NEW PIPERIDINE DERIVATIVES AS LOCAL ANESTHETICS *

C. L. Rose, A.B., T. P. Carney, Ph.D., K. K. Chen, M.D.
Indianapolis, Ind.

AND

S. M. McElvain, Ph.D.
Madison, Wis.

Received for publication June 11, 1947

In 1924, McElvain (1) elucidated the structural relationship between cocaine and substituted piperidine derivatives. He considered the latter as a portion of the ecgonine molecule, thus explaining in part the local anesthetic action of the substituted piperidines. Further work on this subject led to the introduction of 'Metycaine' [γ-(2-methyl-piperidino)-propyl Benzoate Hydrochloride, Lilly] to medicine (2). It has been used successfully in topical, (3) infiltration, and continuous caudal anesthesia (4). McElvain and Carney (5) recently extended their investigation by synthesizing 89 additional compounds, all derivatives of 'Metycaine,' differing from it by substitutions on the piperidine and the benzene rings, and by changes in the chain connecting the two rings. The present communication deals with the pharmacological comparisons of 95 substances, 5 of which were not included in McElvain and Carney's recent paper (5).

Methods

In order to avoid unnecessary testing only a few methods were adopted for the estimation of relative anesthetic potency, irritation and toxicity of various compounds. The duration of anesthesia was determined by instillation of the solutions in the rabbit's eye, and by intracutaneous injection in the guinea pig. The minimal concentration which paralyzed the rabbit's sciatic nerve was established with several compounds. These three procedures, roughly, gave information on surface, infiltration and nerve block anesthesia, respectively. In every instance the degree of irritation was observed after intracutaneous injection in the rabbit, and the acute toxicity was determined in mice by both intravenous and subcutaneous injections. One compound which showed marked activity on the rabbit's sciatic nerve was tested further

* From the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Ind., and the Department of Organic Chemistry, University of Wisconsin, Madison.

by intrathecal injections in dogs by the method of Dvorak and Manson (6). A minimum of 30 animals each was employed for toxicity tests, and a minimum of 3 animals each for other tests. All compounds were used as hydrochlorides in aqueous solution.

In the evaluation of corneal anesthesia of the rabbit, the precautions enumerated by Schmitz and Loevenhart (7) were observed. The technic of measuring skin anesthesia following intracutaneous injection in the guinea pig was previously described by one of us (C.L.R.) (8). The sciatic nerve block of the rabbit was judged by the criteria set forth by Schmitz and Loevenhart (9). The degree of irritation which developed after intracutaneous injection of each solution in white rabbits was classified arbitrarily as follows:

—	negligible:	indistinguishable from surrounding tissue;
+	slight:	a trace of hyperemia or ischemia, a point of elevation;
++	mild:	hyperemia or ischemia, fibrosis;
+++	moderate:	hyperemia or ischemia extending to more than one centimeter, fibrosis with extension; edema;
++++	severe:	necrosis, sloughing, induration, or marked edema.

The median lethal dose ($LD_{50} \pm$ Standard Error) following intravenous or subcutaneous injection in white mice was computed by the formula of Bliss (10).

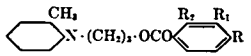
RESULTS

Table 1 lists results of tests of 34 compounds which are substituted benzoates of 3-(2-methylpiperidino) propyl alcohol. The first member, 'Metycaine,' serves as a standard of comparison. It can be observed readily that substitution of the *p*-position of the benzene ring by halogens does not appreciably improve the corneal anesthetic action but results in marked irritation to the rabbit's skin. Alkoxy radicals at the same position are apparently more desirable than alkyl substituents. The lengthening of the alkoxy chain is attended frequently by prolonged activity on the cornea, and not necessarily accompanied by increased toxicity and irritation. The most outstanding products of this series are Nos. 12 and 26. They are devoid of irritation in a 0.05 per cent solution. The benzoyl benzoate (No. 34) is appreciably active, but highly toxic. Three pairs of iodo-methoxy and *n*-butoxy benzoates (Nos. 4, 5, 8, 9, 12, and 13) illustrate the difference of *p*- and *o*-substitutions. It appears that the *p*-isomers are slightly more active on the rabbit's cornea than the *o*-isomers. This is most pronounced with the *n*-butoxy derivatives. Also, *p*-iodo, and *p*-*n*-butoxy benzoates are less toxic to mice by intravenous injection than their *o*-isomers. Of special interest are the hydroxybenzoates (Nos. 27, 28, 29, 30). Both the *o*-

and *m*-substituents are active, free from irritation, and not particularly toxic—the *o*-form being commonly known as a salicylate. Substitution by hydroxyl groups at *p*- and at both *p*- and *m*-positions, results in a loss of corneal anesthesia. The presence of a sulfhydryl group at *o*-position, too, nullifies the local anesthetic action (No. 33). Replacement of a *p*-propoxy group by *p*-allyloxy offers no special advantage as exemplified by compound No. 15.

TABLE 1

SUBSTITUTED BENZOATES OF 3-(2-METHYLPIPERIDINO)PROPYL ALCOHOL:



No.	R_2	R_1	R	Solution	Duration of Anesthesia		Irritation, Rabbit's Skin	Sciatic Nerve Block	LD_{50} ± S. E. in Mice	
					Rabbit's Eye	Guinea Pig's Skin			Intravenous	Subcutaneous
				%	min.	min.	degree	% Solution	mg. per Kg.	mg. per Kg.
1	H	H	H	1	10	32	−	0.75	22.5±1.0	589±65.0
2	H	H	Cl	1	10		+++		25.4±1.8	
3	H	H	Br	1	15		++++		28.2±2.5	
4	H	H	I	1	12		++++		48.2±1.4	
5	I	H	H	1	9		++++		23.0±1.2	
6	H	H	CH_3	1	9		+++		25.1±0.7	
7	H	H	$CH(CH_3)_2$	1	9		+++		29.5±1.2	
8	H	H	OCH_3	1	13		++	6+	21.6±1.1	
9	OCH_3	H	H	1	8		+	3	23.3±1.2	
10	H	H	$OCH_2{\cdot}CH_3$	0.5	6		++	3	21.0±0.7	120± 6.1
11	H	H	$O(CH_2)_2{\cdot}CH_3$	0.1	10		−	3	15.7±1.2	115± 2.6
12	H	H	$O(CH_2)_3{\cdot}CH_3$	0.05	14	14	−	3	22.0±1.8	177±11.8
13	$O(CH_2)_3{\cdot}CH_3$	H	H	0.1	12		++		12.4±0.4	
14	H	H	$O(CH_2)_4{\cdot}CH_3$	0.1	20		+		24.5±2.5	202±26.2
15	H	H	$OCH_2{\cdot}CH{:}CH_2$	0.25	10			3+	26.7±2.0	
16	H	H	$OCH(CH_3)_2$	0.1	15		++		26.6±2.0	217± 7.6
17	H	H	$OCH_2{\cdot}CH(CH_3)_2$	0.1	17		+		32.4±1.3	161±23.0
18	H	H	$OCH_2{\cdot}CH_2{\cdot}CH(CH_3)_2$	0.1	15		+++		31.0±1.2	
19	H	H	$O(CH_2)_5{\cdot}CH_3$	0.05	20		++		23.5±1.0	222±17.3
20	H	H	$OCH(CH_3){\cdot}CH_2{\cdot}CH_3$	0.1	15		+		22.4±0.9	270±21.1
21	H	H	$OCH(CH_3){\cdot}(CH_2)_2{\cdot}CH_3$	0.05	25	37*	++		27.7±2.1	309±48.0
22	H	H	$OCH_2{\cdot}C_6H_5$	0.1	18		+		53.5±2.1	187±11.8
23	H	H	$O(CH_2)_2{\cdot}C_6H_5$	0.1	22		++		26.1±1.9	272±28.9
24	H	H	C_6H_5	0.1	5		+		35.0±2.5	
25	H	H	$C_6H_4{\cdot}OCH_3(p)$	0.1	8		+		46.0±2.5	235±14.0
26	H	H	$OCH(CH_3)_4{\cdot}CH_3$	0.05	12	27*	−	1+	54.7±4.0	447±22.8
27	H	H	OH	1	0	25†	++	2	17.8±0.5	
28	H	OH	H	0.5	4		−	0.25	32.0±1.7	
29	OH	H	H	0.5	12		−	2	34.3±1.1	
30	OH	H	OH	1	0	8	+		15.2±1.6	
31	H	H	OC_6H_5	0.125	25		−	3+	35.0±2.4	156±17.0
32	OH	H	$O(CH_2)_5CH_3$	1	22		+++		30.7±1.9	
33	SH	H	H	1	0	15	++++		42.0±2.8	230±23.0
34	CO·C_6H_5	H	H	0.1	20		+		9.0±0.5	155±24.0

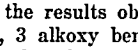
* A 0.1% solution was used.
† A 0.5% solution was used.

Table 2 summarizes data on 21 compounds consisting of 15 esters other than benzoates, 2 carbamates, 3 ethers, and one ketone, all containing the 3-(2-methylpiperidino)propyl radical. It will be noted that the majority of them are inactive. The 7 compounds (Nos. 36, 39, 44, 45, 47, 48, 55) which show evidence of corneal anesthesia are irritating to the rabbit's skin, following intracutaneous injection. The group as a whole is inferior to that in table 1.

Included in table 3 are the results obtained with 14 benzoates, 5 salicylates, 1 thiosalicylate, 3 alkoxy benzoates, 2 phenylacetates, 1 phenoxy benzoate, 1 cyclohexyloxy benzoate, and 1 nicotinate of substituted piperidino propyl alcohols. There is a suggestion that as the alkyl chain is lengthened, irritation is augmented. It is interesting to

TABLE 2

DERIVATIVES OTHER THAN BENZOATES CONTAINING THE 3-(2-METHYLPIPERIDINO)PROPYL RADICAL:



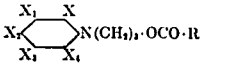
No.	R	Solution	Duration of Anesthesia		Irritation, Rabbit's Skin	Sciatic Nerve Block	LD_{50} ±S. E. in Mice	
			Rabbit's Eye	Guinea Pig's Skin			Intravenous	Subcutaneous
		%	min.	min.	degree	% Solution	mg. per Kg.	mg. per Kg.
35	OCO·C:CH·CH:CH·N:CH	1	0	8	+		100.0±8.8	500± 11.3
36	OCO·C:CH·CH:CHS	1	5		+		26.5±1.4	730± 43
37	OCO·CH_2·C_6H_5	1	0	10*	−	0.25	51.8±2.0	800± 6.4
38	OCO·CH_2·OC_6H_5	1	0	22	−	2+	36.7±2.1	
39	OCO·CH:CH·C_6H_5	1	5		+++		23.5±1.0	
40	OCO·CH_2CH_2·C_6H_5	1	0	23	−	3+	59.0±2.5	690±117
41	OCO·CH_2·$CH(CH_2)_4$·CH_2	1	0	50	++++		31.5±4.5	290± 39
42	OCO·CH_2·$C_6H_4OH(p)$	1	0	28	−	3+	74.0±3.9	1550±185
43	OCO·$CH_2C_6H_4OCH_3(p)$	1	0	7	+		42.6±3.9	235± 15
44	OCO·NH·C_6H_5	1	10		++		39.9±1.5	206± 13.2
45	OCO·NH·$C_{10}H_7(\alpha)$	0.5	12		++		24.4±1.0	109± 8.8
46	OCO·CH(C_2H_5)·C_6H_5	1	0	34	+		18.0±1.0	305± 30
47	OCO·CH_2·C_6H_4·$O(CH_2)_3$·$CH_3(p)$	0.25	3		+		29.0±5.5	275± 21
48	OCO·$CH(C_6H_5)_2$	1	18		++		27.5±1.4	
49	OCO·$(CH_2)_{12}$·CH_3	1	0	0	++++		117.0±2.7	
50	OCO·$CH(CH_2)_4$·CH_2	1	0	25	−	3+	40.0±2.0	570± 56
51	OCO·C:CH·CH:CHO	1	0	5	−	3	36.0±2.0	420± 19
52	$O(CH_2)_3$·CH_3	1	0	16	++++		17.8±0.4	
53	OC_6H_5	1	0	16	++		25.2±1.1	
54	OCH_2·C_6H_5	1	0	14	++		18.4±1.2	
55	CO·C_6H_5	1	15		++		32.5±5.5	

* A 0.05% solution was used.

observe that the phenyl derivative (No. 69) has a reasonable degree of activity, comparatively low toxicity in mice by intravenous injection, and negligible irritation. Of the 5 salicylates the 2,6-dimethylpiperidino derivative (No. 73) is the most potent, and devoid of irritation. The thiosalicylate of the same configuration (No. 80), on the other hand, is inactive on rabbit's cornea and very irritating. With the exception of No. 73, none of these compounds in table 3 is outstanding.

TABLE 3

ALKYL SUBSTITUTED PIPERIDINOPROPYL BENZOATES AND OTHER ESTERS:

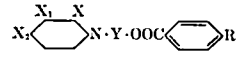


No.	X	X_1	X_2	X_3	X_4	R	Solution	Duration of Anesthesia		Irritation, Rabbit's Skin	Sciatic Nerve Block	LD_{50} ± S. E. in Mice	
								Rabbit's Eye	Guinea Pig's Skin			Intravenous	Subcutaneous
							%	min.	min.	degree	% Solution	mg. per Kg.	mg. per Kg.
56	H	CH_3	H	H	H	C_6H_5	1	8		++		34.5±1.3	
57	H	H	CH_3	H	H	C_6H_5	1	11		+++		32.0±2.8	
58	CH_3	CH_3	H	H	H	C_6H_5	1	5		−	0.5	35.0±1.7	1600±69
59	CH_3	H	CH_3	H	H	C_6H_5	0.5	6		++		28.0±1.1	
60	CH_3	H	H	CH_3	H	C_6H_5	1	12		++		23.5±0.9	
61	CH_3	H	H	H	CH_3	C_6H_5	0.5	18		−	3	21.0±0.9	
62	CH_3	H	CH_3	H	CH_3	C_6H_5	0.5	17		−	0.25	15.4±1.5	
63	$CH(CH_3)_2$	H	H	H	H	C_6H_5	1	10		+++		34.3±1.0	
64	H	H	$CH(CH_3)_2$	H	H	C_6H_5	0.5	3		++		28.4±1.0	
65	$CH(C_2H_5)_2$	H	H	H	H	C_6H_5	0.5	8		+++		17.9±0.7	
66	$(CH_2)_4\cdot CH_3$	H	H	H	H	C_6H_5	0.5	12		+++++		10.0±0.7	
67	H	H	$(CH_2)_4\cdot CH_3$	H	H	C_6H_5	0.5	13		+++++		26.7±1.3	
68	$(CH_2)_8\cdot CH_3$	H	H	H	H	C_6H_5	1	23		+++++		22.7±1.7	
69	H	H	C_6H_5	H	H	C_6H_5	0.5	10		−	3+	34.9±1.6	
70	CH_3	CH_3	H	H	H	$C_6H_4OH(o)$	0.5	10		−	0.5	18.0±1.1	345±29
71	CH_3	H	CH_3	H	H	$C_6H_4OH(o)$	1	10	45	−	3+	20.5±0.6	510±48
72	CH_3	H	H	CH_3	H	$C_6H_4OH(o)$	1	15		++		21.0±1.0	365±21
73	CH_3	H	H	H	CH_3	$C_6H_4OH(o)$	0.05	13	30*	−	0.5	34.9±1.3	386±27
74	CH_3	H	CH_3	H	CH_3	$C_6H_4OH(o)$	1	15	0	+++		27.0±1.2	510±24
75	H	CH_3	H	H	H	$C_6H_4O(CH_2)_3\cdot CH_3(p)$	0.5	10		+		27.5±1.7	
76	H	H	CH_3	H	H	$C_6H_4O(CH_2)_3\cdot CH_3(p)$	0.25	18		+		27.0±0.9	
77	CH_3	H	H	H	CH_3	$C_6H_4O(CH_2)_3\cdot CH_3(p)$	0.5	30		++++		24.4±0.8	
78	CH_3	H	H	H	CH_3	$C_6H_4OC_6H_5(p)$	0.1	30		−	3+	32.0±2.0	160±16
79	CH_3	H	H	H	CH_3	$C_6H_4O(CH_2)_3\cdot CH_3(p)$	0.5	10		−	3+	33.0±3.0	300±26
80	CH_3	H	H	H	CH_3	$C_6H_4OH(o)$	1	0	50	++++		45.0±3.0	250±12
81	CH_3	H	H	H	CH_3	$CH_2\cdot C_6H_5$	1	0	11	+		28.5±1.0	710±55.5
82	CH_3	H	H	H	CH_3	C:CH·CH:CH·N:CH (ring)	1	0	3	+		115.0±6.0	330±39.7
83	CH_3	H	H	H	CH_3	$CH_2C_6H_4\cdot OCH_3(p)$	1	0	3	+		37.0±3.2	630±39.4

* A 1% solution was used.

TABLE 4

SUBSTITUTED PIPERIDINO ALKYL BENZOATES AND *p*-BUTOXY BENZOATES:



No.	X	X_1	X_2	Y	R	Solution	Duration of Anesthesia		Irritation, Rabbit's Skin	Sciatic Nerve Block	LD_{50} ±S. E. in Mice	
							Rabbit's Eye	Guinea Pig's Skin			Intravenous	Subcutaneous
						%	min.	min.	degree	% Solution	mg. per Kg.	mg. per Kg.
84	CH_3	H	H	$(CH_2)_4$	H	1	7		++		20.5±0.6	
85	CH_3	H	H	$(CH_2)_5$	H	1	17		+		17.5±0.9	
86	CH_3	H	H	$(CH_2)_6$	H	0.5	7		++		28.0±1.5	
87	CH_3	H	H	$CH[(CH_2)_2CH_3]\cdot CH(CH_2CH_3)$	H	0.5	7		++		28.0±0.6	
88	H	H	CH_3	$(CH_2)_2\cdot CH(CH_3)$	H	1	17	23	−	0.1	18.0±1.6	350±40
89	H	H	CH_3	$CH_2\cdot CH(CH_3)\cdot CH(CH_3)$	H	0.5	12		++	2	24.0±1.3	
90	H	H	CH_3	$CH_2\cdot C(CH_3)_2\cdot CH_2$	H	1	8		+++	3+	27.4±1.9	
91	CH_3	H	H	$(CH_2)_2\cdot O(CH_2)_2$	H	1	30	15	++		20.7±5.2	ca 1500
92	CH_3	H	H	$CH_2\cdot CH(CH_3)$	H	1	3	0	++		35.8±2.3	ca 1500
93	H	CH_3	H	$(CH_2)_2\cdot CH(CH_3)$	$O(CH_2)_3\cdot CH_3$	0.1	17		+		31.5±1.7	
94	CH_3	H	H	$CH_2\cdot CH(CH_3)$	$O(CH_2)_3\cdot CH_3$	1	0	0	++		141.2±2.0	ca 800
95	H	H	CH_3	$CH_2\cdot C(CH_3)_2\cdot CH_2$	$O(CH_2)_3\cdot CH_3$	1	*		++		36.0±1.7	

* Unable to determine because the eye was continuously closed due to severe irritation.

The last series of compounds, as shown in table 4, is composed of those which have varying lengths of the chain linking the piperidine nucleus and the benzoate radical. Variation of substitution by a methyl group in the piperidine ring also takes place. One compound (No. 94) was inactive by both local application to the eye and intracutaneous injection. The remaining products with one exception show various degrees of activity but are irritating. The exception is 4-(4-methylpiperidino)-2-butyl benzoate hydrochloride (No. 88). Although it has a low degree of activity on the rabbit's cornea and guinea pig skin, it is very effective when applied to the exposed sciatic nerve of the rabbit. Intrathecal injections of this compound in dogs showed it to be active in doses of 0.225 mg. per kg. as compared to a 1.5 mg. per kg. dose of 'Metycaine.' The last substance (No. 95) is characterized by its local irritation to the rabbit's eye.

Three compounds (Nos. 12, 26, and 73), because of their desirable properties as local anesthetics, were tested in 6 human subjects by intracutaneous injection on the volar surface of the forearm according to the technic of Sollmann (11). A 0.2 per cent solution of Nos. 12 and 26 each, and a 1 per cent solution of No. 73 were employed. The duration of anesthesia was determined by stroking the injected area with a wisp of cotton. It was found that No. 12 caused complete anesthesia for an average of 31 minutes; No. 26, 58 minutes; and No. 73, 45 minutes.

One compound, No. 26, was tried on human eyes. A 0.05 per cent solution when instilled in the eye was hardly effective. A 1 per cent solution caused definite corneal anesthesia for an average of 20 minutes in 5 subjects, but was irritating.

CONCLUSION

A total of 94 compounds, related to 'Metycaine' has been studied. By comparison of corneal and sciatic nerve anesthesia in rabbits, cutaneous anesthesia in guinea pigs, spinal anesthesia in dogs, intracutaneous irritation in rabbits, and toxicity in mice, 4 compounds appear to be outstanding. They are: 3-(2-methylpiperidino)propyl *p*-butoxybenzoate, 3-(2-methylpiperidino)propyl *p*-cyclohexyloxy benzoate, 3-(2,6-dimethylpiperidino)propyl salicylate, and 4-(4-methylpiperidino)-2-butyl benzoate.

ACKNOWLEDGMENTS

We are indebted to Dr. C. C. Scott for the experiments on human subjects and to Mr. Davis Rawlings for his assistance in numerous animal experiments.

REFERENCES

1. McElvain, S. M.: J. Amer. Chem. Soc. 46: 1721–1727, 1924.
2. McElvain, S. M.: J. Amer. Chem. Soc. 49: 2835–2840, 1927.
3. Dietrich, W. C., and Beutner, R.: Anesthesiology 7: 255–259, 1946.
4. Edwards, W. B., and Hingson, R. A.: Amer. J. Surg. 57: 459–464, 1942.
5. McElvain, S. M., and Carney, T. P.: J. Amer. Chem. Soc. 68: 2592–2602, 1946.
6. Dvorak, H. S., and Manson, M. H.: Proc. Soc. Exper. Biol. & Med. 28: 344–347, 1930–31.
7. Schmitz, H. L., and Loevenhart, A. S.: J. Pharmacol. & Exper. Therap. 24: 159–166, 1924.
8. Rose, C. L.: J. Lab. & Clin. Med. 15: 128–131, 1929.
9. Schmitz, H. L., and Loevenhart, A. S.: J. Pharmacol. & Exper. Therap. 24: 167–177, 1924.
10. Bliss, C. I.: Quart. J. Pharm. & Pharmacol. 11: 192–216, 1938.
11. Sollmann, T.: J. Pharmacol. & Exper. Therap. 11: 69–80, 1918.

(*Continued from page 357*)

6. The Aspiration of Gastric Contents during General Anesthesia, William A. Weiss, M.D.

8:30 p.m. to 10:00 p.m. Open Forum on Current Problems.

1. Public Relations, R. J. Whitacre, M.D.
2. The Provisions of Personnel for the Practice of Anesthesiology, Edward B. Tuohy, M.D.
3. The Addition of Vasopressor Drugs to Spinal Anesthetic Agents, Paul Dunphy, M.D.
4. The Physical Hazards of Anesthesia, Curtiss B. Hickcox, M.D.

FRIDAY, OCTOBER 8, 1948

9:30 a.m. to 12:00 p.m. Panel Discussions.

1. Obstetrical Anesthesia, R. J. Whitacre, M.D., Moderator.

   Participants: Bert B. Hershenson, M.D.
   Robert Hingson, M.D.
   Newlin F. Paxson, M.D.
   Perry P. Volpitto, M.D.

2. Controlled Respiration, Robert D. Dripps, M.D., Moderator.

   Participants: D. Dwight Grove, M.D.
   Stevens J. Martin, M.D.
   Robert L. Patterson, M.D.
   John W. Shuman, Jr., M.D.

2:00 p.m. to 4:00 p.m. Formal Papers—Chairman, George J. Thomas, M.D.

1. The Effect of Low Blood Pressure on Coronary Blood Flow, James E. Eckenhoff, M.D.
2. Morphine Sensitivity, William T. Salter, M.D.

(*Continued on page 390*)