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Studies on Local Anesthetics XIV *

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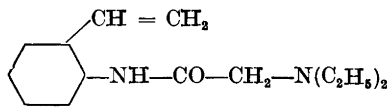
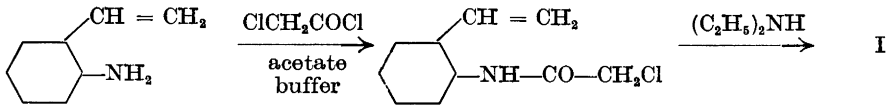
A new compound related to xylocaine [2] *i. e. α-diethylamino-2-vinylacetanilide* has been synthesized, and tested for its local anesthetic potency by subcutaneous anesthesia on man. Furthermore, the lethal dose in white mice was determined.

The compound synthesized in this work has the following structure:



I

Synthesis of the compound was carried out according to the following scheme:



2-Nitrostyrene was prepared as described by Einhorn [3] with some minor alterations. By reduction of this nitro compound according to Komppa [4], 2-vinylaniline was obtained. Due to the instability of the pure amine, it was not isolated. The amine was obtained as an ethereal solution which directly was used in the reaction with chloroacetyl chloride.

The ultraviolet absorption curves of I and α-diethylamino-2-ethylacetanilide are given in Fig. 1. Compound I was tested for its anesthetic activity by subcutaneous injection on man. The duration was found to be approximately 30 % shorter than that of xylocaine. The LD_{50} value measured by intravenous injection on mice was found to be the same as for xylocaine, *i.e.* 0.041 g of base per kg of white mouse **.

* For paper XIII of this series see Lüning [1].
** Experiments performed by S. Wiedling.

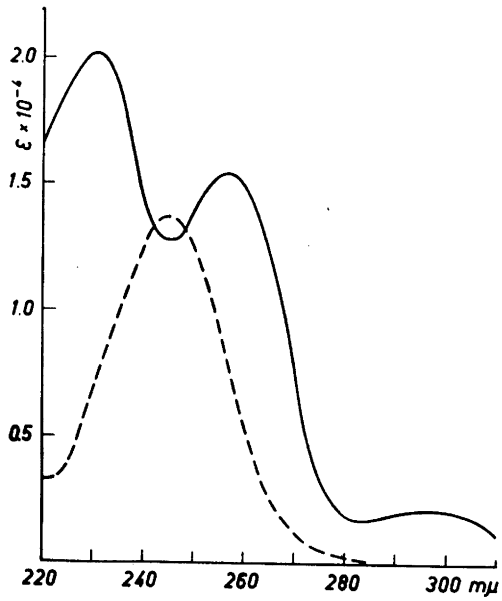


Fig. 1. Ultraviolet absorbtion curves of I (————) and α-dimethylamino-2-ethylacetanilide (— — — — —).

EXPERIMENTAL

β-Bromo-β-(2-nitrophenyl)propionic acid. This acid was prepared according to Einhorn [3]. Since Einhorn's description is rather incomplete, the experimental conditions had to be determined. Acetic acid saturated with hydrogen bromide at 0° was prepared in the following manner. Acetyl bromide, 50 g ,was mixed with 34 g of glacial acetic acid in a thick walled tube of resistant glass. The tube was cooled to 0°, and 10 ml of aqueous hydrobromic acid (d = 1.49) were added in 0.5 ml portions. If in this procedure addition be too fast, hydrogen bromide will escape resulting in an unsaturated solution. In this operation the temperature should be kept at 0°.

To the solution thus prepared, 2-nitrocinnamic acid, 10 g (0.052 mole), was added and the tube sealed. Under shaking, the tube was heated in a water bath at 75°—80° for one hour. During this time all 2-nitrocinnamic acid went into solution and a brown syrup formed. The tube was cooled to about —25° and then opened. Excess of HBr was removed at a bath temperature of 60° and the contents poured into 500 ml of ice-water. The brown precipitate thus formed was sucked off and washed with 100 ml of benzene. The yield was 9.9 g (0.036 mole; 72 %) of a brown crystalline powder; m.p. 138° (decomp.).

2-Nitrostyrene. 2-Nitrostyrene was prepared from β-bromo-β-(2-nitrophenyl)propionic acid according to the method given by Einhorn [3]. However, since Einhorn's yield of 2-nitrostyrene is very low (10 %) some improvements were made. A solution of 30 g of dry sodium carbonate in 150 ml of boiling water was introduced into the distilling flask of a steam distillation apparatus. β-Bromo-β-(2-nitrophenyl)propionic acid, 4 g, was added and the 2-nitrostyrene formed was steam distilled until no more came over. Another portion of 4 g of acid was added and the procedure repeated until a total amount of 23 g (0.084 mole) of the acid had been added. The distillate was made acid with a few drops of concentrated hydrochloric acid and the 2-nitrostyrene was taken up in 50 ml of ether. The ether was washed with 25 ml of dilute sodium carbonate solution and twice with 50 ml of water. The ethereal solution was dried over Na_2SO_4 and the ether evaporated.

The residue consisted of 2.2 g (0.015 mole; 17 %) of a brownish oil which solidified in the refrigerator. The crude 2-nitrostyrene was dissolved in ether and chromatographed through an Al_2O_3 (Brockmann's Standardized) column (diam. 14 mm; height 40 mm), coloured impurities being retained at the top of the column. After evaporation of the solvent the remaining oily material was crystallized from a solvent mixture ether-light petroleum 1 : 1 (v/v) at a temperature of −27°. Long pale yellow needles melting at 13°−14° (corr.) were obtained. (Found: C 64.4; H 4.73. Calc. for $C_8H_7NO_2$ (149.2): C 64.7; H 4.69.)

2-Vinylaniline. This compound was prepared according to Komppa's [4] method by reduction of 2-nitrostyrene with $SnCl_2$; however, the following alterations were made: (1) the reduction was carried out in a vessel that was cooled in a bath of running cold tap water, (2) the base obtained as an ethereal solution in the procedure was used directly for the synthesis of α-chloro-2-vinylacetanilide (*cf.* above).

α-Chloro-2-vinylacetanilide. To a mixture of a solution of 2-vinylaniline, prepared from 5.0 g (0.034 mole) of 2-nitrostyrene in 100 ml of ether (*cf.* above), and 12 g (0.15 mole) of dry sodium acetate, a solution of 3.0 g (0.038 mole) of chloroacetyl chloride in 50 ml of dry ether was added under vigorous stirring. After a period of 5 min, 25 ml of water were added and stirring was continued for another 15 min. Without separation of the two phases the ethereal layer was driven off under reduced pressure. α-Chloro-2-vinylacetanilide which precipitated during the evaporation was sucked off and dried. The dry product was dissolved in benzene and purified with charcoal. After evaporation, the residue was recrystallized once from absolute ethanol and once from benzene. Yield (based on 2-nitrostyrene): 1.9 g (0.0095 mole; 30 %) of colourless needles m.p. 92°−92.5° (corr.). Found: C 60.9; H 5.15. Calc. for $C_{10}H_{10}NOCl$ (195.65): C 61.4; H 5.15.)

α-Diethylamino-2-vinylacetanilide. α-Chloro-2-vinylacetanilide 1.8 g (0.0092 mole), was mixed with 2 g (0.0273 mole) of diethylamine in 16 ml of benzene (dried over $CaCl_2$) and the mixture refluxed for 5 h. After cooling, 20 ml of ether were added. The precipitated diethylamine hydrochloride was filtered off and the solution evaporated to dryness. The residue consisted of 2.0 g (0.0086 mole; 94 %) of a pale brownish oil. The oil was dissolved in ether and chromatographed through an Al_2O_3 (Brockmann's Standardized) column (diam. 14 mm; height, 40 mm), coloured impurities being retained at the top of the column. The effluent was washed with 100 ml of water. The base was extracted from the ether with 250 ml of 0.5 N hydrochloric acid. This solution was washed three times with 100 ml of ether. The base was liberated by means of saturated sodium carbonate solution and taken up in 50 ml of ether.

From this ethereal solution the *perchlorate* was prepared. The salt was recrystallized twice from absolute ethanol m.p. 166° (corr.). (Found: C 50.6; H 6.50. Calc. for $C_{14}H_{21}ClN_2O_5$ (332.8): C 50.5; H 6.36.)

The pure perchlorate was dissolved in 20 ml of water and 3 g of dry sodium carbonate were added. The separated oily base was taken up into ether. This ethereal solution was dried over potassium carbonate and then filtered. The ether was evaporated, leaving 1.45 g (0.0063 mole; 68 %) of a colourless oil; $n_D^{20} = 1.5480$. (Found: C 72.0; H 8.67. Calc. for $C_{14}H_{20}N_2O$ (232.3): C 72.4; H 8.68.)

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