

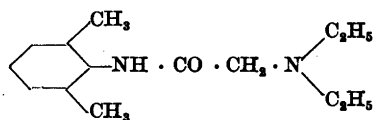
Studies on Local Anesthetics XI*

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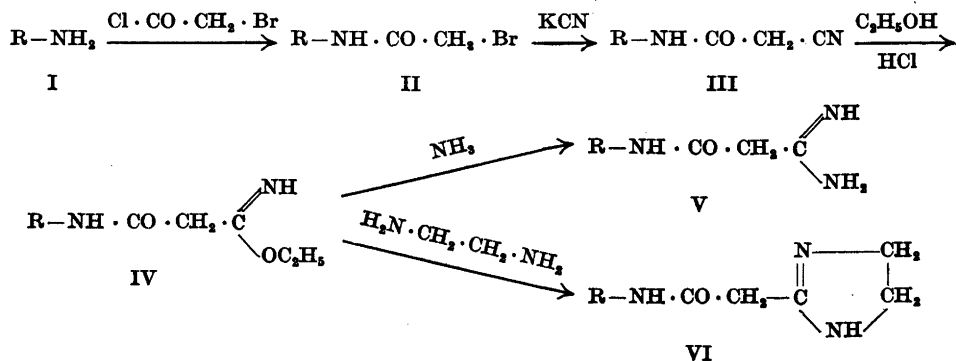
Three new compounds, related to xylocaine (α -diethylamino-2,6-dimethylacetanilide), *viz.* β -imino- β -ethoxy-2,6-dimethylpropionanilide, α -guanyl-2,6-dimethylacetanilide and α -(2-imidazolin-2-yl)-2,6-dimethylacetanilide have been synthesized and tested pharmacologically. In comparison with xylocaine the imido-ester and the imidazoline have very slight anesthetic activities on the rabbit cornea. The amidine is inactive. On the blood pressure the amidine and the imidazoline, like xylocaine, have a weak depressant action.

The syntheses of three compounds in which the diethylamino group of xylocaine



Xylocaine

is replaced by an imidocarbethoxy, a guanyl or a 2-imidazolin-2-yl group were carried out according to the following scheme:



R = 2,6-(CH₃)₂C₆H₃

* For paper X of this series see Löfgren and Tegnér¹.

The bromoacetylation of 2,6-dimethylaniline (I) yielding α -bromo-2,6-dimethylacetanilide (II) was carried out according to the aqueous acetate buffer method described by Löfgren ^{2,3}. Heating of II with KCN in ethanol gave α -cyano-2,6-dimethylacetanilide (III). This derivative was converted into β -imino- β -ethoxy-2,6-dimethylpropionanilide (IV) by reaction with ethanol and dry hydrogen chloride in dioxan solution, the procedure being a modification of that used by Cook and Reed ⁴ for the preparation of 1,4-bis(3-ethoxy-3-iminopropoxy)benzene. The ammonolysis of the imido-ester IV forming α -guanyl-2,6-dimethylacetanilide (V) was carried out in absolute ethanol during 5 days at 0°, and then for 2 days at room temperature. When condensing IV with ethylene diamine to give α -(2-imidazolin-2-yl)-2,6-dimethylacetanilide (VI) we followed the directions given by Klarer and Urech ⁵ who synthesized 2-(hydroxymethyl)-2-imidazoline by reaction between ethyl glycolimidate and ethylene diamine in absolute ethanol. To get a satisfactory yield of VI we had to perform the reaction at a lower temperature and over a longer period than is described in the synthesis of Klarer and Urech who obtained a high yield of their compound.

The compounds IV, V and VI were tested for their local anesthetic activity on the rabbit cornea and compared with xylocaine, the method given by Wiedling being followed ⁶. In these experiments the imido-ester IV and the imidazoline VI gave very slight anesthetic activities. The amidine V was found to be inactive*.

In common with local anesthetics in general xylocaine exercises a weak hypotensive action ^{6,7}. The effect on blood pressure of IV, V, VI and xylocaine were compared in the rabbit**. It was found that the imido-ester IV was devoid of action whereas the amidine V and the imidazoline VI, like xylocaine, gave a weak depressant action according to the following order of magnitude: V > VI > xylocaine.

As shown previously by Wiedling ⁶ in experiments on isolated guinea pig intestine xylocaine is devoid of histaminolytic action but has a slight cholinolytic activity, *i.e.* about 1 % of that of diphenhydramine. For an estimation of the histaminolytic and cholinolytic effects of compounds IV, V and VI the above mentioned method of Wiedling was used. No appreciable effects were found.

By subcutaneous injections in white mice the toxicities were determined for V and VI. The toxicity of IV was not investigated since its solubility in acids was too low to allow a proper determination. The LD₅₀ values of the amidine V and the imidazoline VI, calculated as grams of the base per kilogram of body weight were found to be 0.45 and 0.24, respectively. The corresponding value for xylocaine ⁶ is 0.34. In terms of *molar toxicity*, *i.e.* the toxicity expressed in moles per kilogram of body weight, the LD₅₀ values of V, VI and xylocaine are $2.2 \cdot 10^{-3}$, $1.0 \cdot 10^{-3}$ and $1.4 \cdot 10^{-3}$, respectively.

* No action of 0.25 ml of a 2 % hydrochloride solution of pH 7.3 even after 4 minutes' exposure to the eye.

** Intravenous supply to amytal anesthetized rabbits.

EXPERIMENTAL *

α-Bromo-2,6-dimethylacetanilide (II). This compound was prepared by reaction between 2,6-dimethylaniline and bromoacetyl chloride in an acetate buffer, the general directions of Löfgren ^{2,3} for this type of reaction being followed. The yield of the crude *α*-bromo-2,6-dimethylacetanilide melting at 145–150° was 91 %. On recrystallization from absolute ethanol the compound was obtained as colourless needles. M. p. 155–156° (corr.). (Found: C 49.7; H 4.99. Calc. for C₁₀H₁₂BrNO (242.1): C 49.6; H 5.00.)

α-Cyano-2,6-dimethylacetanilide (III). In a round-bottomed flask equipped with a stirrer and a reflux condenser a solution of 20 g (0.083 mole) of *α*-bromo-2,6-dimethylacetanilide in 140 ml of absolute ethanol was heated to 60°. To the hot solution were added in small portions and during a period of 45 minutes 7.2 g (0.11 mole) of potassium cyanide, dissolved in 9 ml of water. On the addition a precipitate formed. The mixture was then diluted with 20 ml of absolute ethanol and under continued stirring the temperature was maintained at 60° for another 2 hours. Finally, the mixture was heated to 80° and filtered by suction through a pre-heated glass filter. After dilution with a large quantity of water the precipitate was filtered off, washed with water and dried in a vacuum desiccator over silica gel. On recrystallization from 96 % ethanol pale yellow needles were obtained. M. p. 210–212° (corr.); yield 6.4 g (0.034 mole), *i. e.* 41 %. (Found: C 70.4; H 6.43. Calc. for C₁₁H₁₂N₂O (188.2): C 70.2; H 6.43.)

β-Imino-*β*-ethoxy-2,6-dimethylpropionanilide (IV). A mixture of 5.1 g (0.027 mole) of finely ground *α*-cyano-2,6-dimethylacetanilide, 1.3 g (0.027 mole) of absolute ethanol and 60 ml of highly purified dioxan was placed in a 250-ml round-bottomed flask fitted with a gas inlet tube, a thermometer and an ascending reflux condenser with a calcium chloride tube. Through the gas inlet tube a moderate stream of hydrogen chloride, carefully dried by passage through a mixture of phosphorus pentoxide and asbestos, was introduced. The temperature of the reaction mixture was not allowed to rise above 40°. After 4–5 hours the solution was cooled to 5° and the introduction of gas was continued until saturation. The reaction vessel was then closed and kept at a temperature of 4–5° for two days. After that time the expected *hydrochloride* of the imido-ester had partly precipitated. The precipitation was completed by dilution with absolute ether. The substance was filtered off, washed with absolute ether and dried in a vacuum desiccator over potassium hydroxide and silica gel. M. p. 128–129°; yield 6.7 g (0.025 mole), *i. e.* 91 %. (Found: Cl 13.16 (Mohr). Calc. for C₁₃H₁₈ClN₂O₂ (270.8): Cl 13.10.)

In some runs a less pure product was obtained since a small quantity of ammonium chloride contaminated the imido-ester hydrochloride. Satisfactory purification could be obtained by dissolving the substance in cold ethanol followed by fractional precipitation with dry ether. However, a more convenient purification was obtained by preparing the free base followed by recrystallization. For this purpose the salt preparation was dissolved in cold water and the imido-ester base liberated by the addition of dilute ammonia. The base was taken up in ether and after washing with water and drying with sodium sulphate the ether was driven off, leaving the imido-ester as needles. The base was dissolved at room temperature in a little more than the required amount of xylene (commercial mixture of isomers) and after addition of some light petroleum the compound was recrystallized by cooling to about –10°. M. p. 87–89°. (Found: C 66.9; H 7.48. Calc. for C₁₃H₁₈N₂O₂ (234.4): C 66.6; H 7.74.)

α-Guanyl-2,6-dimethylacetanilide hydrochloride (V). An alcoholic ammonia solution was prepared by saturating 10 ml of absolute ethanol at 0° with dry ammonia gas and diluting with 10 ml of alcohol. To this solution, 5.0 g (0.018 mole) of *β*-imino-*β*-ethoxy-2,6-dimethylpropionanilide · HCl were added. The mixture which was kept in a glass stoppered bottle was well shaken and allowed to stand for 5 days at 0° and for another 2 days at room temperature. After that time the mixture was filtered to remove the ammonium chloride which had precipitated. The red-violet filtrate was diluted with absolute ether until no more precipitate was formed. The precipitate was filtered off and washed with dry ether. This product in the form of a fine white crystalline powder was the desired amidine hydrochloride and did not need any further purification. M. p.

* All melting points are uncorrected unless otherwise stated.

230°; yield 3.1 g (0.013 mole), *i. e.* 72 %. (Found: C 54.4; H 6.63; Cl 14.93 (Mohr). Calc. for $C_{11}H_{16}ClN_2O$ (241.7): C 54.7; H 6.76; Cl 14.67).

α -(2-Imidazolin-2-yl)-2,6-dimethylacetanilide hydrochloride (VI). A solution of 1.1 g (0.019 mole) of ethylene diamine in 15 ml absolute ethanol was placed in a 100-ml two-necked flat-bottomed flask equipped with a magnetic stirrer and an ascending reflux condenser with a drierite tube. The solution was cooled to -15° and 5.2 g (0.019 mole) of β -imino- β -ethoxy-2,6-dimethylpropionanilide \cdot HCl were added under vigorous stirring. The mixture was kept at -15° for half an hour and then at 0° for two hours after which time 11 ml of 1.74 *N* alcoholic hydrogen chloride (0.019 mole of HCl) were added under continued stirring. The flask was now allowed to assume room temperature and to remain at that temperature for 2 hours. The mixture was then heated at 40° for 2 hours, stirring being continued. After that time the mixture was filtered by suction through a pre-heated glass filter. On cooling, the hydrochloride of *α -(2-imidazolin-2-yl)-2,6-dimethylacetanilide* separated as colourless crystals. They were collected and washed with dry ether. The product did not need further purification. M. p. 238–240°; yield 2.7 g (0.010 mole), *i. e.* 53 %. (Found: C 57.9; H 6.70. Calc. for $C_{13}H_{18}ClN_2O$ (267.8): C 58.3; H 6.77.)

We are indebted to A.-B. Astra, Södertälje, Sweden, for financial support and to Dr. S. Wiedling of the Biological Department of Astra for performing the pharmacological tests. Our sincere thanks are also due to Professor A. Girardet of the University of Lausanne who read through the manuscript.

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Received December 29, 1954.