Local Anesthetic Agents: The Chemistry and Pharmacology of Twelve Carbamates*

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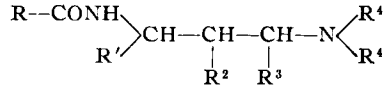
The chemistry and local anesthetic action of twelve carbamates are described. 1-(1-Phenyl-3-dimethylaminopropyl) carbanilate hydrochloride which possesses a high degree of potency and a low degree of toxicity and irritation appears to be the best local anesthetic agent of this series.

A RECENT SEARCH for local anesthetic compounds of greater potency and stability than those already available showed that certain members of a series of amides of 3-dialkylaminopropylamines (I) are particularly active in animals and elicit a minimum of undesirable reactions (1, 2).



(I)

The preparation and local anesthetic properties of a series of substituted carbamic esters, analogs in part to these amides, are reported in this paper.

EXPERIMENTAL[1]

Preparation of 3-Dialkylamino-1-phenyl-1-propanols.—These carbinols were prepared by a lithium aluminum hydride reduction of the corresponding Mannich base in ether solution. The preparation of 3-dimethylamino-1-phenyl-1-propanol will serve to illustrate the general procedure. A solution of 198 Gm. (1.1 moles) of β-dimethylaminopropiophenone in 500 ml. of ether was added dropwise with stirring to a suspension of 22 Gm. (0.58 mole) of lithium aluminum hydride in 2500 ml. of ether. The reaction mixture was refluxed for three hours and carefully decomposed by the addition of water. The ether was decanted and dried over magnesium sulfate. It was then distilled and the residual oil crystallized from Skellysolve® A, m. p. 46–47°; 189 Gm. (95%). This compound has been prepared previously by catalytic hydrogenation (3).

3-Piperidino-1-phenyl-1-propanol crystallized from Skellysolve® A, m. p. 63–64°; yield 80%.

Anal. calcd. for $C_{14}H_{21}NO$: N, 6.39. Found: N, 6.10.

3-Diethylamino-2-methyl-1-phenyl-1-propanol boiled at 112–113° (0.4 mm.); n_D^{25} 1.5039; yield 79%.

Anal. calcd. for $C_{14}H_{23}NO$: N, 6.33. Found: N, 6.03.

2-Methyl-1-phenyl-3-piperidino-1-propanol boiled at 125–126° (0.2 mm.); n_D^{25} 1.5238; yield 92%.

Anal. calcd. for $C_{15}H_{23}NO$: C, 77.21; H, 9.93. Found: C, 77.15; H, 9.85.

Preparation of 1-Dialkylamino-2,3-epoxypropanes.—The 1-dialkylamino-2,3-epoxypropanes were prepared by the procedure of Gilman (4). 1-Piperidino-2,3-epoxypropane boiled at 94–96° (20 mm.); n_D^{25} 1.4630; yield 74%.

Anal.—Calcd. for $C_8H_{15}NO$: N, 9.92. Found: N, 9.88.

1-(2-Pipecolino)-2,3-epoxypropane boiled at 115° (30 mm.); yield 21%.

Anal.—Calcd. for $C_9H_{17}NO$: N, 9.03. Found: N, 8.95.

Preparation of 3-Dialkylamino-1-phenyl-2-propanols.—The preparation of 3-piperidino-1-phenyl-2-propanol will serve to illustrate the general procedure. Phenylmagnesium bromide was prepared from 173 Gm. (1.1 moles) of bromobenzene, 27 Gm. (1.1 moles) of magnesium and 400 ml. of ether. A solution of 141 Gm. (1.0 mole) of 1-piperidino-2,3-epoxypropane in 150 ml. of toluene was added dropwise with stirring to the Grignard reagent. The reaction mixture was stirred overnight and was then poured onto dilute hydrochloric acid and ice. The acid aqueous layer was made basic with ammonium hydroxide and the resulting oil taken up in ether and dried over magnesium sulfate. The product distilled at 130° (0.4 mm.); weight 114 Gm. (52%); n_D^{25} 1.5242.

Anal.—Calcd. for $C_{14}H_{21}NO$: N, 6.39. Found: N, 6.55.

The hydrochloride melted at 180–181° and gave no mixture melting point depression with a sample prepared by the reaction of piperidine with 1-phenyl-2,3-epoxypropane according to the method of Fourneau (5).

3-Diethylamino-1-phenyl-2-propanol distilled at 105–106°; weight 124 Gm. (60%); n_D^{25} 1.5048.

Anal.—Calcd. for $C_{13}H_{21}NO$: N, 6.76. Found: N, 6.81.

3-(2-Pipecolino)-1-phenyl-2-propanol distilled at 132–133° (0.4 mm.); 156 Gm. (70%).

Anal.—Calcd. for $C_{15}H_{23}NO$: N, 6.00. Found: N, 5.67.

1-(1-Phenyl-3-dimethylaminopropyl) Carbanilate Hydrochloride.—A description of the synthesis of two of the present series, namely 1-(1-phenyl-3-dimethylaminopropyl) carbanilate hydrochloride and 2-(1-diethylamino-3-phenylpropyl) carbanilate hydrochloride (Nos. 2 and 9, respectively, of Table I) will serve to illustrate the general methods of preparation.

A solution of 366 Gm. (2.07 moles) of 3-dimethylamino-1-phenyl-1-propanol in 1.5 liters of anhydrous ether was stirred with external cooling during the dropwise addition of 279 Gm. (2.34 moles) of phenylisocyanate. After standing at room temperature for twenty-four hours, the reaction mix-

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[1] Melting points and boiling points are uncorrected.

TABLE I.—CHEMICAL AND PHYSICAL CHARACTERISTICS OF TWELVE CARBAMATES

$$R_1NHCO-O-CH(R_2)-CH(R)-R_3$$

Compd. No.	R	R_1	R_2	R_3	m. p. °C.	% Yield	Formula	% Nitrogen Calcd.	% Nitrogen Found	% Halogen Calcd.	% Halogen Found
1	C_6H_5	C_6H_5NHCO-	H	$C_5H_{10}NCH_2-$[c]	230–231	55	$C_{21}H_{26}N_2O_2\cdot HCl$	7.47	7.53	9.46	9.41
2	C_6H_5	C_6H_5NHCO-	H	$(CH_3)_2NCH_2-$	169–170	89	$C_{18}H_{22}N_2O_2\cdot HCl$	8.37	8.13	10.59	10.43
3	C_6H_5	C_6H_5NHCO-	CH_3	$(C_2H_5)_2NCH_2-$	183–184	55	$C_{21}H_{28}N_2O_2\cdot HCl$	7.43	7.23	9.41	9.23
4	C_6H_5	C_6H_5NHCO-	H	$C_4H_8NCH_2-$[d]	201–202	94	$C_{20}H_{24}N_2O_2\cdot HCl$	7.76	7.56	9.83	9.83
5[a]	C_6H_5	C_6H_5NHCO-	CH_3	$C_5H_{10}NCH_2-$[c]	229–230	59	$C_{22}H_{28}N_2O_2\cdot HCl$	7.20	7.17	9.12	9.14
6[b]	C_6H_5	C_6H_5NHCO-	CH_3	$C_5H_{10}NCH_2-$[c]	223–224	68	$C_{22}H_{28}N_2O_2\cdot HBr$	7.20	7.01	9.12	8.83
7	C_6H_5	C_2H_5NHCO-	H	$C_5H_{10}NCH_2-$[c]	134–135	33	$C_{17}H_{26}N_2O_2\cdot HBr$	7.54	7.27	21.58	21.59
8	C_6H_5	C_6H_5NHCS-	H	$C_5H_{10}NCH_2-$[c]	170–171	50	$C_{21}H_{26}N_2OS\cdot HCl$	7.17	6.98	...	...
9	$C_6H_5CH_2$	C_6H_5NHCO-	H	$(C_2H_5)_2N-$	159–160	58	$C_{20}H_{26}N_2O_2\cdot HCl$	7.72	7.86	9.77	9.75
10	$C_6H_5CH_2$	C_6H_5NHCO-	H	$C_5H_{10}N-$[e]	190–191	15	$C_{21}H_{28}N_2O_2\cdot HCl$	7.47	7.56	9.46	9.32
11	$C_6H_5CH_2$	C_6H_5NHCO-	H	$CH_3C_5H_9N-$[f]	194–195	30	$C_{22}H_{28}N_2O_2\cdot HCl$	7.20	7.44	9.12	9.08
12	H	C_6H_5NHCO-	H	$(CH_3)_2N-$	162–163	76	$C_{11}H_{16}N_2O_2\cdot HCl$	11.45	11.13	14.45	14.48

[a] *α-dl* isomer. [b] *β-dl* isomer. [c] Piperidinomethyl. [d] Pyrrolidinomethyl. [e] Piperedino. [f] 2-Pipecolino.

ture was poured onto ice and hydrochloric acid. The aqueous phase was separated, washed with ether, and then made alkaline with concentrated ammonium hydroxide. The liberated oil was taken up in ether and dried over magnesium sulfate. Then the filtered ether solution was saturated with anhydrous hydrogen chloride to yield 1-(1-phenyl-3-dimethylaminopropyl) carbanilate hydrochloride. After two recrystallizations from isopropanol-ether solution the product melted at 169–170°; weight 61.4 Gm. (89%).

A solution of 20.7 Gm. (0.1 mole) of 1-diethylamino-3-phenyl-2-propanol in 100 ml. of ether was prepared and 13.8 Gm. (0.12 mole) of phenylisocyanate was added dropwise with stirring. After standing for two hours the solution was poured onto ice and hydrochloric acid. The aqueous phase was made alkaline with concentrated ammonium hydroxide and the liberated oil was taken up with ether and dried over anhydrous magnesium sulfate. 2-(1-Diethylamino-3-phenylpropyl) carbanilate hydrochloride was prepared by saturating this dried ether solution with anhydrous hydrogen chloride. After four recrystallizations from ethanol-ether solution, the preparation melted at 159–160°, weight 21 Gm. (58%).

Local Anesthetic Action.—The compounds were dissolved in distilled water and tested for local anesthetic activity, irritation, and acute toxicity. The duration of anesthesia was assayed by topical application to the eyes of guinea pigs and by intracutaneous injection of 0.1 ml. in the same animals. At least three animals were used for each concentration of a compound, and averages of the results are recorded in Table II.

Irritation.—This was studied by means of intracutaneous injections of 0.1 ml. of the anesthetic solutions in shaved white rabbits. The criteria for assessing the degrees of irritation were published earlier (2, 7). Suffice it to say that a degree of irritation greater than "mild," that is "moderate" or "severe," would make that particular concentration of the compound unsuitable for clinical appraisal.

Acute Toxicity.—As indicated in the table, this was determined by intravenous and subcutaneous injections in white mice. The LD_{50} ± standard error was established by the method of Bliss (6).

DISCUSSION

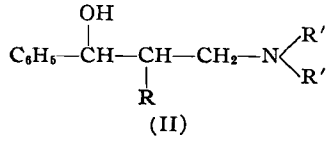
3-Dialkylamino-1-phenyl-1-propanols (II) were prepared by the lithium aluminum hydride reduction of the corresponding Mannich bases. 3-Dialkylamino-1-phenyl-2-propanols (III) were prepared by the reaction of phenyl Grignard reagent with a 1-dialkylamino-2,3-epoxypropane. The aminocarbinols were then allowed to react with phenyl isocyanate to yield the desired carbanilates. These are summarized in Table I.

On the basis of their local anesthetic activity, four of these compounds are of particular interest. Compound No. 2, Table II, 1-(1-phenyl-3-dimethylaminopropyl) carbanilate hydrochloride, seems to be outstanding in this series in that it causes more than four hours of anesthesia when injected in the guinea pig's skin; 0.5 hour, when instilled in the eyes of the same animals; and negligible irritation, when

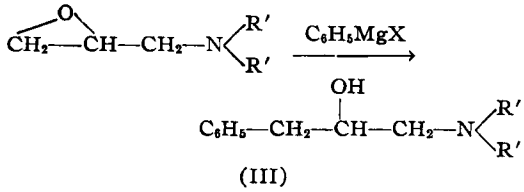
TABLE II.—LOCAL ANESTHETIC ACTION, IRRITATION, AND TOXICITY OF TWELVE CARBAMATES

Compd. No.	Per Cent Solution	Duration of Anesthesia (Min.) Guinea Pigs Eyes	Duration of Anesthesia (Min.) Guinea Pigs Skin	Irritation Rabbit's Skin Degree	LD_{50} ± S. E. Mice (mg./Kg.) I. V.	LD_{50} ± S. E. Mice (mg./Kg.) S. C.
1	1.0	296[a]	355	Moderate	28.8 ± 1.2	265 ± 22
	0.25	116	164	Negligible		
	0.10	58	61	Negligible		
	0.05	16	22	Negligible		
2	1.0	84	522	Moderate	44.0 ± 2.5	250 ± 14
	0.5	50	344	Mild		
	0.25	29	258	Negligible		
	0.10	0	135	Negligible		
	0.05	0	39	Negligible		
3	1.0	90	436	Moderate	22.0 ± 1.0	325 ± 19
	0.5	63	307	Moderate		
	0.25	44	203	Negligible		
	0.10	28	77	Negligible		
	0.05	5	16	Negligible		
4	1.0	157	520	Severe	27.0 ± 1.2	270 ± 43
	0.5	69	265	Mild		
	0.25	40	136	Negligible		
	0.10	10	63	Negligible		
	0.05	0	19	Negligible		
5	1.0	83	420	Moderate	21.8 ± 0.7	258 ± 14.8
	0.25	52	286	Mild		
	0.10	24	208	Negligible		
	0.05	10	66	Negligible		
	0.025	0	11	Negligible		
6	1.0	214	376	Moderate	12.0 ± 0.7	301 ± 18.1
	0.25	92	177	Moderate		
	0.10	62	74	Mild		
	0.05	44	49	Slight		
	0.025	14	18	Negligible		
7	1.0	0	63	Negligible	52.0 ± 0.9	553 ± 50
	0.5	0	29	Negligible		
	0.25	0	10	Negligible		
8	1.0	130[a]	245	Severe	18.5 ± 1.9	140 ± 25.1
	0.25	50[a]	70	Severe		
	0.10	10	25	Severe		
9	1.0	73	420	Slight	16.5 ± 0.9	120 ± 13
	0.5	30	285	Slight		
	0.25	16	185	Slight		
	0.10	9	57	Slight		
	0.05	0	23	Slight		
10	1.0	43	480+	Slight	16.2 ± 4.4	111 ± 11.7
	0.25	12	125	Slight		
	0.10	0	43	Slight		
11	1.0	267	455	Slight	12.8 ± 1.0	72.5 ± 8.8
	0.25	87	184	Negligible		
	0.10	57	72	Negligible		
	0.05	33	37	Negligible		
12	1.0	7	8	Negligible	128 ± 5.9	339.2 ± 37.3

[a] Severe irritation.



(II)



(III)

given in 0.25% concentration by intradermal injection in white rabbits. Its intravenous toxicity in mice is relatively low.

Compound No. 9, 2-(1-diethylamino-3-phenylpropyl) carbanilate hydrochloride, is of the same general order of local anesthetic potency as No. 2, but a little more irritating on injection, and considerably more toxic.

Compound No. 7, 1-(1-phenyl-3-piperidinopropyl) ethyl carbamate hydrobromide, has the same order of toxicity, irritation and local anesthetic action as procaine hydrochloride. Like procaine, a one per cent solution shows no local anesthetic action on the guinea pig's cornea.

Compound No. 8, 1-(1-phenyl-3-piperidinopropyl) thionocarbanilate hydrochloride, is an active local anesthetic agent but produces severe irritation to both the eye and the skin.

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A Review of Anthraquinone Compounds in Lichens*

By SANKARA SUBRAMANIAN†

LICHENS are a class of thallophytes that inhabit the soil, rock, wood, trees, etc. The vegetative thallus is of varying form and color. Lichens differ from all other members of the vegetable kingdom in their composite structure, being formed from the union of two separate plants, an alga and a fungus in intimate symbiotic relationship. In each case the fungus receives its food from materials made by the alga (usually blue-green and the protococcus form of green alga) and in return extracts water from the substratum and shares it with the alga. The association is therefore one of mutual benefit.

Depending upon the type of fungus associated with the alga, there are two distinct classes of lichens, Ascolichens and Basidiolichens. According to the manner of growth and the form of the thallus and its attachment to the substratum, three different sub-groups of lichens may be distinguished. They are foliaceous, crustaceous, and fruticose, and reproduce either by producing spores or by detaching scale-like portions of their bodies; the reproduction may be sexual or asexual.

Lichens have been employed from very early times in medicine, the dyeing industry, perfumery, and as food stuffs (1, 2). As reserve carbohydrates they possess lichenin and isolichenin in the place of starch. The use of certain lichens in perfumery has in the last few years become considerably important, in which case these species are principally found on oak trees. *Evernia*, *Ramalina* and *Usnea* species are among the principal ones employed for this purpose. The dyes cudbear and orchil are ob-obtained from *Lecanora* and *Roccella* species. Even today litmus, a lichen product, is greatly valued in analytical chemistry. Medicinally the use of lichens can be traced back to a very remote age, e.g., as far back as 1700 B. C. *Cetraria islandica*, *Lobaria pulmonaria* and *Usnea* species have been extensively used as demulcents, tonics, febrifuges, purgatives, and antitubercular drugs. Lichens have also been assayed for their vitamin content by nutritionists. Recently Seshadri and Subramanian (3) reported on the isolation of β-carotene, a precursor of Vitamin A, from *Roccella montagnei* and found this constituent in amounts of 30 mg. per cent.

LICHENS AND ANTIBACTERIAL ACTIVITY

Since the discovery of a whole series of antibiotic substances, e.g., penicillin and streptomycin, which represent products of mold metabolism and the reported antibacterial property of the green alga, chlorella, much attention has been focussed on the antibacterial properties of lichen substances. Burkholder and co-workers (4) initiated the study of crude extracts of lichens as antibacterial agents against several typical micro-organisms. Since then extensive studies on lichen substances have been made by other investigators all over the world.[1] As early as 1939, Fuzikawa and co-workers reported on the antimicrobial activity of orcinol carboxylic acid derivatives. The lichen acids which are derivatives of phenol carboxylic acids naturally have certain antibacterial properties. Most of the lichen substances show more or less antibacterial effect against Gram-positive organisms, but not against Gram-negative bacteria. The more promising compounds having pronounced antitubercular activity are usnic acid and its derivatives and derivatives of roccellic acid. Though they are antagonized by components of the serum *in vitro*, they still have positive activity *in vivo*. Systematic studies on the antibacterial effects and the chemical constitution of various lichen substances are being reported and attempts are being made to synthesize simpler compounds having close structural relationship with natural products found in lichens. Here it may be pointed out that a fruitful line of work

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† Department of Pharmacy, Andhra University, Waltair, India. Visiting Foreign Operations Administration and U. S. Public Health Service Post-Doctorate Fellow in Pharmacognosy, College of Pharmacy, University of Washington, Seattle (1955).
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[1] See Asahina, Y., and Shibata, S., "Chemistry of Lichen Substances," Japan Society for the Promotion of Science, Tokyo (1954), pp. 216–224.