SEARCH FOR NEW MEDICINALS

AZACYCLOALKANES

IX. SYNTHESIS AND ANESTHETIZING ACTIVITY OF PYRROMECAINE AND CYCLOMECAINE

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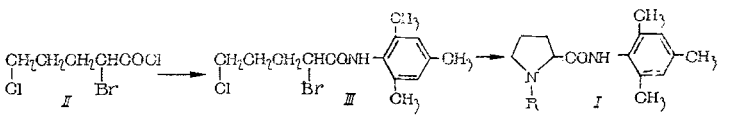
We have synthesized a number of aromatic amides of α-pyrrolidine-carboxylic acids and have studied the relationship between their structure and anesthetizing activity. Two compounds were isolated as a result of these investigations – the mesidide hydrochloride of N-butyl-α-pyrrolidine-carboxylic acid (which we have called "pyrromecaine") and the mesidide hydrochloride of N-cyclohexyl-α-pyrrolidinecarboxylic acid (which we have called "cyclomecaine") – which are of interest for practical medicine as surface anesthetics. The necessity for obtaining these preparations in significant quantities for clinical testing required the development of more convenient methods for their synthesis.

In this paper we propose a new method for obtaining the mesidides of N-substituted α-pyrrolidine-carboxylic acids (I) [1] via the following scheme:



The mesidide of α-bromo-δ-chlorovaleric acid (III), which is readily obtained from α-bromo-δ-chlorovaleryl chloride (II) and mesidine, is cyclized in high yield to the corresponding aryl amides (I) (see [2]) on reaction with primary amines (in molar ratios of 1:3.5). This method is highly efficient and makes it possible to synthesize type (I) compounds of various structures on a large scale.

Pyrromecaine and cyclomecaine are white, crystalline powders which are soluble in water, physiological solution, and alcohol. They are highly stable and do not lose their activity on prolonged storage in solution and during sterilization by boiling.

These preparations have high anesthetizing activity in all forms of anesthesia. A particularly valuable property which determines their significance for medical application is their high effectiveness in surface anesthesia. Pyrromecaine and cyclomecaine in all concentrations studied (0.1, 0.25, 0.5, and 1%) surpass cocaine by factors of two to five. The surface-anesthetizing action of pyrromecaine in 0.5 and 1% solutions and of cyclomecaine in 0.25 and 0.5% solutions is close to that of tetracaine. The curves of the surface-anesthetizing activity of pyrromecaine, cyclomecaine, and tetracaine (see Fig. 1) approach each other asymptotically in those portions which correspond to highly effective concentrations of anesthetics. The time for the development of surface anesthesia induced by pyrromecaine or cyclomecaine varies from 1 to 5 min and depends on the concentration of the preparation. It should be noted that the latent period of activity is manifested more in cyclomecaine. The duration of surface anesthesia for a 0.5% solution of the

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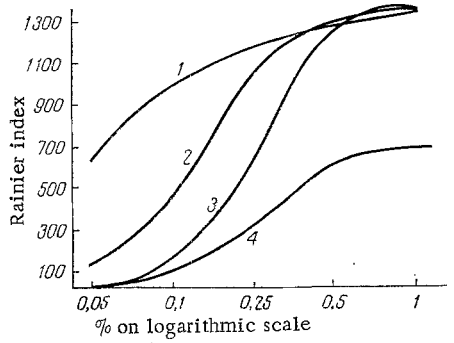

Fig. 1. Comparative activity of pyrromecaine, cyclomecaine, tetracaine, and cocaine in surface anesthesia: 1) cyclomecaine; 2) tetracaine; 3) pyrromecaine; 4) cocaine.

preparations is 15-25 min, compared with 45-60 min for 1% solutions, i.e., pyrromecaine and cyclomecaine do not differ with respect to this index and are somewhat less effective than tetracaine. Pyrromecaine and cyclomecaine induce an insignificant and short-lived dilation of the peripheral vessels. They can be used in combination with adrenaline, which reinforces their anesthetizing activity in the same way as it does in conjunction with other anesthetics.

The toxicities of pyrromecaine and cyclomecaine are relatively low: they are lower by factors of 12 and 16, respectively, than that of tetracaine. In comparison with cocaine and tetracaine, pyrromecaine and cyclomecaine have a greater therapeutic latitude. Pyrromecaine (in 0.25, 0.5, and 1% solutions) and cyclomecaine (in 0.25 and 0.5% solutions) do not have an irritating effect, as confirmed by histological investigations of the conjunctiva of rabbits. In studying the effect of pyrromecaine and cyclomecaine on the blood pattern, it was established that they do not induce any changes in the blood system when they are introduced subcutaneously in 25-mg/kg single doses.

A clinical study of pyrromecaine and cyclomecaine confirmed the experimental results; pyrromecaine was praised more highly by the clinicians. On the basis of these results, the Pharmacological Committee of the Ministry of Public Health of the USSR has recommended pyrromecaine for application to extensive medical practice as a surface anesthetic.

EXPERIMENTAL

α-Bromo-δ-chlorovaleryl Chloride (II). A mixture of 42.6 g of α-bromo-δ-chlorovaleric acid and 35.4 g of thionyl chloride was refluxed for 2 h, and the unchanged thionyl chloride was distilled off. The residue was distilled in vacuo and the fraction with bp 79-80° (1 mm) and n_D^{23} 1.5062 was collected to give 41.61 g (90%) of product. Found %: (Cl + Br) 64.61, 64.72. $C_5H_7BrCl_2O$. Calculated %: (Cl + Br) 64.47.

Mesidide of α-Bromo-δ-chlorovaleric Acid (III). A solution of 9.32 g of (II) and 40 ml of chloroform was added dropwise to a solution of 10.82 g of mesidine in 40 ml of chloroform at 0-10°. The mixture was refluxed for 1 h, the precipitate was filtered, and the filtrate was washed with 3% hydrochloride acid and then with water until a neutral reaction was obtained. After distilling away the solvent, the compound was washed with ether to give 11.5 g (86%) of (III) with mp 114-115°. Found %: Cl 34.37, 34.42. $C_{14}H_{19}BrClNO$. Calculated %: Cl 34.68.

Mesidide Hydrochloride of N-Butyl-α-pyrrolidinecarboxylic Acid (I, R = n-C_4H_9). A solution of 19 g of n-butylamine in 100 ml of toluene was added dropwise to a solution of 24.9 g of (III) in 100 ml of toluene, 0.25 g of potassium iodide was added, and the mixture was refluxed for 30 h. The precipitate was filtered, and the filtrate was shaken with a saturated potassium carbonate solution. The toluene layer was removed and evaporated to dryness. The residue was dissolved in 100 ml of ether, and ether saturated with hydrogen chloride was added. The precipitate was removed and recrystallized twice from an alcohol–ether mixture to give 15.6 g (64%) of product with mp 261-262°.

Mesidide Hydrochloride of N-Isobutyl-α-pyrrolidinecarboxylic Acid (I, R = iso-C_4H_9). This compound [30.2 g (62%), mp 252-253°] was similarly obtained from 49.8 g of (III) and 38 g of isobutylamine.

Mesidide Hydrochloride of N-Isoamyl-α-pyrrolidinecarboxylic Acid (I, R = iso-C_5H_{11}). This compound [24.7 g (73%), mp 251-253°] was similarly obtained from 33.3 g of (III) and 30.5 g of isoamylamine.

Mesidide of N-Cyclohexyl-α-pyrrolidinecarboxylic Acid (I, R = C_6H_{11}). A mixture of 16.6 g of (III), 17.3 g of cyclohexylamine, and 0.2 g of potassium iodide in 70 ml of toluene was refluxed for 30 h. The precipitate was filtered, and the filtrate was shaken with saturated potassium carbonate solution. The organic layer was separated, and the solvent was evaporated to half its volume and cooled. The precipitate was filtered and recrystallized from alcohol to give 9.4 g (84%) of a product with mp 126.5-127.5°. The hydrochloride of this product had mp 267-269°.

LITERATURE CITED

1. A. S. Lebedeva, A. M. Likhosherstov, G. I. Gurevich et al., Author's Certificate No. 202,955; Byull. Isobr. No. 20 (1967).
2. K. H. Mittleberger and J. Kaupp, West German Patent No. 1,098,514 (1961).