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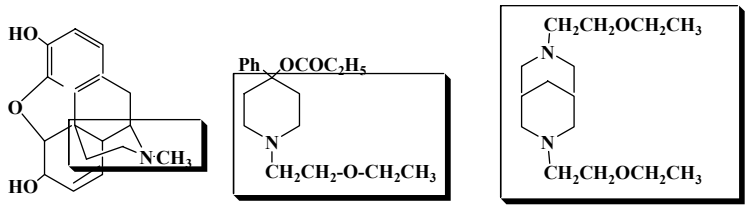
Poster Presentation

A Search for New Analgetic Agents among Mono- and Bicyclic Azaheterocycles

Praliyev K.D., Iskakova T.K., Zhumanova N.A.,
Zhaxibayeva Zh.M., Berganayeva G.Y., Yu V.K.

Institute of Chemical Sciences, Ministry of Education and Science,
106, Sh.Walikhanov str., Almaty,
Tel/fax: 8(3272) 912471
e-mail: yu_vk@rambler.ru

The piperidine skeleton is a moiety constituting the structure of variety of natural alkaloids, e.g., morphine possesses high analgesic properties. Due to this structural relationship, compounds belonging to the ring system of piperidines have been a subject of considerable interest. For instance, high analgesic effect has been demonstrated by piperidine derivative Prosidol, which contains 2-ethoxyethyl group at nitrogen atom of piperidine ring.



MORPHINE PROSIDOL NA-77

As a part of our research related to the synthesis of analgesic agents, we decided to combine two piperidine cycles with alkoxyalkyl groups at nitrogen atom in a one molecular. Within this field we have focused our interest on the synthesis of 3-alkoxyalkyl-7-R-3,7-diazabicyclo[3.3.1]nonane derivatives with a potential biological activity. Using the modified double-Mannich reaction, involving a condensation of 1-R-piperidone-4 with a primary amine and paraformaldehyde number of 3,7-disubstituted 3,7-diazabicyclo[3.3.1]nonan-9-ones had been synthesized. Kishner–Wolf reduction of bicyclic ketones gave corresponding bispidines with high yields. The carbonyl group at C_9 underwent the reduction by $LiAlH_4$ and reactions with Grignard reagents or phenyllithium to give a mixture of two alcohol C_9 epimers of 3-alkoxyalkyl-7-R-3,7-diazabicyclo[3.3.1]nonan-9-oles.

Previous results have indicated that certain groups might influence activity Thus usually phenyl group at C_4-position of piperidine ring provides excellent analgesic effect. Unexpectedly 3,7-dialkoxyalkyl-3,7-diazabicyclo[3.3.1]nonanes, NA-77 in particular, which don't include any substitutes in 9-position of bicyclic ring, possess analgesic activity. It have been shown that the lengthening and branching of alkoxyalkyl chain lead to increasing of analgesic action. As have been expected among esters 3-(2-ethoxyethyl)-7-(2-methoxyethyl)-9-benzoyloxy-3,7-diazabicyclo[3.3.1]nonan demonstrated high analgesia, moreover the alkoxyalkyl chain lengthening lead to effect decreasing. Thus it was shown that bicyclic analogies of 1-alkoxyalkylpiperidines exhibit analgesic properties.