Pharmacologically Active 1-(2-ethoxyethyl)-Piperidines

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Success of scientific investigations and its realisation in practice are determined significantly by availability of the starting chemicals. Vinyl ether of monoethanolamine (VEMEA), which is produced at JSC "CARBIDE", Karaganda, RK, has being attracted our attention since the beginning of 80-s. The present communication demonstrations the results of our research to develop synthetic approaches to practically useful substances on the basis of VEMEA, which has been carrying out at the Laboratory of Medicinal compounds of the Institute of Chemical Sciences of MS-AS RK during more then 15 years.

Since ethoxyethylamine is the product of hydrogenation of monoethanolamine vinyl ether (VEMEA is commercially available in bulk quantities chemical reagent), we chose it as the convenient and available substrate for the synthesis of various piperidine derivatives. The synthesis of 1-(2-ethoxyethyl)-4-oxopiperidine (*prosidol ketone*) includes addition of 2 mole of methylacrylate to ethoxyethylamine with the following Dickman's cyclization of diester in the presence sodium methylate in toluene. At the same time the hydrolysis and decarboxylation of 3-carbometoxysubstituted piperidone-4 was elaborated. Now this method is the base of industrial production of *Prosidol ketone*. Moreover, 1-(2-ethoxyethyl)-3-methylpiperidone-4 was synthesized for stereochemical investigations.

The big block of the investigations was based on the reaction of nucleophilic addition of different reagents to high-active carbonyl group of piperidones-4. A number of 1-(2-ethoxyethyl)-4R-4-hydroxypiperidines (R = H, Ph, ethynyl, vinylethynyl, phenylethynyl, 5-methylpyridyl-2-ethynyl, vinyl, ethyl, phenylethyl etc.) and 1-(2-ethoxyethyl)-4-anilinopiperidines were prepared and identified using NMR-, IR-spectroscopy, mass-spectrometry and etc. The acylation of piperidoles-4 and anilinopiperidines gave the corresponding esters and amides of acetic, propionic and benzoic acids with the good yields. In a case of 3-methylpiperidones-4 the stereochemistry of all reaction was studying and every stereoisomeric pair was separated and each epimer was characterized. The comparison of different pharmacological activity of the synthesized compounds (water-soluble salts were tested) and that used in medical practice was made. It was found that the piperidine derivatives possess high analgesic, anaesthetic, antiarrhythmic, spasmolitic and other actions and are more effective than currently used medical preparations. Furthermore, the comparison of the substituents in the piperidine cycle of the synthesized compounds and its pharmacological properties allowed making the correlation "chemical structure-activity" and helped to choose the direction for further chemical modifications of piperidine.

Prosidol having analgesic action and *Kazcaine* having anaesthetic and antiarrhythmic action were the logic results of these research works. Now *Prosidol* is included in the International List of Used Drugs of Kazakhstan and Russia. *Kazcaine* is recommended for the second stage of clinical testing for 10 medicinal Centers of Russia.