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# Studies on Local Anaesthetics. VI [1–5]

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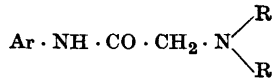
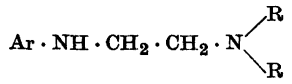
In earlier investigations by Erdtman and Löfgren [6] and by Löfgren *et al.* [1–5], a fairly large number of compounds of the type



were synthesized and studied as to their local anaesthetic properties.

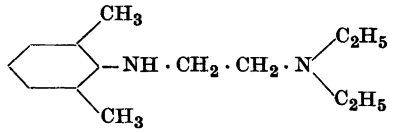
Here, investigations of three new compounds with the formula



I

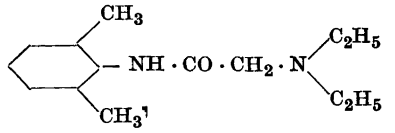
will be reported.

The compound

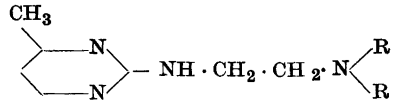


Ia

closely related to xylocaine [1, 2, 5]



was synthesized and studied pharmacologically. Further, by substituting 2-amino-4-methylpyrimidine in Ia for xylidine, two other diamines Ib and Ic were obtained:



Ib: R = methyl

Ic: R = ethyl

Attempts to synthesize N-(β-diethylaminoethyl)-2,6-dimethylaniline (Ia) were made by Löfgren and Widmark [4]; Löfgren [1] earlier showed N-(β-diethylaminoethyl)-aniline to possess local anaesthetic activity. Löfgren and Widmark synthesized N-(β-diethylaminoethyl)-2,6-dimethylformanilide and then tried to split off the formyl group. The compound, however, was so resistant that, despite boiling in strongly acid solution, the formyl group could not be split off.

We have now succeeded in preparing Ia by the reaction between two moles of 2,6-xylidine and one mole of β-diethylaminoethyl chloride, one mole of the former acting as proton acceptor. To separate the excess of xylidine we used a method based on the slight solubility of 2,6-xylidinium nitrate in water. For further purification a fractionated extraction with ether at suitable pH values was performed.

The compounds Ib and Ic were prepared by condensing 2-amino-4-methylpyrimidine with the dialkylaminoethyl chloride in question in the presence of sodamide. Some closely related pyrimidine derivatives have been prepared by Adams and Whitmore [7] and by Huttrer *et al.* [8]. None of these authors studied the anaesthetic properties of their compounds.

Compound Ia is active; on rabbit cornea it has, under the same conditions (pH 5.9), about half the duration of xylocaine and a much longer latency time. Its toxicity as determined from subcutaneous injections in white mice is approximately the same as that of xylocaine. Thus, the $LD_{50}$ values for Ia and for xylocaine are 0.34 g/kg and 0.39 g/kg respectively. Ia is a strong irritant on the cornea and when injected subcutaneously it causes necrosis. Compounds Ib and Ic have only very slight activity. Further, all three compounds were tested for their spasmolytic and histaminolytic power. No appreciable effects were found.

## EXPERIMENTAL *

The β-dialkylaminoethyl chlorides used were prepared by Slotta and Behnisch's method [9].

*N-(β-Diethylaminoethyl)-2,6-dimethylaniline*, $C_{14}H_{24}N_2$ (220.3). 0.297 mole (36.4g) of freshly distilled 2,6-dimethylaniline was heated to 180° in a two-necked flask equipped with a condenser and a dropping funnel. A freshly prepared absolutely dry solution of 0.150 mole (20.5 g) of β-diethylaminoethyl chloride in ether was added drop by drop through the funnel. The ether evaporated immediately. When all the ether solution had been added and the temperature began to rise, the condenser was arranged for refluxing and the mixture kept at 180° for 5 ½ hours. After cooling, the mixture was slowly poured into 60 ml of 6 *N* $HNO_3$ under vigorous stirring. The temperature was kept

* All our melting points are uncorrected.

below 12°. The xylidinium nitrate separated and was filtered off. NaOH-solution was added to the filtrate so that a pH value of 4.8 was obtained. The liquid was extracted once with ether, thus removing the residual excess of xylidine. The water phase was then made strongly alkaline and the liberated base thoroughly extracted with ether. After drying over $MgSO_4$, the ether was driven off. The remaining oil was then twice distilled under reduced pressure. The yield was 0.0437 mole (9.6 g; 29 %) of a colourless oil; b.p. 105°/0.6 mm; $n_D^{22} = 1.5151$.

Calc. C 76.3 H 10.98
Found » 76.2 » 10.81

*2-(β-Dimethylaminoethylamino)-4-methylpyrimidine*, $C_9H_{16}N_4$ (180.2). 100 ml of dry toluene and 0.308 mole (12 g) of sodamide were placed in a three-necked flask, fitted with a mechanical stirrer through a mercury seal, a dropping funnel and a condenser protected with a soda-lime tube. To this mixture a solution of 0.293 mole (32 g) of 2-amino-4-methylpyrimidine in 100 ml of dry toluene was added through the funnel. The flask was kept in an oil bath at 125° for 12 hours. After cooling 0.186 mole (20 g) of freshly prepared dry β-dimethylaminoethyl chloride was slowly added, the mixture heated to 125° for 18 hours, cooled and placed in a refrigerator overnight. The solid was filtered off and well washed with toluene. The toluene solution was thoroughly extracted with 3 *N* HCl. The combined aqueous extracts were purified by ether extraction, then made strongly alkaline and extracted sufficiently with ether. After drying over $K_2CO_3$ the ether was evaporated and the residue distilled under reduced pressure. Contaminating aminomethylpyrimidine sublimated. A slightly yellow fraction with a constant boiling point, 109—110°/2 mm, was obtained; yield 0.0993 mole (17 g; 51 %). The fraction was, however, not quite pure, as it contained some of the starting material, 2-amino-4-methylpyrimidine. The fraction was therefore dissolved in 200 ml of petroleum ether and the solution inocculated with some crystals of aminomethylpyrimidine. After storing in a refrigerator for three months the aminomethylpyrimidine had precipitated. The petroleum ether solution was filtered, the solvent evaporated and the residue twice distilled under reduced pressure. The compound was obtained as a colourless oil; b.p. 140.5—141°/14 mm; $n_D^{20} = 1.5317$.

Calc. C 60.0 H 8.95
Found » 59.7 » 8.85

*Picrate*, $C_{15}H_{19}N_7O_7$ (409.4). Small, yellow laths from ethanol-water; m.p. 186—189°.

Calc. C 44.0 H 4.68
Found » 44.2 » 4.48

*2-(β-Diethylaminoethylamino)-4-methylpyrimidine*, $C_{11}H_{20}N_4$ (208.3). A solution of 0.275 mole (30 g) of 2-amino-4-methylpyrimidine in 100 ml of dry toluene was added as in the preceeding preparation to a mixture of 0.274 mole (10.7 g) of sodamide and 100 ml of dry toluene. The mixture was kept at 100° for three hours, and then 0.138 mole (23.7 g) of freshly prepared dry β-diethylaminoethyl chloride was slowly added. The reaction mixture was kept at 100° for 24 hours. After cooling and filtering the toluene solution was washed with water. The toluene solution was dried over $K_2CO_3$ and the solvent evaporated. The residue was distilled under reduced pressure and a yellow fraction with a constant boiling point, 107°/0.9 mm., was obtained; yield 0.0634 mole (13.7 g; 46 %). To get a pure substance the same petroleum ether method was used as above. The purified compound was again distilled, and a colourless oil was obtained with b.p. 145.5—146°/12 mm. or 163—164°/21 mm; $n_D^{20} = 1.5217$.

Calc. C 63.4 H 9.68
Found » 63.2 » 9.56

*Dipicrate*, $C_{23}H_{26}N_{10}O_{14}$ (666.5). Thin, yellow needles from methanol-water; m.p. 170—172.5°.

Calc. C 41.4 H 3.93
Found » 41.6 » 3.97

## SUMMARY

N-(β-Diethylaminoethyl)-2,6-dimethylaniline, closely related to xylocaine, 2-(β-dimethylaminoethylamino)-4-methylpyrimidine, and the corresponding diethylaminoethylamino compound have been synthesized and tested for their local anaesthetic, spasmolytic, and histaminolytic power.

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