A Study of Monoalkylcarbamates as Local Anesthetics*

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A series of 21 new monoalkylcarbamic acid esters of some tertiary-amino alcohols has been prepared. Two new ureas have been isolated and identified. Single pharmacological tests have been made with each compound using three methods: the rabbit cornea, the guinea pig wheal, and the Rider frog. The results indicate that some of the compounds are local anesthetics and that further pharmacological study of the series is warranted.

A NUMBER of studies have been made of the local anesthetic activity of arylcarbamic acid esters of aminoalcohols. Only three references to analogous monoalkylcarbamic acid esters have been found in the literature (1-3). Of these, 2-diethylaminoethyl 2-propylcarbamate (2) was tested as a local anesthetic; however, no specific statement was made concerning its activity. In the present investigation we have undertaken the synthesis of a series of these compounds, the majority of which are of the general type, $RNHCO_2C_nH_{2n}NR_2$. The work accomplished extends this series to the higher alkyl-, branched alkyl-, and unsaturated alkylcarbamic acid esters of some of the more important tertiary-amino alcohols. The general reactions involved in their synthesis are written below in which R = alkyl and R′ = dialkylaminoalkyl except for 3-piperidino-1,2-propanediol monononylcarbamate in which R′ is the piperidinoalkyl.

$$RCO_2H \xrightarrow{SOCl_2} RCOCl \xrightarrow{NaN_3} RCON_3 \xrightarrow{\text{heat}} RNCO$$

$$RNCO + HOR' \longrightarrow RNHCO_2R'$$

EXPERIMENTAL

The methods used in the synthesis of 2-diethylaminoethyl heptylcarbamate exemplify the general methods used throughout the work.

Preparation of Octanoyl Chloride.—The acid chloride is prepared from 29.5 Gm. (0.25 mole) of thionyl chloride and 33.0 Gm. (0.23 mole) of octanoic acid without the use of a solvent. A yield of 32.3 Gm. (0.20 mole) of octanoyl chloride, b. p. 90–95°/15 mm., is obtained. This represents a yield of 87% of the theoretical based on the acid used.

Preparation of Heptyl Isocyanate.—A mixture of 17.0 Gm. (0.26 mole) of activated sodium azide and 50 cc. of toluene, previously dried over sodium and distilled, is reacted with 32.3 Gm. (0.20 mole) of octanoyl chloride as in the Curtius reaction (4). Slight heating of the resultant mixture initiates a reaction which lasts an hour. The mixture is then heated for an additional ninety minutes, after which it is cooled and filtered and the toluene removed *in vacuo*. Distillation gives 17.5 Gm. (0.12 mole) of a colorless, limpid, sweet-smelling, lacrymatory liquid which boils at 83.5°/15 mm. The yield based on octanoyl chloride is 60%.

Preparation of 2-Diethylaminoethyl Heptylcarbamate.—To 14.2 Gm. (0.10 mole) of heptyl isocyanate in 25 cc. of dry toluene is added 14.0 Gm. (0.12 mole) of 2-diethylaminoethanol. Dry hydrogen chloride gas is later passed into half of the toluene solution for thirty minutes and the product is allowed to stand overnight. Additional HCl gives no further precipitation. The precipitate is collected giving 2.1 Gm. of a product which is recrystallized from chloroform twice and from dry acetone four times, m. p. 127.5 to 130.5°. The remaining toluene solution of the free base is fractionated and 6.4 Gm. of a product, b. p. 156–157°/1 mm., is obtained. The yield is 32% of the theoretical based on the isocyanate.

The dihydrogencitrate is prepared by adding a saturated solution of citric acid to the free base dissolved in dry ether until precipitation is completed. The citric acid solution is prepared by dissolving the acid in a mixture of 10% anhydrous methanol and 90% anhydrous ether. The above precipitate is washed several times with dry ether or petroleum ether and then recrystallized several times from a mixture of ethyl acetate and anhydrous methanol (20:1). The product is a white crystalline material, m. p. 100.5 to 101.5°.

Anal.—Calcd. for $C_{20}H_{36}O_9N_2$: N, 6.22. Found: N, 6.20; 5.81.

DISCUSSION

In most syntheses it was necessary to reflux the acid azide for three hours in order to complete the decomposition to isocyanate. Attempts to prepare isocyanates in a benzene solution were unsuccessful. Repetition of one such unsuccessful attempt using toluene instead of benzene was successful. The additional heat thus afforded is apparently desirable for efficient formation of the acid azide as well as for its subsequent decomposition.

* Received May 5, 1950, from the Research Laboratories, Purdue University, School of Pharmacy, Lafayette, Ind.
Presented to the Scientific Section A. Ph. A., Atlantic City meeting, May, 1950.
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‡ The authors are indebted to Dr. L. D. Edwards for his suggestions concerning the pharmacological work and to the Wm. S. Merrell Co. and Rohm and Haas, Inc., for supplying some of the materials.

TABLE I.—SUMMARY OF EXPERIMENTAL DATA OBTAINED

Compound Prepared	B. P. and/or M. P.	HCl Salt M. P.	Citrate M. P.	Analysis for —Nitrogen[a]— Calcd.	Found	Yield, %
2-Diethylaminoethyl butylcarbamate	124.5–126.5/ 2 mm.	91.5–94.5	...	11.08	11.31[c]	74
3-Diethylaminopropyl butylcarbamate	...	108.5–113.0	53.0–55.0	10.51	10.26[c]	
2-Diethylaminoethyl pentylcarbamate	157.5–159.5/ 2–3 mm.	...	105.5–106.5	12.16	11.91[b]	68
3-Diethylaminopropyl pentylcarbamate	166.0–167.5/ 2 mm.	...	65.5–67.5	6.42	6.21[d]	90
2-Diethylaminoethyl hexylcarbamate	136.5/2 mm.	...	101.0–102.5	11.47	11.28[b]	51
3-Diethylaminopropyl hexylcarbamate	150.5–152.5/ 2 mm.	...	...	10.85	10.75[b]	62
2-Diethylaminoethyl heptylcarbamate	156.0–157.0/ 1 mm.	127.5–130.5	100.0–101.5	6.22	6.01[d]	32
3-Diethylaminopropyl heptylcarbamate	m. p. 90.0–91.5	...	77.5–80.5	10.29	10.48[b]	93
2-Diethylaminoethyl octylcarbamate	...	...	94.0–96.0	6.03	6.12[d]	90
3-Diethylaminopropyl octylcarbamate	...	...	80.5–82.5	5.85	5.80[d]	92
2-Dimethylaminoethyl octylcarbamate	...	95.0–97.0	...	9.98	10.06[c]	92
2-Diethylaminoethyl nonylcarbamate	m. p. 88.5–93.5	97.5–99.5	104.5–106.0	8.68	8.57[c]	78
3-Diethylaminopropyl nonylcarbamate	m. p. 96.5–97.5	...	76.0–77.5	9.32	9.21[b]	80
3-Piperidino-1,2-propanediol monononylcarbamate	...	97.0–102.5	...	7.69	7.68[c]	92
2-Diethylaminoethyl 9-decenylcarbamate	...	127.5–130.5	...	8.37	8.15[c]	7
2-Diethylaminoethyl 3-pentylcarbamate	122.5–124.5/ 2 mm.	...	80.5–82.5	12.16	12.09[b]	62
3-Diethylaminopropyl 3-pentylcarbamate	140.0–144.0/ 4 mm.	...	97.0–99.5	11.46	11.14[b]	57
2-Diethylaminopropyl 3-pentylcarbamate	113.5–116.5/ 2 mm.	...	...	11.46	11.30[b]	57
2-Diethylaminoethyl 2,4,4-trimethylpentylcarbamate	146.5–147.5/ 10 mm.	108.0–109.5	...	9.07	8.88[c]	51
3-Diethylaminopropyl 2,4,4-trimethylpentylcarbamate	151.5–152.5/ 13 mm.	...	82.5–86.5	5.85	5.85[d]	56
2-Dimethylaminoethyl 2,4,4-trimethylpentylcarbamate	126.5–128.5/ 8 mm.	124.5–126.5	...	9.98	9.66[c]	55

[a] All analyses were made at least in duplicate and the values, reported as per cents, are averages.
[b] Analyzed as the free base.
[c] Analyzed as the hydrochloride.
[d] Analyzed as the dihydrogencitrate.

Isocyanates were isolated in the crude form several times but distillation did not give analytically pure products. It is suggested that the isocyanates be used directly for the next step, without attempting isolation. Their reactions with aminoalcohols were carried out at room temperatures for from twenty-four to forty-eight hours in most cases.

Carbamates prepared in commercial anhydrous ether solution more often contain appreciable amounts of symmetrical ureas as impurities than do those prepared in anhydrous toluene. Apparently sufficient moisture is present in the former to cause the reaction $2RNCO + H_2O \rightarrow RNHC(O)NHR + CO_2$ to occur. Nonhygroscopic solvents, properly dried, will eliminate this side reaction to a great extent. N,N′-Dihexylurea and N,N′-dinonylurea were isolated and identified in two instances where ether was used as a solvent.

Product	M. P.	Analysis for N Calcd.	Found
N,N′-dihexylurea	74.5–75.5°	12.27	12.29
N,N′-dinonylurea	96.0–97.5°	8.96	8.75

The lower molecular weight carbamates can be purified by distillation at reduced pressures. Some of the higher molecular weight carbamates can be crystallized as the free bases. Although some hydrochloric acid salts were successfully prepared, the citric acid salts are more readily ob-

tained. The hydrochlorides were best prepared by adding a cold, dry ethereal solution of hydrochloric acid to a cold, dry ethereal solution of the free base. The results obtained are summarized in Table I.

Preliminary pharmacological testing was carried out using the rabbit cornea method (5), the guinea pig wheal method (6), and the Rider frog method (7). Single tests were made on each new carbamate using all three methods in an attempt to determine whether further study of the compounds as local anesthetics is warranted. The results indicate that some of the compounds are local anesthetics and that further pharmacological investigation of the series is warranted.

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Studies on *Mahonia* Genus. II. Botany and Chemistry of *M. acanthifolia* Don*

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***Mahonia acanthifolia* Don is usually confused with *M. nepalensis* D. C. It has been shown by the isolation of the alkaloids of *M. acanthifolia* that this plant may be differentiated from *M. nepalensis*.**

THE species *M. acanthifolia* (family *Berberidaceae*) was described first in 1831 by Don (1) who recognized this as a species distinct from *M. nepalensis* of De Candolle (2). In 1855, Hooker and Thomson (3), however, described the present *M. nepalensis* as *Berberis nepalensis* Spreng and changed *M. acanthifolia* to *B. nepalensis*. Since then all the later workers followed this opinion until 1902, when Fedde (4) recommended that *Mahonia* should be treated separately from *Berberis*. The former genus was distinguished from the latter by its imparipinnate leaves, the terminal inflorescence, and the absence of spines (5). Since then only one species of *Mahonia*, e.g., *M. nepalensis*, was known to be a native of India, and this species was supposed to be distributed over the whole range of the Himalayas, Nepal, and Assam. According to Takeda (6), true *M. nepalensis* had never been found outside Nepal andtrue specimens were those collected from Nepal by Buchanon in 1802 and by Wallich in 1821. *Mahonia acanthifolia* described by Don (1), which was formerly thought to be synonymous with *M. nepalensis* D. C., was found to be most widely distributed from Nepal, Darjeeling to Assam, and Kumaon. The present authors, however, collected specimens of *M. nepalensis* from Darjeeling where it grew side by side with *M. acanthifolia;* the former species was of stunted growth and did not usually flower in Darjeeling. A field observation of the living plants of both the species, which are not easily distinguished without examination of flowers, showed that the midribs of the young leaves and young leaflets of *M. nepalensis* are coppery red in color which lasted for a year or so and disappeared as the leaflets and leaves matured. Those of *M. acanthifolia*, however, were greenish white.

Mahonia acanthifolia could be distinguished from *M. nepalensis*, by an examination of their flowers. In the absence of flowers, it appeared difficult to identify the mature plants from the leaflets. Table I shows the points of difference of these two plants.

Both the species show great similarities in their anatomical structures and in the distribution of the alkaloids in the different cells. The fibrous and main roots showed that the outer cells of cortical tissues contained a fair concentration of the alkaloids, whereas the central cells were comparatively free. Many isolated cells of the cortex, cells on the inner side of the phellogen, and cell walls near the pith showed a larger accumulation of the alkaloids.

* Received December 10, 1949, from the Departments of Chemistry, University College of Science and Technology, and Presidency College, Calcutta, India.
† The authors are indebted to Dr. S. K. Mukerjee, Herbarium Curator, Royal Botanic Garden, Sibpur, Calcutta, for critical suggestions on botanical matter and to Dr. N. K. Sen, Head of the Department of Chemistry, Presidency College, for providing them with laboratory facilities. R. Chatterjee acknowledges with thanks an ICI Research Fellowship of the National Institute of Sciences of India, during the progress of this work.