NEW DRUGS

PYROMECAINE, A NEW PREPARATION FOR TOPICAL ANESTHESIA

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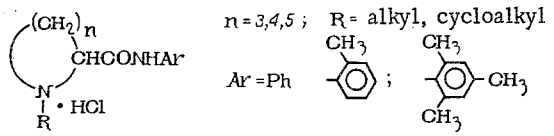
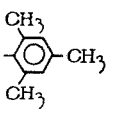
Anesthetizing substances used at the present time in medical practice belong to various classes of organic compounds [1, 2]. There are effective preparations in the field of esters of aromatic acids and amino alcohols (cocaine, novocaine, tetracaine, etc.), amides of aromatic acids (dibucaine hydrochloride: Sovcaine), ethers of dialkylaminoalkanols (pramocaine, cunisocaine), and aminoketones (falicaine, etamine). Anesthetics have extended to aromatic amides of N-substituted α-amino acids (xylocaine, trimecaine, carbocaine, etc.).

Cocaine and tetracaine, which are widely used in our country for topical anesthesia, possess a series of deficiencies. The major of these are brevity of action, high toxicity, and the ability to cause allergic reactions in 1-1.5% of the cases. Used in small doses for the anesthesia of mucous membranes of the upper respiratory passages, cocaine and, especially, tetracaine often lead to overall intoxication; even fatal results have been described [3-5]. This decided the expediency of searching for more ideal anesthetizing substances possessing low toxicity, high effectiveness, and proving to have an extended action.

A large series of hydrochlorides of aromatic amides of N-substituted α-amino acids (I) [6-8] have been obtained in the Institute of Pharmacology of the Academy of Medical Sciences of the USSR with the aim of searching for new substances for topical anesthesia. These have the general formula



As a result of a study of the link between chemical constitution, physicochemical properties, and anesthetizing activity certain compounds appeared to be of interest for further investigation as agents for topical anesthesia.

One of such compounds, the hydrochloride of N-butylpyrrolidine α-carboxylic acid mesidide (I, R = n-C_4H_9; Ar = ), named "pyromecaine" by us, seemed of the most interest for medical practice.

Pyromecaine caused a rapidly advancing topical anesthesia. The time of onset of the topical anesthesia on installation into the conjunctival sac of rabbits of 0.1-2% solutions of pyromecaine was 1-5 min, i.e., less than that of cocaine. The topical anesthesia of the rabbit eye caused by 0.5, 1, and 2% solutions of pyromecaine lasted

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for 20-60 min; this time is sufficient for carrying out various operations and manipulations. According to the depth of anesthesia assessed by the Rene and Valeta index, pyromecaine in all the concentrations studied (0.1-2% solutions) surpassed cocaine two- to fivefold. In 1 and 2% solutions the preparation exceeded tetracaine in anesthetic activity. The great merit of pyromecaine in comparison with preparations used at present is its low toxicity and high latitude of therapeutic action [9, 10].

To clarify the mechanism of action of pyromecaine the physicochemical properties of substances in a series of amides of N-substituted α-azacycloalkane carboxylic acids have been investigated, e.g., lipophilicity, distribution coefficient between dense and liquid phases of nerve, absorption into nerves, surface and interphase activity the effect on a monomolecular layer of fatty acids and lipoproteides of nerve tissue, and the effect on a bilayer phosphatidyl choline membrane.

It was shown that these characteristic physicochemical properties are connected with the anesthetic activity by a symbatic dependence. The establishment of a correlation between the anesthetizing effect of pyromecaine and the other original compounds of the series and their physicochemical constants underlines the importance of the properties studied in the mechanism of action of the anesthetic [10].

The effectiveness of pyromecaine has been studied clinically during various surgical, otorhinolaryngological, ophthalmological, and stomatological operations and manipulations. Also carried out were bronchography, bronchospirography with various intubations of the bronchi by Karlens tube, the removal of foreign bodies, tonsillectomy, polypotomy of the nose, turbinotomy, galvanocautery of cancers, submucous resection of the nasal membrane, tonometry, elastotonometry, gonioscopy, anesthesia of various infected mucous membranes of the oral cavity (multiform exudative erythema, acute aphthous stomatitis, Setton's stomatitis, etc.).

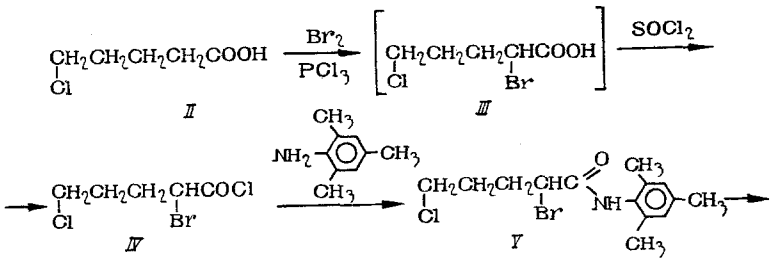
The application of pyromecaine for topical anesthesia in illnesses showed that the preparation was rapid in action, and in comparison with cocaine and tetracaine it was significantly less toxic. It showed vasoconstricting action towards mucous membrane and in contrast to tetracaine does not cause allergic effects. Consequently, according to the clinical conclusions pyromecaine is more convenient in practice than cocaine and tetracaine. The best results were obtained in otolaryngological and surgical clinics [11-12].

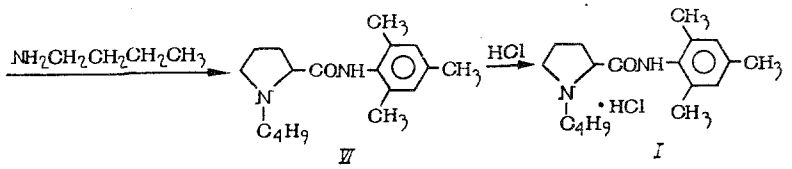
The preparation has been recommended for use in medical practice by the Pharmacological Committee of the Ministry of Public Health of the USSR.

Pyromecaine is used in the form of 0.5, 1, and 2% solutions. In otolaryngological and stomatological practice 1-5 ml of 1-2% solutions of the preparation is used with the addition of adrenaline in certain cases (1 drop 0.1% adrenaline solution in 2-3 ml anesthetic solution).

In surgical practice pyromecaine is used in form of 2% solutions. The overall consumption of 2% pyromecaine solution for carrying out anesthesia on bronchography amounted to 10-15 ml and on divided intubation of the bronchi, from 14 to 35 ml (average 20 ml). The maximal single dose is 1 g.

For the preparation of pyromecaine in the required amounts a more practicable method for its synthesis under industrial conditions was developed according to the following scheme:





Under the action of bromine in the presence of catalytic amounts of phosphorus trichloride δ-chlorovaleric acid (II) gives α-bromo-δ-chlorovaleric acid (III), which was converted without isolation into the acid chloride (IV) in 88% yield by the action of thionyl chloride. The mesidide of α-bromo-δ-chlorovaleric acid (V) was readily obtained from (IV) and mesidine in 86% yield on interacting them in chloroform solution at a temperature of 0-10°. Subsequently, on boiling (V) with butylamine in alcoholic solution in the presence of catalytic amounts of potassium iodide pyromecaine (VI) was obtained, which was converted into the hydrochloride of (I) by the action of alcoholic hydrogen chloride solution. In comparison with previously published data [7], a series of changes was introduced into the process of obtaining pyromecaine. Thus, at the stage of going from (II) to (IV) the isolation of (III) in a homogeneous state was omitted; this increased the yield and facilitated the progress of the synthesis. At the stage of making (VI) absolute alcohol was used in place of toluene with subsequent preparation of crystalline (VI) and conversion of it into the hydrochloride. The crude product was purified cleanly by recrystallization from absolute isopropyl alcohol. The development of this variant of the conversion of (V) to pyromecaine facilitated its preparation and purification.

The drug form of pyromecaine was developed in the Laboratory of Finished Drug Forms, the methods of analysis of pyromecaine and of its drug form were developed in the analytical laboratory of our Institute.

Pyromecaine is manufactured in the form of 0.5, 1, and 2% solutions in ampoules of 10, 30, and 50 ml (see Table 1). They are stored with precautions (register B) under the usual conditions.

A sterile solution of pyromecaine is a colorless clear liquid with a solution pH of 4.4-5.4. The MRTU (Interrepublic Technical Specification) of pyromecaine is No. 3924-71. The MRTU of 0.5, 1, and 2% pyromecaine solutions is No. 3970-71.

Authentication Reactions. A. The preparation (5 mg) was mixed with 1 drop copper sulfate solution, 0.5 ml concentrated sulfuric acid, and the solution was heated gradually to 175°. On cooling, 10 drops of concentrated ammonia solution was added: a red-pink fluorescence was observed in UV light. B. To a solution of 0.01 g of preparation in 2 ml water was added 0.5 ml potassium iodide solution. A white crystalline precipitate formed. C. On slowly heating the preparation to 185-200° it sublimed and settled on the walls of the test tube in the form of needle-shaped stars. The preparation gives a characteristic reaction for chloride; mp 252-259°.

Purity Testing. A solution of 0.1 g preparation in 5 ml freshly boiled water must be transparent and colorless; the pH of this solution is 4.4-5.4 (potentiometric), loss in weight on drying at 105° not more than 1%, content of sulfate ash not more than 0.1%, heavy metals no more than 0.001%, sulfate no more than 0.02%, hydrochloride and hydrobromide of n-butylamine not greater than 0.5%. The determination of n-butylamine hydrochloride and hydrobromide was carried out by thin-layer chromatography on binder-free layers of aluminum oxide of degree of activation III or IV in the solvent system acetone—chloroform—water (8 : 2 : 1). Contaminants were detected by spraying the lower portion of the plate with 1% ninhydrin in acetone solution and heating at 100° for

TABLE 1. Composition and Proportions of Ingredients in One Ampoule at Various Concentrations

Pyromecaine (g)	0.05	0.3	1.0
Isotonic sodium chloride solution (ml)	10	30	50
Concentration of pyromecaine solution (%)	0.5	1	2

20 min. Pyromecaine was detected with bromine or iodine vapor. R_f of pyromecaine was ~0.96; R_f of a contaminant was 0.16. Quantitative determination was carried out by a nonaqueous titration with 0.1 N perchloric acid in glacial acetic acid medium in the presence of mercuric acetate, the indicator was Crystal Violet: 1 ml 0.1 N perchloric acid solution corresponds to 0.03249 g N-butylpyrrolidine α-carboxylic acid mesidide hydrochloride, which must be not less than 99% in total in the dry substance.

For determining the purity of pyromecaine in solutions the latter were evaporated to dryness on a water bath, and the crystalline residue of pyromecaine was analyzed as described above. Testing for sterility was effected in conformity with the instructions on bacteriological checking of chemicopharmaceutical preparations for injection.

Quantitative determination of pyromecaine in solutions was also carried out by a spectroscopic method, measuring the optical density of the solutions being analyzed and of standards in cuvettes of thickness 1 cm at a wavelength of 260 nm.

EXPERIMENTAL

α-Bromo-δ-chlorovaleric Acid Chloride (IV). A mixture of 54.6 g (II), 83.1 g dry bromine, and 3 ml phosphorus trichloride was heated for 20 h at 80° and then for 2 h at 100°. The reaction mixture was washed with water, the oily layer removed, and the aqueous layer extracted several times with benzene. The benzene extracts were combined with the oil and the solution was dried over magnesium sulfate. After distilling off the benzene 85.2 g (III) of technical purity was obtained in the residue. Thionyl chloride (71 g) was added to (III), and the mixture was boiled for 2 h. The excess of thionyl chloride was distilled off, the residue was distilled in vacuum, collecting the fraction of bp 79-80° (1 mm), n_D^{20} 1.5068. Yield was 82.3 g (88%). Literature data [7]: bp 79-80° (1 mm), n_D 1.5062.

α-Bromo-δ-chlorovaleric Acid Mesidide (V). Obtained as described previously [7].

N-Butyl-α-pyrrolidine α-Carboxylic Acid Mesidide Hydrochloride (Pyromecaine). To 33.1 g (V) in 100 ml absolute alcohol was added a solution of 29 g butylamine in 100 ml absolute alcohol in small portions, then 0.3 g potassium iodide, and the mixture was boiled with stirring for 25 h. The reaction mass was poured into 1 liter cold water. The oily layer (VI), which separated, crystallized completely on standing. The solid was filtered off, washed with water, and dissolved in 200 ml of benzene. The benzene solution was dried over magnesium sulfate and filtered. To the filtrate was added 14 g 27% alcoholic hydrogen chloride solution. The reaction mixture was stored for a day. The precipitate was filtered off and dried. Yield was 24 g (73.8%). After recrystallization from 120 ml absolute isopropyl alcohol and drying 20.5 g (63%) pyromecaine mp 252-259° was obtained.

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