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Studies on Local Anesthetics IX[1-8]

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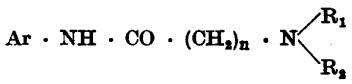
Many N-(aminoacyl)-amines, mainly of the type

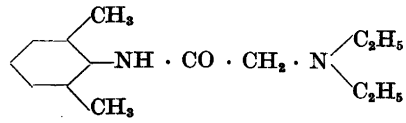


$n = 1$ or 2, R_1 = H or alkyl, R_2 = alkyl

have been synthesized by Löfgren *et al.*[1-8]. The compounds have been investigated pharmacologically and especially as to their local anesthetic action. Also, in many cases, physico-chemical properties (distribution coefficients oleyl alcohol/water [5], molar refractions [5], absorption spectra in the ultraviolet [5], ionization constants [5], and dipole moments [9]) have been determined and their relation to structure and anesthetic activity studied.

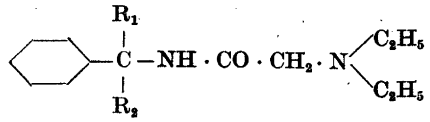
The interfacial tension/time curve, as obtained when anesthetics are distributed through an interface paraffin oil/water at which an ergosterol film is adsorbed has been studied by Seelich [10] (general anesthetics) and by Tammelin and Löfgren [11] (local anesthetics of xylocaine type). Mainly on the basis of these experiments a new theory for the mechanism of anesthesia has been presented (Tammelin and Löfgren [11], Löfgren [5]).

One of the compounds synthesized earlier [1] is xylocaine



which has outstanding local anesthetic and physico-chemical properties as compared with the other closely related compounds [1,5,9]. Xylocaine is now used extensively in all kinds of clinical local anesthesia.

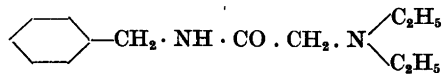
In the present work three benzylamides of the formula



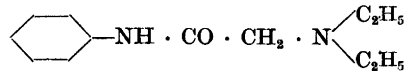
I: $R_1 = H$, $R_2 = COOC_2H_5$
II: $R_1 = CH_3$, $R_2 = COOC_2H_5$
III: $R_1 = H$, $R_2 = CH_2COOC_2H_5$

have been synthesized and their local anesthetic action studied.

Earlier [1] the benzylamide

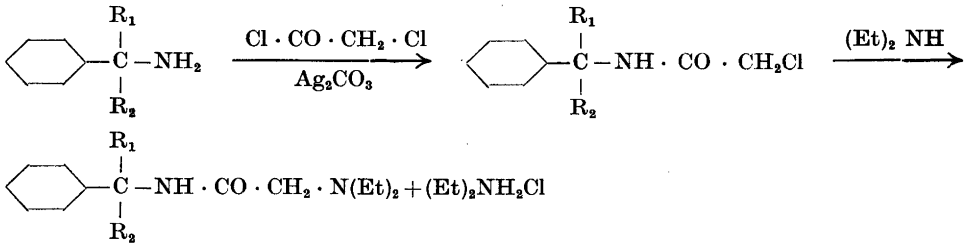


was investigated. The compound was demonstrated to have a shorter duration than xylocaine or about the same effect as the corresponding anilide (test performed on the tongue):



Whereas the anilide was found to be almost free from an irritating effect, the benzylamide was shown to be a strong irritant.

The compounds were synthesized according to the following scheme:



The chloroacetylation step was carried out in dry ether, silver carbonate being used to catch the hydrogen chloride produced.

In the earlier works by Löfgren *et al.* (*cf.* above) the reaction between acyl halides and amines was usually carried out according to the aqueous acetate buffer method described by Löfgren[1, 5]. In the present work the chloroacetylation of water-sensitive esters was made in the absence of water and with *silver carbonate* as a hydrogen chloride acceptor. It is known from the literature that silver carbonate has been used as a hydrogen halide acceptor in some reactions but as far as we know the salt has never been used in the reaction between acyl halides and amines.

After removal of the silver chloride and the ether, the remaining crude chloroacetyl derivative was heated with diethylamine in ethanol solution to give the desired product.

The three compounds were tested for their local anesthetic action on the rabbit cornea. For this purpose 2 % hydrochloride solutions of pH 6 were

prepared. In this test, compound I was inactive whereas the other two were active. The duration of II and III was a fourth and a fifth, respectively, of the value of xylocaine. As compared with xylocaine the latency times of II and III were much longer. — The toxicities of the three compounds were found to be low. Thus, when injected subcutaneously in white mice, the LD_{50} values for I, II, and III are 2.2, 0.78, and 2.2 g/kg, respectively. The corresponding value for xylocaine is 0.39 g/kg.

The three compounds, especially II, have some structural similarities with analgesic agents (compounds with a morphine-like action) *. Therefore by the toxicity determinations, special attention was paid to the occurrence of the Straub phenomenon (erection of tail). This effect is typical of analgesic agents. However, some compounds are known which give a weak Straub reaction but are devoid of analgesic action (Heinekamp [13]). All three compounds gave a positive but weak Straub test, compound II having the most pronounced effect. Because of the weak effects a more detailed evaluation of a possible analgesic action did not seem worth while.

The compounds were also tested for their spasmolytic and histaminolytic power. No appreciable effects were found.

EXPERIMENTAL **

Ethyl N-(diethylaminoacetyl)-α-aminophenylacetate (I). α-Aminophenylacetic acid was prepared as described by Steiger [14]. To synthesize the ethyl ester, we followed the directions given by Kossel [15]. It was obtained as a colourless oil; b. p. 129—131°/9 mm; yield 61 %.

In a 150-ml Erlenmeyer flask 5.30 g (0.0296 mole) of ethyl α-aminophenylacetate were dissolved in 10 ml of absolute ether. The solution was cooled to 5° and 3.34 g (0.0296 mole) of chloroacetyl chloride diluted with 5 ml of absolute ether were added drop by drop under vigorous stirring. During this process the temperature was allowed to rise slowly to about 20°. To the mixture, now protected against the light, 4.11 g (0.0149 mole) of silver carbonate, freshly prepared and dried, were added in portions during half an hour and under continued stirring which was carried on for another four hours. After this time the evolution of carbon dioxide had ceased, and the silver chloride was filtered off. On removing the ether by distillation, colourless needles separated. A very small amount was recrystallized from di-*n*-butyl ether; m. p. 68—69°.

The crude chloroacetyl derivative was dissolved in 60 ml of absolute ethanol, and 5.85 g (0.0800 mole) of diethylamine were added. The mixture was kept at 70° for six hours in a sealed bottle. The alcohol and the excess of diethylamine were then driven off under reduced pressure and at a bath temperature of 40°. After dilution with absolute ether, diethylammonium chloride separated and was filtered off. The solvent was driven off and on fractional distillation of the residue, a colourless oil was collected; b. p. 160—162°/0.8 mm; $n_D^{20} = 1.5015$; yield 4.95 g (0.0169 mole), *i. e.* 57 %, calculation based on ethyl α-aminophenylacetate. (Found: C 65.8; H 8.33; Equiv.w. 288 ***. Calc. for $C_{16}H_{24}N_2O_3$ (292.4): C 65.7; H 8.27; Equiv.w. 292).

Perchlorate. Colourless needles from absolute ethanol; m. p. 179—181°. (Found: $HClO_4$ 25.8 ****. Calc. for $C_{16}H_{25}ClN_2O_7$ (392.8): $HClO_4$ 25.6).

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* For a survey of the relationships between structure and analgesic action see for instance Eddy [12].

** All melting points and boiling points are uncorrected.

*** Titration of the base in 30 % ethanol with 0.1 *N* HCl; mixed indicator methylene blue-methyl red.

**** Analysis by precipitating the potassium perchlorate — see Löfgren [1].

Ethyl N-(diethylaminoacetyl)-α-amino-α-phenylpropionate (II). α-Amino-α-phenylpropionic acid was obtained in accordance with the description given by Steiger [16]. The esterification with ethanol was carried out as described by Mc Kenzie and Myles [17]. The fraction with b. p. 134—136°/14 mm was collected; yield 49 %.

From this ester the final base was obtained by chloroacetylation and subsequent treatment with diethylamine as described in the preceding preparation. The base was obtained as a colourless oil; b. p. 137—139°/0.1 mm; $n_D^{20} = 1.5017$; yield 58 %, calculation based on ethyl α-amino-α-phenylpropionate. (Found: Equiv.w. 303 *. Calc. for $C_{17}H_{26}N_2O_3$ (306.4): Equiv.w. 306).

Ethyl N-(diethylaminoacetyl)-β-amino-β-phenylpropionate (III). β-Amino-β-phenylpropionic acid was prepared as described by Steiger [18] and was esterified according to Mc Kenzie and Richardson [19]. On distillation a colourless oil was collected; b. p. 133—134°/9 mm; $n_D^{20} = 1.5112$; yield 52 %.

From this ester the final base was obtained by chloroacetylation and subsequent treatment with diethylamine as described under the preparation of compound I. The product was collected as a colourless oil; b. p. 150—151°/0.08 mm; solidifying p. 5°; yield 45 %, calculation based on ethyl β-amino-β-phenylpropionate. (Found: Equiv.w. 308 *. Calc. for $C_{17}H_{26}N_2O_3$ (306.4): Equiv.w. 306).

SUMMARY

Ethyl N-(diethylaminoacetyl)-α-aminophenylacetate, ethyl N-(diethylaminoacetyl)-α-amino-α-phenylpropionate and ethyl N-(diethylaminoacetyl)-β-amino-β-phenylpropionate have been synthesized and tested for their local anesthetic, spasmolytic and histaminolytic power.

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* The same analytical method as described under compound I.