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Studies on Local Anaesthetics. VIII[1–7]

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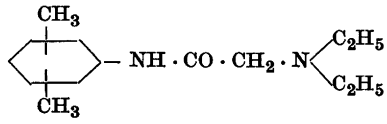
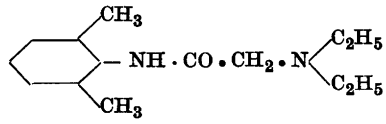
It has been shown earlier [1, 2, 5] that of the six isomers,

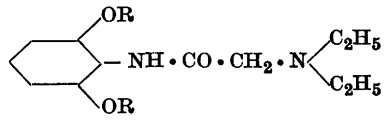


the one with the two methyl groups in the *o*-positions to the anilide nitrogen has outstanding physico-chemical and local anaesthetic properties. The *o*-effect in this compound, *i. e.* xylocaine



has been demonstrated by rather extensive measurements [5, 8].

Now, it seemed to us of interest to investigate such compounds in which the two methyl groups in xylocaine are replaced by other groups. In this work we have synthesized two alkoxy derivatives (I) and (II),



I: R = methyl

II: R = ethyl

and studied their pharmacological properties.

When tested on rabbit cornea, under the same conditions (pH 6.0), the methoxy compound I has a duration somewhat shorter than that of xylocaine; the ethoxy compound II shows about the same duration as that of xylocaine.

In latency time, both compounds are inferior to xylocaine. The methoxy derivative was also tested intercutaneously on man and found to have a much shorter duration than xylocaine. In this experiment the compound proved, unlike xylocaine, to be slightly irritating. The ethoxy compound is a strong irritant when tested subcutaneously on man. Both compounds are less toxic than xylocaine, the LD_{50} values as determined from subcutaneous injections in white mice, being 1.4 g/kg for the methoxy compound and 0.70 g/kg for the ethoxy compound. Further, the two compounds were tested for their spasmolytic and histaminolytic power. No appreciable effects were found.

EXPERIMENTAL *

2-Nitroresorcinol. This compound, required as starting material for both I and II, has been synthesized by Kauffmann and de Pay [9], and we followed their method. Their description, however, is rather incomplete, and we had to determine the reaction conditions. 44 g of finely powdered resorcinol (0.40 mole) was gradually added to 300 g of fuming sulfuric acid of sp. gr. 1.875 (2.89 moles H_2SO_4 + 0.204 mole SO_3) under vigorous stirring and the mixture then heated on a water bath for 30 min. After cooling, a mixture of 25.2 g of fuming nitric acid of sp. gr. 1.52 (0.40 mole) and 80 g of fuming sulfuric acid of sp. gr. 1.875 (0.77 mole H_2SO_4 + 0.054 mole SO_3) was cautiously added under vigorous stirring and external cooling at such a rate that the temperature did not exceed 15°. The suspension was agitated another hour, and steam distilled after addition of 290 ml of water. After 30 minutes, superheated steam (150°) was used. Yield 25 g (41 %) of almost pure product. M.p. after recrystallization from 50 % ethanol at 85°.

2,6-Dimethoxyaniline. This compound has previously [10] been synthesized by reduction of the corresponding nitro compound with tin and hydrochlorid acid, but we used catalytical reduction. 73 g of 2,6-dimethoxynitrobenzene (0.40 mole) was dissolved in 400 ml of hot ethanol. The solution was hydrogenated at 80° and a hydrogen pressure of 75 kg/cm^2 in the presence of Raney nickel (10 g, moist). After one hour no more hydrogen was consumed and after cooling and filtration the reaction mixture was evaporated to about 100 ml. This solution was cooled in ice and after standing overnight the crystals formed were collected. Yield 57 g (93 %). After recrystallization from light petroleum (b.p. 40—60°) they melted at 75.5—77°.

ω-Chloro-2,6-dimethoxyacetanilide, $C_{10}H_{13}ClNO_3$ (230.7). The compound was prepared according to Löfgren's general method [1,5]. 46 g of 2,6-dimethoxyaniline (0.32 mole) was dissolved in 255 ml of glacial acetic acid. After cooling to 10°, first 37 g of chloroacetyl chloride (0.38 mole) and then 99 g of sodium acetate (0.73 mole) in 445 ml of water were added under mechanical agitation. The resulting mixture was shaken for 30 minutes and the precipitate collected, washed with much water and after drying, recrystallized from ethanol (600 ml). Yield 52.4 g (75 %). M.p. 166—167°.

Calc. Cl 15.4
Found » 15.4

* All our melting points are uncorrected.

ω-Diethylamino-2,6-dimethoxyacetanilide, $C_{14}H_{22}N_2O_3$ (266.3). 22 g of the chloro compound (0.095 mole) and 27 ml of diethylamine (0.26 mole) were refluxed in benzene for five hours. The reaction mixture was filtered, benzene and excess of diethylamine evaporated and the residue dissolved in 3 *N* HCl (35 ml). After filtering the aqueous solution was extracted with ether (50 ml), made alkaline with concentrated ammonia and the liberated base sufficiently extracted with ether (3 × 50 ml). After drying, the combined ethereal extracts were evaporated and the residue distilled twice at a bath temperature of 200° and a pressure of 0.01 mm. Yield 18 g (68 %).

Calc. C 63.2 H 8.26
Found » 63.2 » 8.26

2,6-Diethoxyaniline. This has previously [10] been prepared in the same way as the corresponding methoxy compound. We reduced the nitro compound, prepared by Turner's method [10], with iron and acetic acid by Löfgren's method [1,5]. However, after separation of the ethereal layer and evaporating the solvent only a small residue was left, but the very weak base could be obtained by treating the iron oxide sludge with superheated steam in a yield of 46 % *.

After recrystallizing from light petroleum the m.p. was 57°. It could also be distilled *in vacuo;* b.p. 142–143°/13 mm.

ω-Chloro-2,6-diethoxyacetanilide, $C_{12}H_{16}ClNO_3$ (257.7). Prepared in the same way as the corresponding methoxy compound from 2,6-diethoxyaniline and chloroacetyl chloride in a yield of 89 %. M.p. after recrystallization from benzene was 129–130°.

Calc. C 55.9 H 6.26
Found » 55.7 » 6.28

ω-Diethylamino-2,6-diethoxyacetanilide, $C_{16}H_{26}N_2O_3$ (294.4). Prepared in the same way as the methoxy compound by refluxing ω-chloro-2,6-diethoxyacetanilide and diethylamine in dry benzene for six hours. Yield 66 %, b.p. 169°/0.6 mm, solidifying p. 32.5°; $n_D^{20} = 1.5174$ (supercooled substance).

Calc. C 65.3 H 8.90 Equiv. wt.: 294
Found » 64.8 » 8.92 » » 293 **

SUMMARY

ω-Diethylamino-2,6-dimethoxyacetanilide and the corresponding diethoxy compound have been synthesized and tested for their local anaesthetic, spasmolytic, and histaminolytic power.

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* The reduction method has previously been used on a large number of nitro compounds and always given good yields. Turner does not mention the yield obtained.

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

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