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Amides of 4-Diethylaminoacetamido-3,5-dimethylphenylcarbamic Acid

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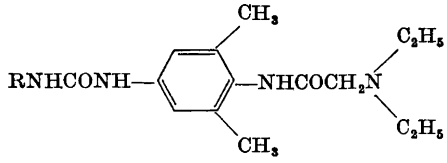
Five new amides of 4-diethylaminoacetamido-3,5-dimethylphenylcarbamic acid have been prepared and tested for local anesthetic activity.

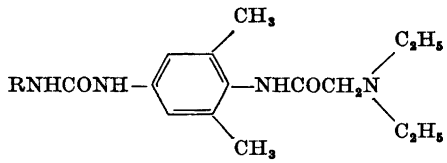
Only a few derivatives of urea have been tested for local anesthetic activity. Thus Chabrier, Najer and Giudicelli [1] have described the properties of some ureas and others have been reported by Koelzer and Wehr [2], who also give a review of earlier investigations. The results of the investigations are, however, contradictory with regard to the value of the urea grouping in local anesthetics.

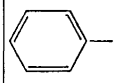
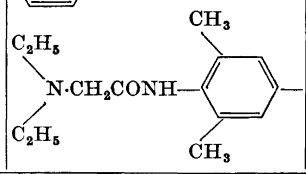
Some esters of 4-diethylaminoacetamido-3,5-dimethylphenylcarbamic acid have been shown to have a high local anesthetic activity when tested on rabbit cornea [3]. Because of the close similarity of the imino group to an oxygen atom it was of interest to study the effect of replacing one of the oxygen atoms in these carbamates by an imino group, *i.e.* to study amides of the general formula



In the present investigation a series of compounds of this formula has been synthesised with R = *n*-C_4H_9— (I), *n*-C_5H_{11}— (II), *n*-C_6H_{13}— (III), C_6H_5— (IV) and 4-[$(C_2H_5)_2N{\cdot}CH_2{\cdot}CO{\cdot}NH$] -3,5-$(CH_3)_2{\cdot}C_6H_2$— (V). The compounds I—IV were prepared by reaction of the appropriate *iso*cyanate with α-diethylamino-4-amino-2,6-dimethylacetanilide [4] in benzene solution. Two of the *iso*cyanates required (*n*-pentyl and *n*-hexyl) were prepared *via* their corresponding azides and Curtius degradation. This method yielded pure compounds but attempts to prepare the *iso*-cyanates by other methods gave impure products.

Table 1.



Compd.	R	Yield %	Solvent[a] for recryst.	M. p. °C	Empirical formula	Analyses %					
						Found			Calc.		
						C	H	N	C	H	N
I	*n*-C_4H_9—	84	Me—Aq	141—143	$C_{19}H_{32}N_4O_2$	65.6	9.33	15.9	65.5	9.26	16.1
II	*n*-C_5H_{11}—	95	Me—Aq	131—132	$C_{20}H_{34}N_4O_2$	66.4	9.56	15.7	66.3	9.45	15.5
III	*n*-C_6H_{13}—	89.5	Me—Aq	126—127	$C_{21}H_{36}N_4O_2$	66.9	9.82	15.1	67.0	9.64	14.9
IV		99	Bu	222—224	$C_{21}H_{28}N_4O_2$	68.1	7.78	15.2	68.4	7.66	15.2
V		65	Chl—A	261—264	$C_{29}H_{44}N_6O_3$	66.1	8.20	15.7	66.4	8.45	16.0

[a] A = ethanol; Aq = water; Bu = *n*-butanol; Chl = chloroform; Me = methanol.

For the preparation of compound V 1 mole of α-diethylamino-4-amino-2,6-dimethylacetanilide was reacted with 0.5 mole of phosgene. The hydrochloride of the α-diethylamino-4-chlorocarbonylamino-2,6-dimethylacetanilide is formed as an intermediate.

The compounds I—V were tested * for local anesthetic activity on rabbit cornea using xylocaine as a standard [5]. Compounds I, II and III were respectively 1.6, 3 and 9 times more active than xylocaine and IV showed the same activity as xylocaine but V was inactive. The subcutaneous toxicities of the compounds I—V, determined as LD50 values in white mice were 0.45, 0.57, > 1.0 **, > 1.0 ** and and > 0.5 *** g base/kg bodyweight. Compared with the corresponding esters [3] I—III had a lower anesthetic activity. As the amides were all found to be irritants no further tests were carried out.

* Thanks are due to Drs. S. Wiedling and A. Åström for carrying out the biological tests.

** LD50 values of more than 1.0 g/kg were not determined.

*** Owing to the low solubility of the compound higher dosages could not be tested.

EXPERIMENTAL *

n-Butyl and phenyl *iso*cyanates, which are commercially available, were purified by fractional distillation and the fractions b.p. 114—115° and 165—166°, respectively, were used for synthesis. The *n*-pentyl [6] and *n*-hexyl [7] *iso*cyanates were both prepared *via* their azides as described for the preparation of undecyl *iso*cyanate [8]. An *n*-pentyl *iso*cyanate fraction b.p. 138—139.5° and an *n*-hexyl *iso*cyanate fraction b.p. 162—163° were used.

The compounds I—IV (see Table 1) were prepared as described for the following example:

α-Diethylamino-4-amino-2,6-dimethylacetanilide [4] (5.6 g, 0.020 mole) was dissolved in dry benzene (50 ml), a solution of *n*-butyl *iso*cyanate (2.2 g, 0.022 mole) in dry benzene (15 ml) was added and the mixture was heated on a water bath for 1.5 h. The solvent was then evaporated and the residue was recrystallised from methanol-water (3:1) giving colourless crystals, m. p. 141—143°.

For the yields, solvents used for recrystallisation, melting points and analytical data for the individual compounds I—IV, see Table 1.

1,3-Bis(4-diethylaminoacetamido-3,5-dimethylphenyl)urea (V). α-Diethylamino-4-amino-2,6-dimethylacetanilide [4] (12.5 g, 0.050 mole) was added to a 10 % (v/v) solution of phosgene (25 g, 0.025 mole) in toluene and the solution was boiled under reflux for 8 h. After standing over night the mixture was shaken with 2 N sodium hydroxide and the precipitate was collected and dried in a desiccator. It was then treated with hot chloroform (50 ml) and filtered. Recrystallisation of the residue from chloroform-ethanol (3:1) gave colourless crystals, m. p. 261—264° (8.5 g, 65 %). (For analyses, see Table 1.)

* All melting points are corrected.

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