PHARMACOLOGY

RELATIONSHIP BETWEEN STRUCTURE AND ADRENOLYTIC ACTION OF β-HALOGENATED ALKYLAMINES

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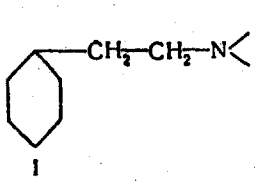
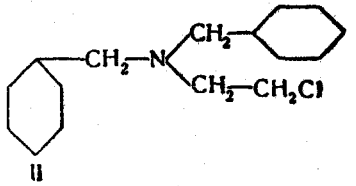
In comparing the formula of adrenaline and dibenamine, S. V. Anichkov has drawn attention to the similarity in chemical structure of dibenamine and the basic skeleton of adrenaline, i.e., with the phenylethylamine grouping (I). At the base of dibenamine lies a related benzyl group (II) in which one nitrogen bond is substituted by a second benzyl group and the other by the chlorethyl radical.



I



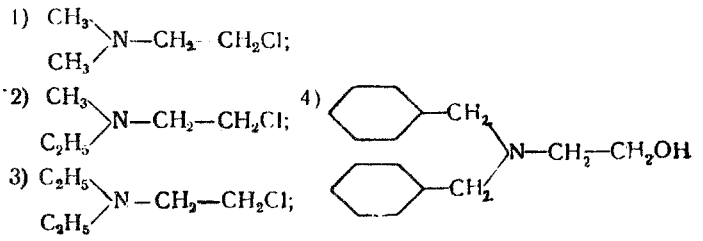
II

One may assume that due to the presence of the benzylamine group, dibenamine and the related halogenated alkylamines compete with adrenaline and combine with adrenoreactive systems; the presence of an aliphatic radical with a labile halogen atom leads to damage of these systems, ensuring the duration of adrenolytic action characteristic of dibenamine (I). In the view of S. V. Anichkov the strength and duration of action of adrenolytic substances must depend, on the one hand, on the similarity of the basic skeleton of the substance to the skeleton of the sympathomimetic amines and, on the other, on the lability of the halogen in the aliphatic radical.

In order to confirm this point of view we studied a number of halogenated alkylamines synthesized by G. I. Himpelson in 1948-1951.

The experiments were performed on decerebrated cats. The adrenolytic properties of the preparations were determined by their capacity to modify the pressor effect of adrenaline.

The experiments showed that substances not containing an aromatic radical or a halogenated alkyl group do not possess adrenolytic action (for example, four of the studied compounds, the formulae of which are set out below):



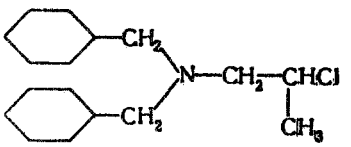
Thus, the thesis of S. V. Anichkov that the compounds of this series possessing adrenolytic effect must contain in the molecule an aromatic radical and a halogenated alkyl group was confirmed. Some foreign scientists have reached the same conclusions[3].

In order to clarify the influence of the lability of the halogen on the strength of the adrenolytic effect we investigated three compounds differing only in the halogen included: dibenzyl-β-chloroethylamine (dibenamine), dibenzyl - β - bromoethylamine (sympatholitin), dibenzyl - β - iodoethylamine.

It was found that the character of the halogen exerts an influence both on the strength of the effect and on solubility. The investigated compounds were insoluble in water and oil, the first two could be dissolved in alcohol. Dibenamine dissolved most readily (it was possible to obtain a 10% solution), sympatholitin was more difficult to dissolve (2% solution). The iodine analogue did not dissolve in alcohol. It was possible to dissolve a little in dioxane, which is itself toxic, and to give such a solution to the animal intravenously. Thus, it was not possible, in fact, to use it for the purpose of comparison in the experiments on animals although its adrenolytic properties were revealed.

Upon comparison of the effect of dibenamine and sympatholitin it was found that sympatholitin exceeds dibenamine in adrenolytic effect 8-10 times and in toxicity 2.5 times [2]. Comparative study of the chlorine and bromine analogues has been made by American investigators. According to them both compounds possess uniform activity in relation to adrenolytic effect (change in adrenaline pressor effect in cats); in toxicity the bromine analogue exceeds the chlorine by 1.5 times [3].

Sympatholitin is widely employed for physiological investigations, however, its clinical use, as with dibenamine, is limited owing to its local irritating effect. Upon intravenous introduction thrombophlebitis was observed, and with oral use, vomiting and nausea. Since the irritating effect of these compounds depends on the presence of β-halogenated alkyl group, we investigated a compound in which this group was somewhat changed:



However, no reduction in the local irritation effect in this case was observed (experiments on rats with intradermal injection).

LITERATURE CITED

[1] S. V. Anichkov, Novosti Med. (Moscow) 1949, No. 12, 1-10.

[2] R. A. Khaunina, Sympatholytic and Adrenolytic Effect of Sympatholitin, Dissertation * (Leningrad, 1951).

[3] M. Nickerson and W. S. Gump, J. Pharmacol. Exptl. Therap. 97, 1, 25-47 (1949).

* In Russian