	77
p-Isopropylbenzoyl[d]	121 (10)	87
o-Methoxybenzoyl[e]	133 (10)	90
p-Methoxybenzoyl[c]	143 (13)	92
p-Ethoxybenzoyl[f]	144 (10)	90
p-Butoxybenzoyl[g]	160 (8)	96
p-Chlorobenzoyl[c]	107 (10)	76
p-Bromobenzoyl[c]	155 (12)	95
p-Iodobenzoyl[c]	. . . . .	. .
Phenylacetyl[c]	102 (16)	97
p-Methoxyphenylacetyl[h]	143 (10)	88
Cinnamoyl[c]	137 (10)	94
Thiosalicylyl[i]	170 (20)	45
Phenoxyacetyl[j]	112 (10)	89
Thienyl[k]	85 (14)	60

[a] *Anal.* Calcd. for C_4H_6BrClO: BrCl, 62.21. Found: BrCl, 61.95. [b] Izar, *Biochem. Z.,* **40**, 402 (1912). [c] Meyer, *Monatsh.,* **22**, 425 (1901). [d] *Anal.* Calcd. for $C_{10}H_{11}ClO$: Cl, 19.41. Found: Cl, 19.24. [e] Fischer, *Ber.,* **36**, 2585 (1903). [f] Cohen and Dudley, *J. Chem. Soc.,* **97**, 1741 (1910). [g] Rohmann and Scheurle, *Arch. Pharm.,* **274**, 110 (1936). [h] Cain, *et al., J. Chem. Soc.,* **103**, 1037 (1913). [i] *Anal.* Calcd. for C_7H_5ClOS: Cl, 20.53. Found: Cl, 20.73. [j] Blaise, *Compt. rend.,* **152**, 269 (1911). [k] Ref. 11.

Miscellaneous Compounds.—γ-Bromopropylphenyl ether was prepared from phenol and trimethylene bromide[19]; γ-bromobutyrophenone[20] was prepared from γ-bromobutyryl chloride, benzene and aluminum chloride by the procedure[21] used for α-bromobutyrophenone; γ-

(11) Blicke and Zienty, THIS JOURNAL, **63**, 2945 (1941).
(12) Wahl and Meyer, *Bull. soc. chim.,* [4] **3**, 958 (1908).
(13) "Organic Syntheses," Coll. Vol. II, 557 (1943).
(14) Hope and Perkin, *J. Chem. Soc.,* **95**, 1364 (1909).
(15) Long and Henze, THIS JOURNAL, **63**, 1939 (1941).
(16) Kipper, *Ber.,* **38**, 2941 (1905).
(17) Fieser and Bradsher, THIS JOURNAL, **58**, 1738 (1936).
(18) Johnson, Gutsche and Offenhauer, *ibid.,* **68**, 1648 (1946).
(19) "Organic Syntheses," Coll. Vol. I, 2nd ed., 435 (1941).
(20) Perkin, *J. Chem. Soc.,* **47**, 842 (1885).
(21) Collet, *Bull. soc. chim.,* **15**, 1100 (1896).

chloropropyl benzoate[2] and γ-chloropropyl benzyl ether[22] were prepared by methods previously described. The following compounds are new and were prepared by the procedures given.

3-Hydroxybutyl Benzoate.—To a solution of 9 g. of 1,3-butanediol and 8.5 g. of pyridine in 40 ml. of carbon tetrachloride was added, with stirring and over a period of thirty minutes, 14 g. of benzoyl chloride. The resulting mixture was stirred and refluxed for fifteen minutes. Then water was added and the carbon tetrachloride layer taken up in ether. After drying and distillation of the ether extract, 10 g. (52%) of 3-hydroxybutyl benzoate, b. p. 132-133° (3 mm.), $n^{20}D$ 1.5130 was obtained.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.22; H, 7.15.

Diethylene Glycol Monobenzoate.—To a solution of 106 g. of diethylene glycol and 79 g. of pyridine in 400 ml. of carbon tetrachloride was added 140 g. of benzoyl chloride and the solution refluxed for two hours. Distillation of the reaction mixture gave 60 g. (29%) of the monobenzoate, b. p. 153-154° (2 mm.); $n^{20}D$ 1.5193. In addition to the monobenzoate a 45% yield of diethylene glycol dibenzoate, b. p. 235-237 (7 mm.); $n^{20}D$ 1.5448 was obtained.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.67; H, 6.66. Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 69.44; H, 6.00.

3-Chlorobutyl Benzoate.—To a mixture of 15.5 g. of 3-hydroxybutyl benzoate and 10 g. of pyridine was added, over a period of thirty minutes, 15 g. of thionyl chloride. The resulting mixture was stirred for an additional thirty minutes. The unreacted thionyl chloride was then removed under a vacuum, water added to the residue and the mixture extracted with ether. Distillation of the ether layer gave 7.5 g. (45%) of 3-chlorobutyl benzoate, b. p. 111-112° (3 mm.); $n^{20}D$ 1.5140.

Anal. Calcd. for $C_{11}H_{13}ClO_2$: Cl, 16.67. Found: Cl, 16.50.

2-(2-Chloroethoxy)-ethyl Benzoate.—This compound was prepared from diethylene glycol monobenzoate in the same manner as described above for 3-chlorobutyl benzoate. The product boiled at 126-127 (1.5 mm.), $n^{20}D$ 1.5183, and the yield was 73%.

Anal. Calcd. for $C_{11}H_{13}ClO_3$: Cl, 15.51. Found: Cl, 15.41.

The hydrochlorides of variously substituted piperidines listed in Table I were prepared by five general methods, illustrated by the following examples.

Method A. Reaction of a Piperidino Alcohol with an Acyl Halide; γ-(2-Methylpiperidino)-propyl p-Methylbenzoate Hydrochloride.—A solution of 13.3 g. of γ-(2-methylpiperidino)-propyl alcohol in 70 ml. of benzene was placed in a three-necked flask equipped with a reflux condenser, stirrer, and dropping funnel, and heated to refluxing. Over a period of thirty minutes 13 g. of p-methylbenzoyl chloride was added to the refluxing solution. Refluxing was continued for two hours after the addition of the acid chloride. On cooling the reaction mixture, a precipitate formed. After recrystallization from isopropyl alcohol, 18.3 g. of the desired hydrochloride was obtained.

Method B. Reaction of a Piperidinopropyl Chloride with an Acid: γ-(2-Methylpiperidino)-propyl Salicylate Hydrochloride.—In a flask fitted with a reflux condenser was placed 14.0 g. of γ-(2-methylpiperidino)-propyl chloride, 11.0 g. of salicylic acid, and 100 ml. of dry isopropyl alcohol. The mixture was refluxed for twelve hours. On cooling, a precipitate formed, which after recrystallization from isopropyl alcohol amounted to 18.5 g. of no. 9, Table I.

Method C. Reaction of a Chloroalkyl Benzoate with an Alkylpiperidine: γ-(2-n-Amylpiperidino)-propyl Benzoate Hydrochloride.—A mixture of 31.2 g. (2 mol) of 2-(n-amyl)-piperidine and 20 g. (1 mol) of γ-chloropropyl

(22) Bennett and Hock, *J. Chem. Soc.,* 472 (1927).

benzoate was heated at 175° for four hours. As heating progressed the mixture turned semi-solid due to the precipitation of 2-(n-amyl)-piperidine hydrochloride. When the reaction was complete the mixture was cooled, ether added, and the solid filtered off. Dry hydrogen chloride was passed into the filtrate and the precipitated hydrochloride recrystallized from isopropyl alcohol.

In cases where the reaction was incomplete, it was necessary to evaporate the ether filtrate from the original reaction mixture and distil off the unreacted piperidine before adding the hydrogen chloride; otherwise a practically inseparable mixture of the piperidine hydrochloride and the hydrochloride of the benzoate was obtained.

Method D. Reaction of a Piperidinoalkyl Halide with a Sodium Alkoxide: γ-(2-Methylpiperidino)-propyl Butyl Ether Hydrochloride.—To a solution of 3.8 g. of sodium in 100 ml. of n-butyl alcohol heated to refluxing was added 25 g. of γ-(2-methylpiperidino)-propyl chloride over a period of thirty-five minutes. The mixture then was refluxed for an additional six hours. After the mixture had been cooled and the sodium chloride filtered off, the filtrate was distilled. The distillate (18 g.), which boiled at 130° (9 mm.), was dissolved in dry ether and precipitated as the hydrochloride by the addition of hydrogen chloride. The resulting hydrochloride was recrystallized from an isopropanol–ether mixture.

Method E: Reaction of an Alcohol with an Isocyanate: γ-(2-Methylpiperidino)-propyl Phenylcarbamate Hydrochloride.—To 20 g. of γ-(2-methylpiperidino)-propyl alcohol was added 15 g. of phenyl isocyanate. An immediate reaction took place. The resulting product was dissolved in 150 ml. of benzene, and hydrogen chloride gas passed into the solution. The resulting solid was filtered off and recrystallized from a mixture of ethyl and isopropyl alcohols.

Summary

The physical and pharmacological properties of eighty-nine structural variations of γ-(2-methylpiperidino)-propyl benzoate hydrochloride (Metycaine) are reported. A number of the compounds are potent local anesthetics.

The relationships of the structures of these compounds to their anesthetic actions and toxicities are pointed out and discussed.

Numerous new compounds, intermediates in the preparation of these piperidine derivatives, are listed.
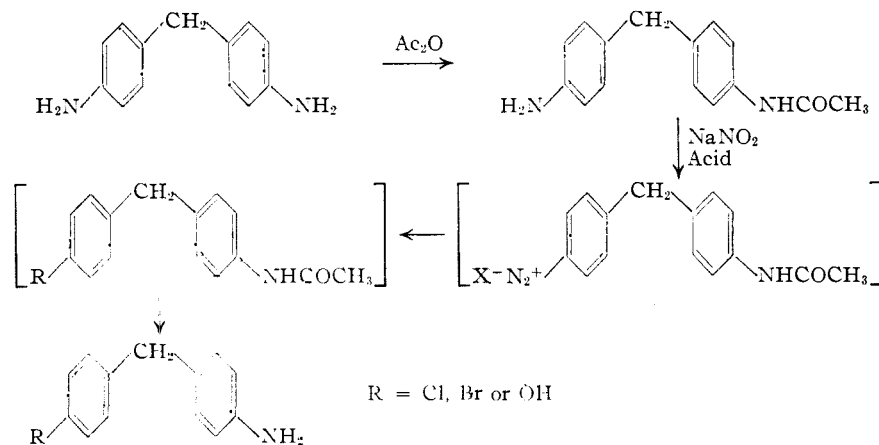

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

Substituted 4-Aminodiphenylmethanes[1]

BY C. E. KASLOW AND R. D. STAYNER[2,3]

A method has been developed for the preparation of substituted 4-aminodiphenylmethanes from 4,4'-diaminodiphenylmethane. The reaction is illustrated by the equations,

R = Cl, Br or OH

The first step in the synthesis involves the monoacetylation of 4,4'-diaminodiphenylmethane with acetic anhydride in dilute alcoholic hydrochloric acid solution in 35–43% yields. Considerable unchanged 4,4'-diaminodiphenylmethane

may be recovered from the acetylation reaction but increasing the amount of acetic anhydride serves only to increase the amount of diacetylated amine and to decrease the percentage yield of monoacetyl derivative.

The diazotization of the 4-acetamido-4'-aminodiphenylmethane proceeded smoothly and replacement of the diazonium group by chlorine and bromine atoms as well as by the hydroxy group proceeded satisfactorily. It was found more satisfactory to prepare the 4-acetamido-4'-methoxydiphenylmethane by alkylation of the 4'-hydroxy compound than by direct replacement of the diazonium group by the methoxy group. Better yields were obtained if no attempt was made to isolate the intermediate acetamido compound after replacement of the diazonium group had been carried out.

Attempts at nitration of 4-acetamido-4'-methoxydiphenylmethane gave only tars from which no identifiable substance could be isolated. Nitration of 4-acetamido-4'-aminodiphenylmethane gave a 53% yield of p-nitroacetanilide as well as some unidentified high melting material which was insoluble in all of the ordinary solvents.