which was dried at 100° (0.1 mm.) for 3 hours over phosphorus pentoxide; yield 0.318 g. (57.3%), m.p. 178°; λ_{max} in mμ ($\epsilon \times 10^{-3}$); *p*H 1, 270 (27.0); *p*H 7, 277 (28.3); *p*H 13, 277 (28.2).

Anal. Calcd. for $C_{13}H_{19}N_5O$: C, 59.75; H, 7.33; N 26.80. Found: C, 60.15; H, 7.64; N, 27.17.

BIRMINGHAM, ALA.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE U. S. VITAMIN CORPORATION]

Local Anesthetics. I. Esters of 2-(Dialkylamino)-1-phenylethanols

BY SEYMOUR L. SHAPIRO, HAROLD SOLOWAY, EDWARD CHODOS AND LOUIS FREEDMAN

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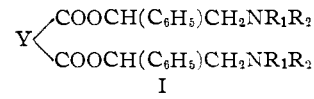
The bisesters of succinic, terephthalic and phthalic acids, and the esters of mono-, di- and trichloroacetic acids have been synthesized with the use of alcohols of the type $R_1R_2NCH_2CH(C_6H_5)OH$ and these esters have been examined for pharmacological activity. The bisesters derived from succinic acid were potent anesthetic agents and showed curarimimetic activity.

This paper evaluates the effect of substitution of $R_1R_2NCH_2CH(C_6H_5)$–[1] groups for $R_1R_2NCH_2CH_2$– in pharmacologically active systems in compounds of the type I and II



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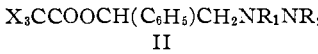

II

where Y is a residue derived from a dicarboxylic acid such as succinic, phthalic and terephthalic acid, and X_3C– represents mono-, di- and trichloromethyl groups.

Although esters of aliphatic acids[2] have generally been associated with poor anesthetic efficiency, it was of interest to explore the bisesters derived from succinic acid, particularly since the bismethyl quaternaries of structure I would be structural analogs of the clinically effective muscle relaxant, succinylcholine.[3,4]

Selected bisesters of terephthalic acid[5] have shown anesthetic potencies comparable to procaine, and similar compounds were prepared in this series. Finally, the effect of a small "fat soluble," aliphatic, hydrophobic[6] group as provided by the X_3C– substituent, was evaluated in preparation of products of the type II.

The compounds prepared of type I are described in Table I, and those of type II in Table II.

The synthesis of the compounds listed in Table I proved to be unexpectedly difficult. In general, yields were poor, ranging from 4–41%. Method A entailed treatment of succinyl chloride with the requisite 2-dialkylamino-1-phenylethanol[1] in benzene, while method B utilized the more polar solvent, acetonitrile. Method C utilized condensation of the amino alcohol with phthalic anhydride and subsequent conversion to the bisester with hydrogen chloride. Method D employed the procedure of Fusco, *et al.*,[7] wherein the hydrochloride of the amino alcohol was allowed to react with succinyl chloride in refluxing chlorobenzene.

The esters of the chloroacetic acids (II) formed readily from the corresponding acid chlorides and were obtained in 50–65% yields.

The compounds were studied for anesthetic potency using the method of Chance and Lobstein,[8] and for curare-like action using the method of Chou.[9] It was of particular interest to establish whether or not a compound would exhibit both an anesthetic and a curare effect. The pharmacological findings are reported in Table III.

In view of the marked enhancement in toxicity noted with the bis-quaternaries (compounds 5 and 6 *vs.* 4, 12 *vs.* 11), this phase of the work was not explored too extensively.

The derivatives of succinic acid (compounds 1, 4) showed excellent anesthetic activity, relative to that noted with xylocaine, while compound 3 was approximately equal to xylocaine in contrast to the derivatives of the aromatic dicarboxylic acids, which were without anesthetic effect (compounds 9, 10, 11). Compounds 1 and 4 showed good curare activity and thus make available compounds which showed both anesthetic and curare-like properties. Compound 5, the methobromide of compound 4, also showed curare-like properties but, interestingly, while it was far more toxic, it required higher levels for the curare ED_{80} than the non-quaternized structure.

The findings of significant curare-like activity in bis-tertiary amino esters is in direct contrast to the presumptive requirement of a bis-onium structure.[10,11]

The esters of the chloroacetic acids (Table II) were without significant anesthetic activity.

Experimental[12]

Di-(2-[N-isopropyl-N-methylamino]-1-phenylethyl) Succinate. Method A (Table I, Compound 2).—A solution of 7.7 g. (0.04 mole) of 2-(N-isopropyl-N-methylamino)-1-

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(2) T. E. Jones and C. O. Wilson, *J. Am. Pharm. Assoc., Sci. Ed.*, **42**, 340 (1953).

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(4) S. Norton and E. J. DeBeer, *J. Pharmacol. Exp. Therap.*, **110**, 392 (1954).

(5) W. C. North and K. F. Urbach, *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 382 (1956).

(6) R. B. Barlow, "Chemical Pharmacology," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 100.

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(8) M. R. A. Chance and H. Lobstein, *J. Pharmacol. Exp. Therap.* **82**, 203 (1944).

(9) T. C. Chou, *Brit. J. Pharmacol.*, **2**, 1 (1947).

(10) S. Loewe and S. C. Harvey, *Arch. exp. Pathol. Pharmakol. Naunyn-Schmiedeberg's*, **214**, 214 (1952).

(11) F. Brücke, *Pharmacol. Revs.*, **8**, 265 (1956).

(12) Data shown in Table I are not reproduced in the Experimental section. Typical preparations are described.

TABLE I

COMPOUNDS OF TYPE I $Y\langle^{COOCH(C_6H_5)CH_2NR_1R_2}_{COOCH(C_6H_5)CH_2NR_1R_2} \cdot 2R_3X$

No.	R_1	R_2	R_3X[a]	M.p.,[b,c] °C.	Method	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
				Y = $-CH_2CH_2-$								
1	CH_3-	CH_3-		[e1]	A	$C_{24}H_{32}N_2O_4$					6.8	6.3
2	CH_3-	i-C_3H_7-		[e2]	A	$C_{28}H_{40}N_2O_4$	71.8	71.8	8.6	8.3		
	CH_3-	i-C_3H_7-	Pic.[f]	97–200[c1]		$C_{40}H_{46}N_8O_{18}$	53.0	52.9	5.1	4.9	12.4	11.9
	CH_3-	i-C_3H_7-	HCl	223–225[c2]		$C_{28}H_{42}Cl_2N_2O_4$					5.0	5.3
3	C_2H_5-	C_2H_5-		[e3]	D	$C_{28}H_{40}N_2O_4$	71.8	71.1	8.6	8.4	6.0	5.7
4		$-(CH_2)_4-$		[e4]	A	$C_{28}H_{36}N_2O_4$					6.0	6.3
5		$-(CH_2)_4-$	CH_3Br	123–126[c3]		$C_{30}H_{42}Br_2N_2O_4$	55.1	55.4	6.5	6.8	4.3	4.1
6		$-(CH_2)_4-$	CH_3I	239–242[c4]		$C_{30}H_{42}I_2N_2O_4$	48.1	48.2	5.7	5.6	3.7	3 9
7		$-(CH_2)_6-$	HCl	204–207[c5]	B	$C_{32}H_{46}Cl_2N_2O_4$	64.7	64.1	7.8	8.3	4.7	4.3
				Y = $C_6H_4\langle^{1}_{2}$								
8	CH_3-	CH_3-	HCl	153–156[c3]	A	$C_{28}H_{34}Cl_2N_2O_4$					5.3	4.8
9	C_2H_5-	C_2H_5-	HCl	191–194[c6]	B	$C_{32}H_{42}Cl_2N_2O_4$	65.2	65.1	7.2	7.3	4.8	4.6
	C_2H_5-	C_2H_5-	Pic.[f]	148–150[c1]		$C_{44}H_{46}N_8O_{18}$	54.2	53.8	4.8	4.8	11.5	11.8
10		$-(CH_2)_4-$	HCl	201–202[c7]	C	$C_{32}H_{38}Cl_2N_2O_4$					4.8	4.9
				Y = $C_6H_4\langle^{1}_{4}$								
11	CH_3-	CH_3-	HCl	238–240[c5]	A	$C_{28}H_{36}Cl_2N_2O_5$[g]	61.0	61.1	6.6	6.7	5.1	4.8
12	CH_3-	CH_3-	CH_3I	219–221[c8]		$C_{30}H_{42}I_2N_2O_6$[h]	46.2	46.4	5.4	5.3	3.6	3.4

[a] Two equivalents of R_1R_2 and R_3X, in all instances, are present in the compound described. [b] Melting points are not corrected, and were taken on a Fisher–Johns melting point block. [c] Solvent for recrystallization: [c1] acetone–acetonitrile, [c2] isopropyl alcohol–i–propyl ether, [c3] isopropyl alcohol, [c4] methanol–methyl ethyl ketone, [c5] ethanol, [c6] ethyl acetate–ethanol, [c7] acetonitrile, [c8] ethanol–water. [d] Analyses by Weiler and Strauss, Oxford, England. [e1] B.p. 196–198° (0.02 mm.). [e2] B.p. 216–218° (0.03 mm.). [e3] B.p. 196° (0.06 mm.). [e4] B.p. 206–208° (0.05 mm.). [f] Pic. = picric acid. [g] Monohydrate. [h] Dihydrate.

TABLE II

CHLOROACETATE ESTER HYDROCHLORIDES $X_3CCOOCH(C_6H_5)CH_2NR_1R_2 \cdot HCl$[a]

No.	X_3C	R_1	R_2	M.p.,[b,c] °C.	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	$ClCH_2-$	C_2H_5-	C_2H_5-	133–139[c3]	$C_{14}H_{21}Cl_2NO_2$	54.9	54.7	6.9	7.1	4.6	4.5
2	$ClCH_2-$	$-(CH_2)_4-$		196–197[c5]	$C_{14}H_{19}Cl_2NO_2$	55.3	54.9	6.3	6.2	4.6	4.4
3	Cl_2CH-	C_2H_5-	C_2H_5	147–148[c5]	$C_{14}H_{20}Cl_3NO_2$	49.4	48.9	5.9	6.2	4.1	4.1
4	Cl_2CH-	$-(CH_2)_4-$		201–203[c5]	$C_{14}H_{18}Cl_3NO_2$	49.6	49.9	5.4	5.2	4.1	4.7
5	Cl_3C-	C_2H_5-	C_2H_5-	108–109[c3]	$C_{14}H_{19}Cl_4NO_2$	44.8	44.7	5.1	5.3	3.7	3.7
6	Cl_3C-	$-(CH_2)_4-$		136–138[c2]	$C_{14}H_{17}Cl_4NO_2$	45.1	45.1	4.6	4.4	3.8	3.9

[a] Footnotes of Table I apply to this table.

TABLE III

PHARMACOLOGICAL RESPONSE OF COMPOUNDS OF TABLE I

Table I cmpd. no.	$LD_{min.}$[a]	Anesthetic[b] ED_{50}	Curare[c] ED_{30}
1	>1000	1.7	480
3	400	9.5	0[e]
4	750	0.46	80
5	10	0	200
6	0.5	0	0[e]
9	300	0	0
10	300	0	[d]
11	1000	0	[d]
12	25	0	0
Xylocaine	225	6.8	
Tubocurarine			1.6[f]

[a] The minimal lethal dose was established (subcutaneous) in mice. [b] The effective dose in mg./ml. which reduces the number of blinks (see ref. 8) by 50% is used to express ED_{50}. [c] The effective dose in micrograms/ml. is used to express the ED_{30}. [d] Slight curare-like action at 1 mg./ml. [e] The highest dose tested was 40 micrograms/ml. [f] ED_{50} = 140 micrograms/ml.

phenylethanol[1] in 50 ml. of benzene was added over a 30-minute period to a stirred, refluxing solution of 3.1 g. (0.02 mole) of succinyl chloride in 50 ml. of benzene. After refluxing for 2 hours, a hard gum was obtained. The supernatant liquid was decanted and the residue dissolved in 100 ml. of water, cooled, made basic with 40% sodium hydroxide and extracted with five 20-ml. portions of ether. After drying the combined extracts (magnesium sulfate), the solvent was removed and the residue distilled, yielding 3.9 g. (32%) of product which boiled at 216–218° (0.03 mm.).

Di-(2-diethylamino-1-phenylethyl) Phthalate Dihydrochloride. Method B (Table I, Compound 9).—To a cold solution of 4.4 g. (0.02 mole) of phthaloyl chloride in 15 ml. of acetonitrile, 7.7 g. (0.04 mole) of 2-diethylamino-1-phenylethanol[1] in 15 ml. of acetonitrile was added during 2 hours with stirring and continued cooling. After 20 hours, the reaction mixture, treated with ether, yielded 10 g. of crude product which was dissolved in water. The solution was made alkaline with 40% sodium hydroxide and the separated base was extracted with five 10-ml. portions of ether. The combined extracts were dried (magnesium sulfate). Filtration and removal of solvent gave 6.0 g. of oil from which 1.0 g. of 2-diethylamino-1-phenylethanol was separated, b.p. 68–69° (0.08 mm.). The residue (4.0 g.) was dissolved in ethanol, cooled and 10 ml. of 10% ethanolic hydrogen chloride added. After addition of ether, the dihydrochlo-

ride precipitated as a gum which upon trituration with additional portions of dry ether yielded 4.0 g. of solid; yield after recrystallization, 9%.

Di-(2-pyrrolidino-1-phenylethyl) Phthalate Dihydrochloride. Method C (Table I, Compound 10).—A mixture of phthalic anhydride (4.55 g., 0.033 mole) and 100 ml. of toluene was stirred and heated to reflux in a flask fitted with a Dean–Stark water trap. Upon addition of 12.4 g. (0.06 mole) of 2-pyrrolidino-1-phenyl-ethanol,[1] a clear homogeneous solution was obtained. Dry hydrogen chloride was passed through the reaction mixture for a total of 32 hours with continued stirring and azeotropic reflux. A precipitate which formed immediately, remained throughout the process. Separation of water was substantially completed at the end of the 32-hour period. The precipitate was separated and triturated with ether yielding 16.4 g. of crude product; yield after recrystallization was 41%.

Di-(2-diethylamino-1-phenylethyl) Succinate. Method D (Table I, Compound 3).—A solution of 7.8 g. (0.04 mole) of 2-diethylamino-1-phenylethanol in 100 ml. of chlorobenzene was treated with 1.6 g. (0.04 mole) of dry hydrogen chloride. Succinyl chloride (3.1 g., 0.02 mole) was added at reflux temperature during a 0.5-hour period and refluxing and stirring were continued for 30 hours. At the end of this period, evolution of hydrogen chloride had practically ceased and a black, gummy reaction product had separated. The chlorobenzene was removed by decantation and the product was dissolved in water, the solution was washed with ether and made basic with 40% sodium hydroxide. The resultant oil which separated was extracted with five 20-ml. portions of ether and the combined extracts dried (magnesium sulfate). Filtration of the solution and evaporation of the solvent gave 2.4 g. of residue which was distilled to yield a small fore-run of 2-diethylamino-1-phenylethanol and then 0.9 g. (8%) of product boiling at 196° (0.06 mm.).

Di-(2-pyrrolidino-1-phenylethyl) Succinate Dimethobromide (Table I, Compound 5).—A solution of 4.3 g. (0.008 mole) of di-(2-pyrrolidino-1-phenylethyl) succinate dihydrochloride dihydrate in water was made basic with 40% sodium hydroxide and the free base extracted with ether. The ether extracts were dried (magnesium sulfate), filtered, the solvent removed and the residue of the free base was dissolved in 60 ml. of acetonitrile and treated with 3.0 g. of methyl bromide. After standing 20 hours, 3.1 g. of product was obtained; the yield after recrystallization was 52%.

2-Pyrrolidino-1-phenylethyl Dichloroacetate Hydrochloride (Table II, Compound 4).—A solution of 4.9 g. (0.033 mole) of dichloroacetyl chloride in 70 ml. of ether was cooled in an ice-bath. To this was added, with stirring, a solution of 5.8 g. (0.03 mole) of 2-pyrrolidino-1-phenylethanol[1] in 30 ml. of ether over a 20-minute period. Stirring and cooling were continued for an additional hour. The precipitate, after recrystallization from ethanol, weighed 6.9 g. (65%).

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YONKERS 1, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE U. S. VITAMIN CORPORATION]

Local Anesthetics. II.[1] Esters of 2-Amino-1-phenyl- and 2-Amino-2-phenyl-ethanols

BY SEYMOUR L. SHAPIRO, HAROLD SOLOWAY, EDWARD CHODOS AND LOUIS FREEDMAN

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A series of 2-amino-1-phenylethanols and 2-amino-2-phenylethanols have been esterified with benzoic, aryloxyacetic and cinnamic acids, and the resultant basic esters and their quaternary ammonium salts have been examined for pharmacological activity. Many compounds have been found which show a high order of local anesthetic activity, and within this series significant relationships between structure and activity are indicated. Certain compounds in this series show anti-tremorine action, hypotensive and ganglionic blocking effects, as well as adrenergic blocking and adrenergic potentiation effects.

Much of the published work on local anesthetics concerns procaine analogs of the type $RCOO–Y–NR_1R_2$ wherein R represents a substituted aryl or styryl group, Y is an alkylene radical and $–NR_1R_2$ is a secondary amino function.

This investigation was concerned chiefly with the effect on local anesthetic response when the alkylene linking element Y was varied as $–CH(R_4)CH_2–$ and $–CH_2CH(R_4)–$. The group R_4 represented phenyl, *p*-tolyl, *p*-chlorophenyl, α-naphthyl and cyclohexyl, but was largely retained as phenyl.

This structural feature of the R_4 substituent was retained throughout the work while R and $–NR_1R_2$ were varied principally to encompass factors contributing to anesthetic activity noted by other workers. In addition to the free bases and salts of the anesthetics described, a fairly broad evaluation of the quaternary ammonium salts (R_3X) was undertaken.

Typical of the compounds studied were I and II, and the products prepared have been described in Tables I and II, respectively.

$$RCOOCH(R_4)CH_2NR_1R_2\cdot R_3X \quad (I)$$

$$RCOOCH_2CH(R_4)NR_1R_2\cdot R_3X \quad (II)$$

The synthesis of the compounds listed in Tables I and II was effected by conventional procedures through reaction of the acid chloride RCOCl with the aminophenylethanol,[2] $R_1R_2NCH_2CH(R_4)OH$ or $R_1R_2NCH(R_4)CH_2OH$, with acetonitrile proving to be the preferred solvent. In most instances the hydrochloride of the desired compound precipitated or it could be recovered in sufficiently pure state for recrystallization upon evaporation of the solvent. In those instances in which the hydrochloride was not crystalline or granular, it was converted to the free base and the ester was purified by distillation.

The nitro compounds were reduced to the corresponding amino derivatives by familiar procedures.

Pharmacology.—The results and methods of the pharmacological tests have been given in Tables III and IV. The local anesthetic effect shows strong dependence on structure. Variation of the substituent R^3 correlates with Burger's[4] order in

(1) Paper I of this series, S. L. Shapiro, H. Soloway, E. Chodos and L. Freedman, THIS JOURNAL, **81**, 201 (1959).

(2) S. L. Shapiro, H. Soloway and L. Freedman, *ibid.*, **80**, 6060 (1958).

(3) For papers citing many references to this type of variation, see (a) J. S. Pierce and H. A. Rutter, Jr., *ibid.*, **74**, 3954 (1952); (b) W. H. Houff and R. D. Schuetz, *J. Org. Chem.*, **18**, 916 (1953).

(4) A. Burger, "Medicinal Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1951, p. 100.