[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

N-METHYL-N-PHENYLALKYL-AMINO-ALKYL BENZOATES AND PARA-AMINOBENZOATES

BY ARTHUR C. COPE AND S. M. MCELVAIN

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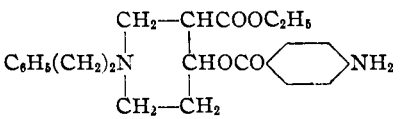
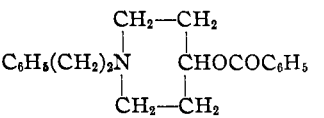
All of the pharmacological data resulting from studies of the various types of local anesthetics which have been prepared in this Laboratory have shown very definitely that unusually powerful local anesthetic action is associated with those compounds containing a phenylalkyl group attached to the basic nitrogen atom. For example, 1-phenylethyl-3-carbethoxy-4-piperidyl *p*-aminobenzoate[1] (I) and 1-phenylethyl-4-piperidyl benzoate[2] (II) show, respectively, about two and seven times the power of cocaine for mucous membrane anesthesia.



I



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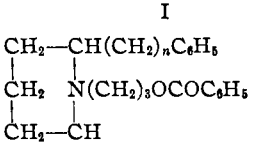
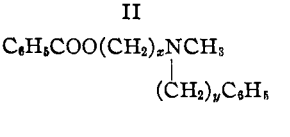


III



IV

Compounds of type III in which n is 1 or 2, were found[3] to be extraordinarily potent anesthetics, producing in 2% solution anesthesia of the rabbit's cornea that lasted from five to six days. When, however, the phenylalkyl substituent of the piperidine ring was shifted from the 2-position to the 4-position, there was a considerable diminution of the anesthetic action. This latter observation suggested that for maximum anesthetic effect the optimum number of carbon atoms in the chain between the phenyl group and the nitrogen atom would be less than five.

For this reason it seemed desirable to prepare and submit for pharmacological study a series of compounds of the procaine type in which various phenylalkyl groups would be attached to the nitrogen atom. This paper gives the preparation and a brief pharmacological report of a series of N-methyl-N-phenylalkyl-aminoalkyl benzoates (IV) in which x is 2 and 3 and y is varied from 1 to 4.

These compounds were prepared by condensing β-chloroethyl and γ-chloropropyl benzoates with the N-methylphenylalkylamines, which were

[1] Thayer and McElvain, THIS JOURNAL, **49**, 2862 (1927).

[2] Bolyard and McElvain, *ibid.*, **51**, 922 (1929).

[3] Bailey and McElvain, *ibid.*, **52**, 1633 (1930).

obtained from the hydrolysis of the N-methyl-N-phenylalkyl *p*-toluenesulfonamides. The benzoates were isolated as the hydrochlorides.

When an attempt was made to evaluate these benzoate hydrochlorides pharmacologically it was found that they produced an excessive amount of irritation in the rabbit's eye; consequently their anesthetic effect was so uncertain that any comparison on the basis of this property would have no particular meaning. For this reason the corresponding *p*-aminobenzoates were prepared in the hope that the increased basicity of the molecule would eliminate this undesirable property of the benzoates.[4] The *p*-aminobenzoates were obtained by the reduction of the corresponding *p*-nitrobenzoates. On account of the difficulties encountered in the purification of these *p*-aminobenzoates some were isolated as the monohydrochlorides and others as the dihydrochlorides.

Experimental Part

All boiling and melting points herein given are corrected.

Phenylalkylamines.—Benzylamine was prepared from benzyl chloride and hexamethylenetetramine according to the procedure of Delépine.[5] β-Phenylethylamine, γ-phenylpropylamine and δ-phenylbutylamine were prepared by the catalytic reduction of the corresponding cyanides by the method described by Carothers and Jones.[6]

N-Methylphenylalkylamines.—These amines were prepared from the phenylalkylamines by the method of Carothers, Bickford and Hurwitz.[7] This method involves the preparation of the N-phenylalkyl *p*-toluenesulfonamides, the methylation of these sulfonamides with methyl iodide to the N-methyl-N-phenylalkyl *p*-toluenesulfonamides and the hydrolysis of these latter compounds to the N-methylphenylalkylamines. The N-methylbenzylamine and N-methyl-β-phenylethylamine and the intermediate sulfonamides from which the amines were obtained have been described by these authors. The intermediate sulfonamides obtained in the preparation of N-methyl-γ-phenylpropylamine and N-methyl-δ-phenylbutylamine are new compounds and are summarized in Table I. There was one modification of the procedure necessary for the purification of the N-methyl-N-phenylalkyl *p*-toluenesulfonamides that should be noted. It was found that the N-methyl sulfonamides as obtained from the methylation reaction when the phenylalkyl group was phenylpropyl and phenylbutyl could not be caused to crystallize as they did when the phenylalkyl group was benzyl and phenylethyl. If, however, these oily sulfonamides were distilled under diminished pressure, the distillate solidified and could be recrystallized as easily as the lower homologs.

[4] *Cf.* McElvain, THIS JOURNAL, **48**, 2239 (1926).

[5] Delépine, *Bull. soc. chim.*, [3] **17**, 293 (1897).

[6] Carothers and Jones, THIS JOURNAL, **47**, 3051 (1925).

[7] Carothers, Bickford and Hurwitz, *ibid.*, **49**, 2908 (1927).

TABLE I

N-PHENYLALKYL *p*-TOLUENESULFONAMIDES AND N-METHYL N-PHENYLALKYL *p*-TOLUENESULFONAMIDES

N-substituents	Formula	M. p., °C.	B. p., °C.[a]	% S Calcd.	% S Found
γ-Phenylpropyl[b]	$C_{16}H_{19}O_2NS$	65.1–65.7	.....	11.08	10.97
δ-Phenylbutyl[c]	$C_{17}H_{21}O_2NS$	53.5–53.9	.....	10.57	10.47
Methyl and γ-phenylpropyl	$C_{17}H_{21}O_2NS$	41.8–42.4	234–238 (3 mm.)	10.57	10.48
Methyl and δ-phenylbutyl	$C_{18}H_{23}O_2NS$	60.5–61.1	241–245 (2 mm.)	10.10	9.97

[a] These boiling points were uncorrected. [b] Along with this compound was obtained a small quantity of the N-phenylpropyl di-*p*-toluenesulfonamide, $C_{23}H_{25}O_4NS_2$, m. p. 113.3–113.7°, % S, calcd., 14.46; found, 14.51. [c] There was no appreciable quantity of the corresponding disulfonamide formed in this case.

The data for the N-methylphenylalkylamines and their hydrochlorides are shown in Table II. Since the hydrochloride of the N-methyl-β-phenylethylamine was found in this work to have a considerably higher melting point than that previously reported in the literature, it is included in Table II.

TABLE II

N-METHYLPHENYLALKYLAMINES AND THEIR HYDROCHLORIDES

No.	Phenylalkyl group	Formula	B. p., °C.	d_{25}^{25}	n_D^{25}
1	β-Phenylethyl	$C_9H_{13}N$	.....	....	....
2	γ-Phenylpropyl[b]	$C_{18}H_{15}N$	85.5–86.1 (5 mm.)	0.9205	1.50877
3	δ-Phenylbutyl	$C_{11}H_{17}N$	95.0–95.4 (5 mm.)	0.9126	1.50350

No.	M_D Calcd.	M_D Found	% N Calcd.	% N Found	Hydrochloride, m. p., °C.	% Cl Calcd.	% Cl Found
1	...	...	..	..	164.1–164.9[a]	20.66	20.57
2	48.66	48.37	9.39	9.30	145.6–146.1	19.10	19.19
3	53.26	53.27	8.58	8.51	126.2–126.8	17.76	17.73

[a] The following melting points have been reported in the literature for this hydrochloride: 152–154° [Johnson and Guest, *Am. Chem. J.*, **42**, 340 (1909)]; 154–156° [Decker and Becker, *Ber.*, **45**, 2408 (1912)]; 156–157° [Decker and Becker, *Ann.*, **395**, 367 (1913)]; 155–157° [Hamilton and Robinson, *J. Chem. Soc.*, **109**, 1034 (1916)]. [b] This compound has been prepared [v. Braun, *Ber.*, **43**, 3216 (1910)] by the action of cyanogen bromide on N,N-dimethyl-γ-phenylpropylamine and was found to boil at 110° (17 mm.).

N-Methyl-N-phenylalkylaminoalkyl Benzoate Hydrochlorides.—Each of the secondary amines described in the preceding section was condensed with β-chloroethyl and γ-chloropropyl benzoates according to a method previously described.[8] The benzoates obtained were isolated as the hydrochlorides, which were formed by passing dry hydrogen chloride into an ether solution of the amino ester. These hydrochlorides were purified by recrystallization from the solvents indicated in Table III. The N-methyl-N-phenylalkyl-aminoethyl benzoates required additional purification by treatment with benzoyl chloride in the presence of sodium hydroxide in

[8] McElvain, THIS JOURNAL, **49**, 2837 (1927).

order to remove unreacted secondary amine. The yields of pure hydrochlorides were 50–75% of the theoretical. The data for these compounds are summarized in Table III.

β-Chloroethyl and γ-Chloropropyl *p*-Nitrobenzoates.—These esters were prepared by heating ethylene chlorohydrin and trimethylene chlorohydrin with *p*-nitrobenzoyl chloride. The chloroethyl ester after purification melts at 55–56°.[9] The chloropropyl ester does not appear to have been described in the literature It boils at 168.5–169.5° (2 mm.), is a liquid at ordinary temperatures, d_{25}^{25} 1.3222, n_D^{25} 1.54736, M_D calcd., 57.91, found, 58.44. *Anal.* Calcd., Cl, 14.55. Found: Cl, 14.74.

N-Methyl-N-phenylalkyl-aminoalkyl *p*-Nitrobenzoate Hydrochlorides.—While good yields of these hydrochlorides were obtained from the condensation of the chloro esters with N-methylbenzyl, β-phenylethyl, and δ-phenylbutylamines, the products of similar condensations with N-methyl-γ-phenylpropylamine could not be purified. Consequently the N-methyl-γ-phenylpropylamine was condensed with ethylene and trimethylene chlorohydrins, and the tertiary amino alcohols thus produced were esterified with *p*-nitrobenzoyl chloride. This procedure gave the hydrochlorides of the *p*-nitrobenzoates of these amino alcohols in about 90% yields. The amino alcohols are described below.

TABLE III

N-METHYL-N-PHENYLALKYLAMINO-ALKYL BENZOATE HYDROCHLORIDES

$C_6H_5COO(CH_2)_xN(CH_3)C_6H_5(CH_2)_y$

x	*y*	Formula	M. p., °C.	Recryst. solvent	% Cl Calcd.	% Cl Found
				Ether +		
2	1	$C_{17}H_{20}O_2NCl$	145.6–146.4	EtOH	11.60	11.72
2	2	$C_{18}H_{22}O_2NCl$	134.2–134.8 (Softens at 114)	EtOH	11.09	11.14
2	3	$C_{19}H_{24}O_2NCl$	106.3–107.1	*n*-BuOH	10.62	10.68
2	4	$C_{20}H_{26}O_2NCl$	106.9–107.5	*n*-BuOH	10.20	10.29
3	1	$C_{18}H_{22}O_2NCl$	145.4–146.3	EtOH	11.09	11.06
3	2	$C_{19}H_{24}O_2NCl$	128.8–129.4	EtOH	10.62	10.64
3	3	$C_{20}H_{26}O_2NCl$	117.5–118.3	*n*-BuOH	10.20	10.27
3	4	$C_{21}H_{28}O_2NCl$	124.7–125.7	*n*-BuOH	9.80	9.85

As in the case of the benzoates the condensation was more complete with γ-chloropropyl *p*-nitrobenzoate than with β-chloroethyl *p*-nitrobenzoate, making purification of the product by treatment with benzoyl chloride as well as by recrystallization necessary in the latter case. The yields of purified products were 45–70% of the theoretical.

N-Methyl-N-γ-phenylpropylaminoethanol.—Fifteen g. (0.1 mole) of N-methyl-γ-phenylpropylamine and 4.05 g. (0.05 mole) of ethylene chlorohydrin were condensed by heating for four hours at 100–120°. On diluting the reaction mixture with ether a yield of 9.35 g. of N-methyl-γ-phenylpropylamine hydrochloride was obtained after filtering and drying. The ether solution of the tertiary amino alcohol was dried over

[9] *Cf. Friedländer*, **8**, 993 (1906).

TABLE IV

N-METHYL-N-PHENYLALKYLAMINOALKYL *p*-NITROBENZOATE HYDROCHLORIDES

p-$NO_2C_6H_4COO(CH_2)_xNCH_3$ (with $C_6H_5(CH_2)_y$)

x	*y*	Formula	M. p., °C.	Recryst. solvent	% Cl Calcd.	% Cl Found
2	1	$C_{17}H_{19}O_4N_2Cl$	216.6–217.6	EtOH	10.11	10.12
2	2	$C_{18}H_{21}O_4N_2Cl$	170.9–171.9	EtOH + ether	9.72	9.70
2	3	$C_{19}H_{23}O_4N_2Cl$	122.6–123.6	*n*-BuOH + ether	9.36	9.38
2	4	$C_{20}H_{25}O_4N_2Cl$	120.6–121.6	*n*-BuOH + ether	9.03	9.08
3	1	$C_{18}H_{21}O_4N_2Cl$	206.6–207.4	EtOH	9.72	9.73
3	2	$C_{19}H_{23}O_4N_2Cl$	147.2–148.2	EtOH + ether	9.36	9.48
3	3	$C_{20}H_{25}O_4N_2Cl$	99.5–100.3	Acetone	9.03	8.98
3	4	$C_{21}H_{27}O_4N_2Cl$	159.3–160.3	*n*-BuOH + ether	8.71	8.76

sodium sulfate and distilled under diminished pressure; yield, 7.30 g. (75.3%); b. p. 132.6–133.0° (5 mm.); d_{25}^{25} 0.9883; n_D^{25} 1.51723; M_D calcd. 59.38, found 59.15; calcd. for $C_{12}H_{19}ON$: N, 7.24; found: N, 7.10.

N-Methyl-N-γ-phenylpropylaminopropanol.—From 15 g. (0.10 mole) of N-methyl-γ-phenylpropylamine and 4.75 g. (0.05 mole) of trimethylene chlorohydrin, 8.56 g. (82.9%) of N-methyl-N-γ-phenylpropylaminopropanol was obtained by the procedure described above: b. p. 147.3–147.9° (5 mm.); d_{25}^{25} 0.9785; n_D^{25} 1.51335; M_D calcd. 63.99, found 63.98. Calcd. for $C_{13}H_{21}ON$: N, 6.75; found: N, 6.57.

N-Methyl-N-phenylalkylaminoalkyl *p*-Aminobenzoate Hydrochlorides.—Those *p*-aminobenzoates which are tabulated in Table V as the monohydrochlorides were prepared by the catalytic reduction of the corresponding *p*-nitrobenzoates by a procedure previously described.[4] The other *p*-aminobenzoates shown in Table V could not be obtained crystalline from the catalytic reduction either as the monohydrochlorides or as the dihydrochlorides. It was possible, however, to obtain these aminobenzoates as crystalline dihydrochlorides from the reduction of the nitrobenzoates with iron. The procedure consisted simply of stirring the hydrochloride of the *p*-nitrobenzoate into a paste made from ten times its weight of iron powder, water, and a small amount of dilute hydrochloric acid until the heat of reaction subsided, extracting the free base with benzene, and precipitating the dihydrochloride from this benzene solution with dry hydrogen chloride. It was not possible to obtain an analytically pure

TABLE V

N-METHYL-N-PHENYLALKYL-AMINOALKYL *p*-AMINOBENZOATE HYDROCHLORIDES

p-$NH_2C_6H_4COO(CH_2)_xNCH_3 \cdot z$HCl (with $C_6H_5(CH_2)_y$)

x	*y*	*z*	Formula	M. p., °C.	Recryst. solvent	% Cl Calcd.	% Cl Found
2	1	2	$C_{17}H_{22}O_2N_2Cl_2$	209.6–210.6	EtOH	19.85	19.79
2	2	2	$C_{18}H_{24}O_2N_2Cl_2$	245.2–247.4	EtOH	19.10	18.99
2	3	2	$C_{19}H_{26}O_2N_2Cl_2$	182.3–184.3	EtOH + ether	18.41	18.26
3	1	2	$C_{18}H_{24}O_2N_2Cl_2$	219.1–220.1	EtOH	19.10	18.91
3	2	1	$C_{19}H_{25}O_2N_2Cl$	190.7–192.2	EtOH + ether	10.16	10.14
3	3	1	$C_{20}H_{27}O_2N_2Cl$	178.8–179.8	EtOH	9.77	9.76
3	4	1	$C_{21}H_{29}O_2N_2Cl$	156.0–158.0	Acetone	9.41	9.39

hydrochloride of N-methyl-N-δ-phenylbutylaminoethyl *p*-aminobenzoate from either of the reduction procedures. The yields of the monohydrochlorides after purification from the catalytic reduction were 60–70% and of the dihydrochlorides from the iron reduction 50–95% of those theoretically possible. The hydrochlorides of the *p*-aminobenzoates are summarized in Table V.

Pharmacological Report

The N-methyl-N-phenylalkylamino-alkyl benzoates and *p*-aminobenzoates are being studied pharmacologically by Mr. Charles L. Rose of The Lilly Research Laboratories, Indianapolis, Indiana. The preliminary pharmacological observations are summarized in Table VI. The corneal anesthesia values were determined by application of a solution of the anesthetic to the rabbit's cornea and noting the duration of anesthesia. In this determination a 2% solution of the benzoate hydrochlorides was used in each case, but with the *p*-aminobenzoates a 1% solution of the monohydrochloride was used on account of the low solubility of certain members of this series. The monohydrochlorides of those *p*-aminobenzoates which are listed in Table V as the dihydrochlorides were obtained by dissolving the latter salt in water and titrating off one of the

TABLE VI

PHARMACOLOGICAL DATA: N-METHYL-N-PHENYLALKYLAMINOALKYL BENZOATES AND *p*-AMINOBENZOATES

$$ARCOO(CH_2)_xN(CH_3)(CH_2)_yC_6H_5$$

AR	*x*	*y*	Av. duration of anesthesia: Corneal, minutes	Av. duration of anesthesia: Infiltration, minutes	Subcutaneous toxicity to white mice (mg./kg.) M. L. D.	Intravenous toxicity to white rats (mg./kg.) M. L. D.
Phenyl	2	1	7[a]	20[b]	3500	45
Phenyl	2	2	7	15	2500	50
Phenyl	2	3	10	12	3000	50
Phenyl	2	4	3	29	3000	50
Phenyl	3	1	9	17	2500	45
Phenyl	3	2	13	21	1800	35
Phenyl	3	3	15	34	1500	60
Phenyl	3	4	16	18	2000	50
p-Amino phenyl	2	1	16	..	400	50
p-Amino phenyl	2	2	60	..	300	30
p-Amino phenyl	2	3	27	..	200	22.5
p-Amino phenyl	3	1	21	..	150	30
p-Amino phenyl	3	2	33	..	150	14
p-Amino phenyl	3	3	32	..	200	24
p-Amino phenyl	3	4	114	..	200	22
Cocaine			29	..	150	17.5
Procaine			0	..	1000	40

[a] For those compounds in which AR is phenyl a 2% solution was used and for those in which AR is *p*-aminophenyl a 1% solution was used. [b] The doses producing the values in this column were 0.1 cc. of a 1% solution.

halogen acid molecules with standard alkali. On account of the uncertain corneal anesthesia values obtained with the benzoate hydrochlorides, the infiltration anesthesia values for these compounds as determined from intracutaneous injection into the guinea pig are included in Table VI. The toxicities as determined by subcutaneous injection into white mice and by intravenous injection into white rats are reported as minimum lethal doses in milligrams per kilogram body weight. The anesthetic and toxicity values for cocaine and procaine are included in the table for comparison.

Discussion of the Pharmacological Data.—As pointed out above, the excessive amount of irritation which was caused in the case of each of the benzoate hydrochlorides when applied to the rabbit's cornea does not allow for very much, if any, significance to be attached to these values in the above table. This undesirable property which was so pronounced in the benzoate series is entirely absent in the *p*-aminobenzoate series.

There is some indication from the data in Table VI that maximum anesthetic effect is associated with certain intermediate sizes of the phenylalkyl groups in some of the more closely related groups of compounds. For example, with the aminopropyl benzoates (AR is phenyl and x is 3) the maximum infiltration anesthetic effect is shown by the phenylpropyl group (where y is 3), and in the *p*-aminobenzoate group where x is 2 the maximum corneal anesthesia value is found where the nitrogen substituent is a phenylethyl group. Unfortunately for any generalization a similar relationship does not exist in the infiltration anesthesia values for the aminoethyl benzoates (AR is phenyl, x is 2) or in the corneal anesthesia values for the aminopropyl *p*-aminobenzoates (AR is *p*-aminophenyl, x is 3).

The extremely low toxicities of the N-methyl-N-phenyl-alkyl benzoates are worthy of note. As a group they are much less toxic than procaine both subcutaneously and intravenously. The corresponding *p*-aminobenzoates show a decidedly different and most unusual toxic effect. Their intravenous toxicities are rather low as a group, certain ones approaching the toxicity of procaine. The subcutaneous toxicities, however, are considerably higher than would be expected from the intravenous values. An outstanding case is the N-methyl-N-benzylaminoethyl *p*-aminobenzoate. This compound is about 80% as toxic as procaine intravenously but is over twice as toxic subcutaneously. It is quite probable that this unusual behavior is due to the very rapid absorption of the *p*-aminobenzoates when they are injected subcutaneously.

Summary

A series of local anesthetics of the formula, $ARCOO(CH_2)_xN(CH_3)(CH_2)_yC_6H_5$, in which AR is phenyl and *p*-aminophenyl, x is 2 and 3, and y is varied from 1 to 4 has been prepared and described.

A brief report of the preliminary pharmacological study of these compounds together with a discussion of some relationships between their structure and pharmacological action is given.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY OF AMHERST COLLEGE]

PREPARATION OF DICHLOROACETIC ACID

BY HOWARD WATERS DOUGHTY AND GERHARD JULIUS DERGE[1]

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In 1925 Doughty and Black[2] described the preparation of dichloroacetic acid by the reaction of copper powder with trichloroacetic acid or aniline trichloroacetate, in benzene. They obtained yields of aniline dichloroacetate, from which they prepared dichloroacetic acid, up to 75% of the theoretical. Other experimenters have used this method with varying success, and the irregularity of yield, as reported privately to the senior author, has led to a reëxamination of the procedure by the present authors. We first repeated the procedure of Doughty and Black and found that when insufficient hydrogen chloride is used for complete saturation in precipitating the copper chlorides and aniline hydrochloride, a complex substance containing copper and aniline is formed, which is unsatisfactory to work with. We did, however, obtain yields from 50 to 70% of the theoretical, without making especial effort for maximum yield.

The reaction of trichloroacetic acid in aqueous solution on various metals has been studied to some extent in this Laboratory, and in 1929 Doughty and Lacoss[3] showed that the reaction between trichloroacetic acid and zinc in water proceeds quantitatively according to the equation

$$2CCl_3COOH + 2Zn = (CCl_2HCOO)_2Zn + ZnCl_2$$

and it has also been found[4] that cadmium, iron and copper act similarly with trichloroacetic acid in aqueous solution, while with magnesium and aluminum considerable quantities of hydrogen are formed and the reaction is evidently more complicated. In view of the difficulties which have been reported in obtaining consistent yields by the method of Doughty and Black, we decided to investigate the reaction in aqueous solution and, if practicable, develop a procedure for the preparation of dichloroacetic acid, though earlier attempts in this direction have given low yields. It seemed possible that the hydrolysis of trichloroacetic acid to chloroform and

[1] The work here reported is in partial fulfilment of the requirement for "Honors in Chemistry" by Gerhard J. Derge. The work has been checked by Howard W. Jones, to whom we wish to express our thanks.

[2] Doughty and Black, THIS JOURNAL, **47**, 1091 (1925).

[3] Doughty and Lacoss, *ibid.*, 51, 852 (1929).

[4] Unpublished work by H. W. Doughty.