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Esters of Aminoacylamido Substituted Methylphenylcarbamic Acids I

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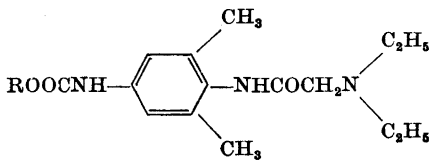
A series of new aliphatic and alicyclic 4-diethylaminoacetamido-3,5-dimethylphenylcarbamates have been prepared and tested for local anesthetic activity. Some of these compounds showed a high surface anesthetic effect.

In the search for new local anesthetics several variations of the structure of α-diethylamino-2,6-dimethylacetanilide (Xylocaine®) have been tried [1]. Amongst others, investigations on changes in the local anesthetic activity by the introduction of different groups into the *para* position of the aromatic nucleus have been carried out. Thus Büchi *et al.*[2] have examined the effect of a butoxy group and Löfgren and Tegnér[3] have evaluated the influence of hydroxy, methoxy, butoxy and butyryloxy groups. The anesthetic properties of the *p*-hydroxy derivative of Xylocaine has also been reported by Krantz, Lu and O'Malley[4]. Recently Dahlbom, Tegnér and Willman[5] have described the preparation and the local anesthetic activity of some acyl and alkyl derivatives of Xylocaine while a series of *p*-alkoxycarbonyl derivatives has been investigated by Löfgren, Tegnér, Willman and Dahlbom[6].

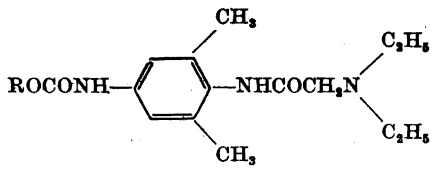
Since some alkoxycarbonylamino substituted local anesthetics * have been described [8,9] and reported to show favourable anesthetic properties, a study of the influence of inserting an imino group between the alkoxycarbonyl group and the aromatic nucleus in the alkoxycarbonyl derivatives of Xylocaine seemed to be of interest, *i.e.* the preparation of alkyl 4-diethylaminoacetamido-3,5-dimethylphenylcarbamates.

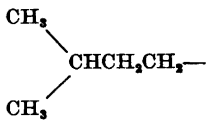
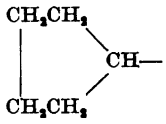
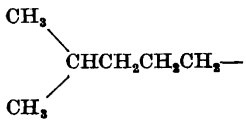
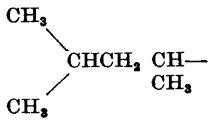
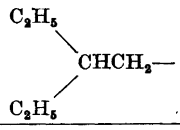
The present paper describes the synthesis of esters of 4-diethylaminoacetamido-3,5-dimethylphenylcarbamic acid of the following general formula



* For a review of earlier investigations on local anesthetics containing the carbamate grouping, see Soehring and Rautmann [7].

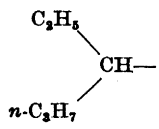
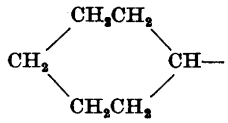
Table 1. Chemical data of bases of the general formula



Compound	R	Method [a]	Yield %	Solvent [b] for recryst.	M. p.°C corr.
II	n-C_2H_5–	A	67	A–Aq	124–126
		C	92		
III	n-C_3H_7–	B	87	A–Aq	101–103
IV	n-C_4H_9–	B	77	E–P	87–89
V	n-C_5H_{11}	B	89	A–Aq	95–97
VI		C	88	I	96–98
VII		B	92	I	128–129
VIII	n-C_6H_{13}–	B	70	E	90–91
IX		A	71	I	104–105
X		C	86	I	117–119
XI		C	82	I	98–100

Empirical formula	Analyses %					
	Found			Calc.		
	C	H	N	C	H	N
$C_{17}H_{27}N_3O_3$	63.7	8.57	13.1	63.5	8.47	13.1
$C_{18}H_{29}N_3O_3$	63.8	8.73	12.8	64.5	8.71	12.5
$C_{19}H_{31}N_3O_3$	65.3	9.12	12.0	65.3	8.94	12.0
$C_{20}H_{33}N_3O_3$	66.2	9.05	11.6	66.1	9.15	11.6
$C_{20}H_{33}N_3O_3$	66.5	9.33	11.3	66.1	9.15	11.6
$C_{20}H_{31}N_3O_3$	66.3	8.56	11.5	66.5	8.64	11.6
$C_{21}H_{35}N_3O_3$	66.9	9.24	10.9	66.8	9.35	11.1
$C_{21}H_{35}N_3O_3$	66.6	9.26	11.4	66.8	9.35	11.1
$C_{21}H_{35}N_3O_3$	66.7	9.38	11.1	66.8	9.35	11.1
$C_{21}H_{35}N_3O_3$	66.8	9.20	11.0	66.8	9.35	11.1

Table 1, continued.

Compound	R	Method [a]	Yield %	Solvent [b] for recryst.	M. p.°C corr.
XII		C	94	I	128–129
XIII		C	88	B	143–146
XIV	n-C_7H_{15}–	B	73	A–Aq	76–78
XV	n-C_8H_{17}–	B	74	E	80–81

[a] *cf.* p. 889.
[b] A = ethanol; Aq = water; B = benzene; E = ether; I = *iso*propyl ether; P = petroleum ether b.p. 40–60°.

where R is a *cyclo*pentyl, *cyclo*hexyl or an alkyl radical containing from two to eight carbon atoms (compounds II–XV, Table 1).

The compounds II and IX were prepared by the reaction of an alkyl chloroformate with α-diethylamino-4-amino-2,6-dimethylacetanilide [5]. Compounds III–V, VII, VIII, XIV and XV were synthesised by transesterification of ethyl 4-diethylaminoacetamido-3,5-dimethylphenylcarbamate (II) by heating under slightly reduced pressure with the appropriate alcohol, using sodium as catalyst.

During the isolation of compound V, a high-melting base, only slightly soluble in ether, was obtained in low yield. The infrared spectrum of this base did not show any urethane band at 1 725 cm^{-1} (KBr disc). It was identified as 1,3-bis(4-diethylaminoacetamido-3,5-dimethylphenyl) urea by comparison of its infrared spectrum and melting point with that of synthetic material [10]. A mixed melting point showed no depression.

Compounds VI and X–XIII were synthesised by reaction of α-diethylamino-4-amino-2,6-dimethylacetanilide with phosgene in toluene solution, and treatment of the precipitate formed, without purification, with the appropriate alcohol to give the desired carbamate.

The chlorine content of the precipitate formed in the reaction between the 4-amino derivative and phosgene indicated the formation of the hydrochloride of the chlorocarbonylamino compound. Attempts to purify this compound and to convert it into the *iso*cyanato derivative failed.

Empirical formula	Analyses %					
	Found			Calc.		
	C	H	N	C	H	N
$C_{21}H_{35}N_3O_3$	67.0	9.26	11.3	66.8	9.35	11.1
$C_{21}H_{33}N_3O_3$	67.5	8.80	11.3	67.2	8.86	11.2
$C_{22}H_{37}N_3O_3$	67.7	9.51	10.7	67.5	9.53	10.7
$C_{23}H_{39}N_3O_3$	68.0	9.56	10.5	68.1	9.69	10.4

The local anesthetic activity of the compounds II—XV was tested on rabbit cornea, by the method of Wiedling [11]. The toxicity (LD50 value) of each compound was determined by subcutaneous injection in white mice. The results of these tests are given in Table 2. Irritation tests [12] carried out with most of the compounds showed that those containing a carbon chain more than five carbon atoms long in the alkoxycarbonylamino group were strongly irritant while those with five carbon atoms or less gave only slight or no irritation *.

EXPERIMENTAL

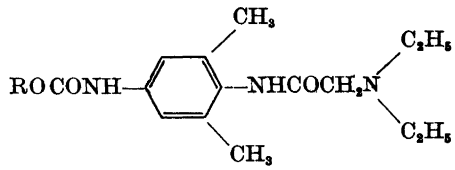
Iso*hexyl chloroformate (I)*. For the synthesis of compound IX *iso*hexyl chloroformate was prepared from *iso*hexanol [13] as described for benzyl chloroformate [14]. The ester was fractionated in a Vigreux column and the fraction b.p. 57—58°/8 mm was collected. Yield 82 %. (Found: C 51.1; H 7.77. Calc. for $C_7H_{13}ClO_2$: C 51.1; H 7.96.)

4-Diethylaminoacetamido-3,5-dimethylphenylcarbamates. The following three general methods were used for the preparation of compounds II—XV (see Table 1). A typical example is given of each method.

Method A. A solution of α-diethylamino-4-amino-2,6-dimethylacetanilide [5] (15 g, 0.060 mole) in benzene (250 ml) was treated with ethyl chloroformate (6.5 g, 0.060 mole) added dropwise with stirring and the reaction mixture was kept at 40—50° for 1 h. It was then extracted with water and the aqueous extract was made alkaline by the addition of ammonia. The oil that separated soon crystallised and was filtered off. Recrystallisation from aqueous ethanol (1:1) gave colourless crystals, m. p. 124—126° (13 g, 67 %).

* Thanks are due to Dr. S. Wiedling for performing the biological tests.

Table 2. Local anesthetic activity and toxicity of compounds II-XV.



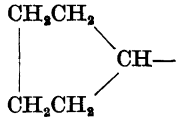
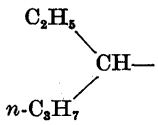
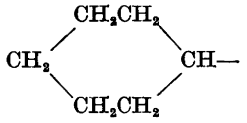
Compound	R	Toxicity * LD50 g base/kg	Anesthetic activity * Xylocaine = 1.0
II	C_2H_5—	0.34	1.2
III	n-C_3H_7—	0.35	1.6
IV	n-C_4H_9—	0.32	10
V	n-C_5H_{11}—	0.38	35
VI	$(CH_3)_2CHCH_2CH_2$—	0.49	20
VII		0.48	2.8
VIII	n-C_6H_{13}—	0.84	60
IX	$(CH_3)_2CHCH_2CH_2CH_2$—	0.93	12
X	$(CH_3)_2CHCH_2CH(CH_3)$—	0.84	11
XI	$(C_2H_5)_2CHCH_2$—	0.86	12

Table 2, continued.

Compound	R	Toxicity * LD50 g base/kg	Anesthetic activity * Xylocaine = 1.0
XII		0.69	4.5
XIII		0.85	12
XIV	n-C_7H_{15}—	1.5	50
XV	n-C_8H_{17}—	1.8	70

* *cf.* p. 889 for explanation.

Method B. A small piece of sodium (0.3 g) was dissolved in n-pentanol * (30 g, 0.34 mole) by heating. Ethyl 4-diethylaminoacetamido-3,5-dimethylphenylcarbamate (II) (20 g, 0.062 mole) was added to this solution and the mixture was heated on a water bath at 80° under slightly reduced pressure (~135 mm). After 3 h the excess pentanol was removed under vacuum (8 mm) and the residue was washed with water. The residual crystalline mass was dissolved in benzene and the solution was filtered, dried over sodium sulphate and then passed through an Al_2O_3 column. The base separated on evaporation and was recrystallised from ethanol-water (3:1), colourless needles, m. p. 95—97° (20 g, 89 %).

The filtration of the benzene solution gave a rather insoluble product (~1 g) which was crystallised from chloroform-ethanol, m. p. 261—264°. It was insoluble in water, and bases but soluble in acids. Infrared spectra ** were recorded of this compound and, for comparison, of n-pentyl 4-diethylaminoacetamido-3,5-dimethylphenylcarbamate and 1,3-bis(4-diethylaminoacetamido-3,5-dimethylphenyl) urea[10]. The following strong bands were observed:

Compound m. p. 261—264°: 3 250, 1 665, 1 605, 1 540, 1 495, 1 405, 1 315 and 1 205 cm^{-1}.

n-Pentyl 4-diethylaminoacetamido-3,5-dimethylphenylcarbamate: 3 210, 2 830, 1 725, 1 670, 1 610, 1 550, 1 495, 1 225 and 1 088 cm^{-1}.

1,3-Bis(4-diethylaminoacetamido-3,5- dimethylphenyl) urea: 3 250, 1 665, 1 605, 1 540, 1 495, 1 405, 1 315 and 1 205 cm^{-1}.

As can be seen the compound showed no band at 1 725 cm^{-1} (urethane); comparison with the urea derivative showed that they were identical. A mixed melting point of the two compounds showed no depression.

Method C. α-Diethylamino-4-amino-2,6-dimethylacetanilide [5] (25 g, 0.10 mole) dissolved in dry toluene (400 ml) was added dropwise with stirring to a 10 % (v/v) solution

* As carbamates prepared from the commercial n-pentanol showed a broad melting point interval the alcohol was purified by fractional distillation and the fraction b. p. 138.5—139°, $n_D^{20} = 1.4097$ was collected for use.

** The infrared spectra were recorded with a Perkin-Elmer model 21 spectrophotometer. All compounds were run in KBr discs.

of phosgene (30 g, 0.30 mole) in toluene. The temperature of the reaction mixture was held at 40° by external heating. After standing overnight at this temperature, the precipitate formed was collected and dried in a desiccator. Attempts to purify this compound by recrystallisation caused discolouration and evolution of hydrogen chloride. No *iso*cyanate could be obtained by heating under reflux in an inert solvent (toluene). The chlorine content of the precipitate was determined by titration (Mohr) as 19.8 % indicating the formation to a large extent of the chlorocarbonylamino compound (calc. for $C_{15}H_{23}Cl_2N_3O_2$: Cl 20.4). When heated with 2 moles of ethanol in benzene solution a 92 % yield of the ethyl carbamate derivative was obtained. The precipitate was therefore used for synthesis without purification.

A suspension of the above precipitate in a mixture of dry toluene (150 ml) and *cyclo*hexanol (20 g, 0.20 mole) was heated on a water bath for 2 h. The solution was then diluted with absolute ether and the precipitate formed was filtered off and dissolved in water. The solution was extracted once with ether and then made alkaline by the addition of ammonia. The base liberated was collected and recrystallised from benzene, m. p. 143—146° (33 g, 88 %).

Methods of preparation, yields, solvents for recrystallisation, melting points and analytical data of the bases thus prepared are given in Table 2.

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