[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Urethans as Local Anesthetics. V. Alkyl γ-Diethylaminopropylcarbamates

BY R. L. SHRINER AND J. H. HICKEY

Although numerous urethans containing aryl residues have been synthesized and their pharmacological action studied, very few purely aliphatic urethans have been examined and none has been prepared which contained a basic amino group in addition to the urethan grouping. The present communication describes the synthesis and tests on a series of urethans of formula I.

$(C_2H_5)_2N(CH_2)_3NHCOOR$ (I) $\quad p\text{-}H_2N\text{—}C_6H_4\text{—}NHCOOR$ (II)

This particular series was made in order to have low molecular weight compounds which would be fairly soluble in water. It was also desired to determine whether these urethans would be as irritating to the tissues as the *p*-aminophenylurethans[1] of formula II.

The series of alkyl γ-diethylaminopropylcarbamates was synthesized by treating γ-bromopropylphthalimide, obtained from potassium phthalimide and trimethylene bromide, with diethylamine. Hydrolysis of the resulting γ-diethylaminopropylphthalimide yielded γ-diethylaminopropylamine. Treatment of the latter with the alkyl chlorocarbonates in the presence of potassium carbonate produced the alkyl γ-diethylaminopropylcarbamates of formula I.

Although the compounds are new, each step in the synthesis represents a well-known reaction which was carried out by modifications of methods already described. The procedures used and the properties and analyses of the urethans are summarized in Table II of the experimental part.

Aqueous solutions of these urethans were alkaline and hence they were adjusted to a *p*H of 7.0 for the pharmacological tests. Through the courtesy of the Lilly Research Laboratories the local anesthetic action of these compounds was studied. The results are summarized in Table I.

The pharmacological data show that the toxicity increases with increase in length of the alkyl group. It is of interest that no topical anesthesia was shown until the *n*-hexyl derivative was reached. No regular variations in injection anesthesia occur. All these urethans were irritating to some extent.

(1) Horne, Cox and Shriner, THIS JOURNAL, **55**, 3435 (1933).

TABLE I

LOCAL ANESTHETIC EFFECT OF $(C_2H_5)_2N\text{—}CH_2CH_2CH_2\text{-}NHCOOR$ IN 1% SOLUTIONS. *p*H 7.0

R Group	Toxicity mice intravenous mg./kg.	Anesthesia duration, min. Rabbit eyes	Guinea pig skin	Degree of irritation Rabbit eyes	Rabbit skin
Methyl	300	None	54	Severe	Severe
Ethyl	175	None	35	Severe	Severe
n-Propyl	90	None	14	None	Severe
n-Butyl	75	None	40	Moderate	Severe
Isobutyl	60	None	36	Moderate	Slight
n-Amyl	40	None	25	Moderate	Mild
Isoamyl	50	None	36	Severe	Severe
n-Hexyl	40	25	30	Mild	Moderate

Experimental

γ-Bromopropylphthalimide.—The procedure described for β-bromoethylphthalimide[2] was utilized. A 78% yield of light tan crystals melting at 72° was obtained.[3]

γ-Diethylaminopropylphthalimide.—A mixture of 50 g. of γ-bromopropylphthalimide and 32 g. of diethylamine was refluxed for eight hours. The excess of diethylamine was distilled and the residue treated with an excess of 10% hydrochloric acid. The unreacted bromo derivative was removed by filtration and the filtrate made alkaline by means of cold 10% sodium hydroxide solution. During the neutralization the solution must be kept below 25° in order to avoid hydrolysis of the phthalimide. The latter was extracted with benzene and the benzene distilled. The γ-diethylaminopropylphthalimide remained as a brown oil. It could not be distilled and was converted to the hydrochloride by treating an absolute ether solution with hydrogen chloride. The hydrochloride was recrystallized from absolute alcohol containing 1% hydrogen chloride. A 56% yield of colorless crystals melting at 144–145° was obtained.

Anal. Calcd. for $C_{15}H_{21}O_2N_2Cl$: N, 9.46. Found: N, 9.40.

γ-Diethylaminopropylamine.—The best yields of this compound were obtained by elimination of the step wherein the γ-diethylaminopropylphthalimide was isolated.

A mixture of 192 g. of γ-bromopropylphthalimide and 160 g. of diethylamine was heated on a steam cone with stirring for twenty hours. The excess diethylamine was removed by distillation, and the residue treated with 300 cc. of water and acidified with hydrochloric acid. An excess of 25 cc. of concentrated hydrochloric acid was added, care being taken to keep the temperature of the solution below 25° during the addition of the acid. The unchanged γ-bromopropylphthalimide (about 6 g.) is removed by filtration and the acid filtrate boiled for two hours. The solution was concentrated to half its original volume, allowed to cool, and the phthalic acid which sepa-

(2) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, 1932, p. 114.

(3) Gabriel and Weiner, *Ber.*, **21**, 2669 (1888).

TABLE II

ALKYL γ-DIETHYLAMINOPROPYLCARBAMATES

Alkyl group	Molecular formula	B. p. °C.	B. p. Mm.	$n^{20}D$	d^{20}_{20}	MD Calcd.	MD Found	Nitrogen, % Calcd.	Nitrogen, % Found	Soly. in water at 25°, g./100 g. solvent
Methyl	$C_9H_{20}O_2N_2$	125–127	9	1.4535	0.9713	52.84	52.42	14.97	15.02	∞
Ethyl	$C_{10}H_{22}O_2N_2$	138	9	1.4515	.9631	57.46	56.59	13.85	13.82	12.5
n-Propyl	$C_{11}H_{24}O_2N_2$	147–149	11	1.4520	.9479	62.08	61.65	12.95	12.91	5.0
n-Butyl	$C_{12}H_{26}O_2N_2$	158–161	11	1.4519	.9318	66.70	66.78	12.21	12.20	0.9
Isobutyl	$C_{12}H_{26}O_2N_2$	144–147	8	1.4504	.9310	66.70	66.64	12.21	12.13	1.1
n-Amyl	$C_{13}H_{28}O_2N_2$	159–163	9–10	1.4531	.9304	71.32	71.11	11.47	11.35	0.5
Isoamyl	$C_{13}H_{28}O_2N_2$	139–143	2	1.4575	.9286	71.32	71.69	11.47	11.41	.6
n-Hexyl	$C_{14}H_{30}O_2N_2$	172–176	10	1.4540	.9241	75.94	75.67	10.85	10.78	.2

rated removed by filtration. The filtrate was concentrated to half its volume and again filtered. Potassium carbonate was added to the solution until it was neutral and then solid potassium hydroxide added until no more would dissolve. The γ-diethylaminopropylamine separated as a brown oil. It was removed and distilled. The fraction boiling between 110 and 172° was collected and dried with magnesium sulfate for two days. Fractional distillation yielded 48 g. (48%) of a light yellow oil boiling at 167–170°: d^{20}_{20} 0.8283; $n^{20}D$ 1.4437; MD calcd., 41.96; MD found, 41.69.

Anal. Calcd. for $C_7H_{18}N_2$: N, 21.54. Found: N, 21.45.

The phenylthiourea was prepared by treatment with phenyl isothiocyanate. Recrystallization of this derivative from alcohol yielded colorless crystals melting at 116–116.5°.

Anal. Calcd. for $C_{14}H_{23}N_3S$: N, 15.85. Found: N, 15.80.

Alkyl γ-Diethylaminopropylcarbamates.—A solution of 10 g. of γ-diethylaminopropylamine in 100 cc. of ether was added to 8 g. of powdered potassium carbonate mixed with just enough water to make a thick paste. To this mixture was added slowly a solution of the alkyl chlorocarbonate[4] in 100 cc. of ether. The mixture was shaken vigorously and cooled to prevent too vigorous a reaction. After standing at room temperature for twenty hours with occasional shaking, the ether layer was decanted and the residue extracted four times with 25 cc. of ether. The combined ether extracts were dried with magnesium sulfate, the ether distilled and the residual oil fractionally distilled *in vacuo*. The urethans were obtained as pleasant smelling oils. The yields were 65–70%. The properties and analyses are given in Table II.

Summary

A series of alkyl γ-diethylaminopropylcarbamates has been synthesized by the following sequence: potassium phthalimide → γ-bromopropylphthalimide → γ-diethylaminopropylphthalimide → γ-diethylaminopropylamine → alkyl γ-diethylaminopropylcarbamate. Their local anesthetic action has been studied.

(4) Adams, Kamm and Marvel, "Org. Chem. Reagents. I," *Univ. of Ill. Bull.*, **43**, 42 (1919).

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Characteristics and Composition of Watermelon Seed Oil (Cuban Queen Variety)[1]

BY ARTHUR J. NOLTE AND HARRY W. VON LOESECKE

The Cuban Queen variety of watermelon (*Citrullus Vulgaris*) is round or slightly oval with a rind alternately striped with dark and light green, giving it the appearance of being ribbed. The seeds are brownish black.

According to Jamieson[2] the seeds of watermelon contain from about 20 to over 40% of oil depending upon the variety and locality. The oil is said to be used for cooking or as an illuminant. The seeds are alleged to have diuretic properties, although there is no convincing evidence to substantiate this contention.

Jamieson[2] gives the range of the characteristics for watermelon seed oil (varieties not stated); Power and Salway[3] examined a sample of the seed oil and found it to consist of the glycerides of linoleic, oleic, palmitic and stearic acids. Other than the work of Power and Salway, no further study of the composition of the oil seems to have

(1) Food Research Division Contribution No. 409.

(2) Jamieson, "Vegetable Fats and Oils," Chemical Catalog Company, Inc., New York, 1932, p. 222.

(3) Power and Salway, THIS JOURNAL, **32**, 360 (1910).