

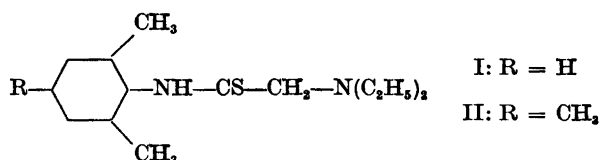
Studies on Local Anesthetics XIII *

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Two compounds related to xylocaine *i.e.* α -diethylamino-2,6-dimethylthioacetanilide and α -diethylamino-2,4,6-trimethylthioacetanilide have been synthesized, and tested for their local anesthetic potency by subcutaneous anesthesia on man. Furthermore, the lethal dose in white mice was determined.

The compounds synthesized in this work have the following structure:



They were both prepared from the corresponding oxygen compounds (xylocaine and LL 31)² by replacing the carbonyl oxygen with sulphur, P_2S_5 in pyridine solution being used for the exchange reactions. The compounds were tested for their anesthetic potency by subcutaneous injection on man, and for compound I the duration was found to be approximately 40 % shorter than that of xylocaine whereas compound II gave practically no effect. The LD_{50} values measured by subcutaneous injection in white mice and calculated as g of I, II and xylocaine per kg of body weight are 0.9, 1.2 and 0.4, respectively **.

EXPERIMENTAL

α -Diethylamino-2,6-dimethylthioacetanilide

α -Diethylamino-2,6-dimethylthioacetanilide (xylocaine³), 23.4 g (0.100 mole), was mixed with 33 g (0.15 mole) of phosphorus pentasulphide, dissolved in 300 ml of dry pyridine (dried by CaH_2) and the mixture was gently refluxed for two hours. The product was

* For paper XII of this series see Löfgren, Lundquist, Lindström¹.

** Experiments performed by S. Wiedling.

allowed to cool, and was poured under vigorous stirring, into 2 000 ml of 6 N hydrochloric acid containing 500 g of ice. A thick grey precipitate (sulphur) formed. After standing overnight, the precipitate was filtered off. The solution was extracted three times with 300 ml of carbon disulphide and twice with 300 ml of ether. The aqueous solution was made weakly alkaline (pH 8–9) with 25 % ammonia and was then extracted twice with 150 ml of ether. The ether was distilled off at atmospheric pressure until a quantity of about 40 ml of pyridine remained, which was evaporated at 18 mm Hg (bath temperature 40°). The last traces of pyridine were removed in a desiccator over silica gel. The resulting brownish crystals were dissolved in ether which was extracted with 60 ml of 1 N hydrochloric acid. The aqueous solution was made alkaline (pH 9) with 2 N ammonia and extracted with ether (60 ml). This purification step was repeated once. The ethereal solution thus obtained was dried over Na_2SO_4 and then chromatographed through an aluminium oxide (Brockmann's Standardized) column (diam. 14 mm; height, 50 mm), coloured impurities being retained at the top of the column. The resulting ethereal solution — after evaporation — gave 9.2 g (0.037 mole; 37 %) of almost colourless crystals. Recrystallization from a mixture of 20 ml of ligroin (b.p. 110°–125°) and 10 ml of *n*-butyl ether yielded 7.4 g (0.029 mole, 29 %) of colourless prisms; m.p. 106.5°–107° (corr.). (Found: C 67.0; H 8.92; equiv. wt.* 250. Calc. for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{S}$ (250.4): C 67.1; H 8.86; equiv. wt. 250.)

Nitrate. Long colourless prisms from absolute ethanol; m.p. 150° (decomp.). (Found: C 53.7; H 7.35. Calc. for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$ (313.4): C 53.7; H 7.40.)

Picrate. Yellow needles from 96 % ethanol; m.p. 193°–194° (corr.). (Found: C 50.2; H 5.12. Calc. for $\text{C}_{20}\text{H}_{25}\text{N}_5\text{O}_7\text{S}$ (479.5): C 50.1; H 5.25.)

Perchlorate. Colourless rhomboidal prisms from absolute ethanol; m.p. 188° (decomp.). (Found: C 47.9; H 6.59. Calc. for $\text{C}_{14}\text{H}_{23}\text{ClN}_2\text{O}_4\text{S}$ (350.9): C 47.9; H 6.60.)

α -Diethylamino-2,4,6-trimethylthioacetanilide

α -Diethylamino-2,4,6-trimethylacetanilide,² 51 g (0.21 mole), was treated with phosphorus pentasulphide as described above. The yield was 4.75 g (0.0180 mole; 8.7 %) of an almost colourless crystalline mass. After two subsequent recrystallizations from isopropyl ether, 3.3 g (0.0125 mole; 6 %) of colourless needles were obtained; m.p. 121° (corr.). (Found: C 68.1; H 9.15; equiv. wt. 264. Calc. for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{S}$ (264.4): C 68.2; H 9.15; equiv. wt. 264.)

Nitrate. Short prisms from ethanol, melting at 119°–120°. (Found: C 55.0; H 7.82. Calc. for $\text{C}_{15}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$ (327.4): C 55.0; H 7.70.)

Picrate. Small yellow prisms from 70 % ethanol; m.p. 207°–208° (decomp., corr.). (Found: C 51.2; H 5.60. Calc. for $\text{C}_{21}\text{H}_{27}\text{N}_5\text{O}_7\text{S}$ (493.5): C 51.1; H 5.52.)

Perchlorate. Small colourless laths from absolute ethanol-isopropyl ether; m.p. 164°–165° (corr.). (Found: C 49.2; H 6.90. Calc. for $\text{C}_{15}\text{H}_{25}\text{N}_2\text{O}_4\text{SCl}$ (364.9): C 49.4; H 6.91.)

REFERENCES

1. Löfgren, N. Lundquist, B. † and Lindström, S. *Acta Chem. Scand.* **9** (1955) 1079.
2. Löfgren, N. *Studies on Local Anesthetics. Xylocaine, a new Synthetic Drug.* (Diss.) Stockholm 1948.

* The determination of equivalent weights of the synthesized bases was made by titrating them in 30 % ethanol with 0.1 N HCl; mixed indicator, methylene blue-methyl red.

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