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BISQUATERNARY DERIVATIVES OF CYCLOBUXINE-D AND THEIR BIOLOGICAL ACTIVITY

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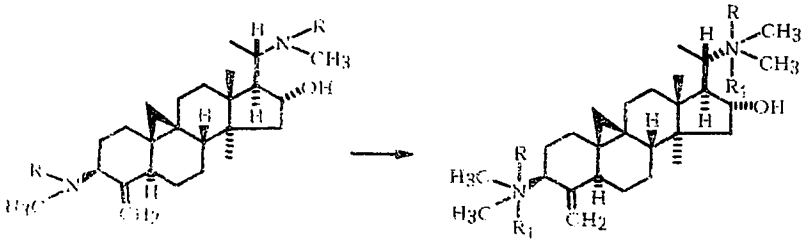
Six new bisquaternary derivatives of cyclobuxine-D have been obtained, and their biological activities have been studied.

Cyclobuxine-D (**1**) is obtained from various species of the genus *Buxus* and is quantitatively the main alkaloid in the mixture obtained from the plant *Buxus sempervirens* [1-4].

It is known that the passage from tertiary to quaternary nitrogen in a number of compounds sharply changes the pharmacological properties of the substances. Peripheral cholinotropic properties appear or are sharply enhanced [5-7]. In view of this, it appeared of interest to obtain some quaternary derivatives of the alkaloid cyclobuxine-D and to study their pharmacological properties. The Hess methylation of cyclobuxine-D gave N,N′-dimethylcyclobuxine-D (**2**) [3]. The treatment of (**2**) with methyl iodide led to the bismethiodide (**3**), the action of silver chloride on which gave the bismethochloride (**4**) of (**2**). The reaction of (**2**) with ethyliodide gave the bisethiodide (**5**) of (**2**). Treatment of (**5**) with silver chloride led to the bisethochloride (**6**). The bispropiodide (**7**) was obtained by boiling (**2**) with propyl iodide, and the interaction of (**7**) with silver chloride gave the bispropochloride (**8**).



1. R=H
2. R=CH_3

3. R=I, R_1=CH_3 **4.** R=Cl, R_1=CH_3
5. R=I, R_1=C_2H_5 **6.** R=Cl, R_1=C_2H_5
7. R=I, R_1=C_3H_7 **8.** R=Cl, R_1=C_3H_7

A pharmacological study was made of the readily water-soluble derivatives: the bismethochloride of N,N′-dimethylcyclobuxine-D (**4**), the bisethochloride of N,N′-diethylcyclobuxine-D (**6**) and the bispropochloride of N,N′-dimethylcyclobuxine-D (**8**). The compounds studied possessed myorelaxant, gangliolytic, and hypotensive actions. At the same time, they exhibited a more pronounced activity in relation to a parasympathetic ganglion. Compound (**8**) showed the greatest difference in this respect. Its influence on cardiac ganglia was more than 10 times greater than that on the superior cervical ganglion. Of course, the gangliar blocking of all sympathetic nodes cannot be judged from the suppression of one superior cervical ganglion. However, it was established for the compounds that we studied that doses not affecting the contraction of a tonified third eyelid do not cause a lowering of the arterial pressure (AP), either. Consequently, in these doses, conductivity in the sympathetic pathways participating in the regulation of the AP is not blocked. The results obtained permit the conclusion that a search for drugs with a high selective action in relation to parasympathetic ganglia among derivatives of the alkaloid cyclobuxine-D and similar alkaloids is of definite interest.

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EXPERIMENTAL

Mass spectra were taken on a MKh-1310 double-focusing mass spectrometer with a system for the direct injection of the specimen into the ion source. The individuality of the substances was checked by chromatography in thin layers of Q brand silica gel and alumina (act. grade II) in the following solvent systems: 1) butan-1-ol–acetic acid–water (10:1:3); 2) ethanol–chloroform (1:1); 3) cyclohexane–chloroform–diethylamine (7:2:1); 4) chloroform–butyl acetate–ethanol (3:2:1). Revelation by the Dragendorff reagent. All the compounds obtained were purified by recrystallization from ethyl alcohol.

N,N′-Dimethylcyclobuxine-D (2). A mixture of 0.42 g of cyclobuxine-D, 8 ml of 85% formic acid, and 8 ml of formalin was boiled for 8 h. Then it was diluted with water and made alkaline with ammonia, and the reaction product was extracted with methylene chloride. The residue after the solvent had been distilled off was treated with ethanol. This led to the isolation of 0.47 g of N,N′-dimethylcyclobuxine-D with mp 198-200°C, $[\alpha]_D$ +97.8° (*c* 0.511; chloroform). R_f 0.14 (system 1), M^+ 414 (mass spectrum).

Bismethiodide (3). A mixture of 0.41 g of N,N′-dimethylcyclobuxine-D, 0.41 ml of methyl iodide, and 25 ml of benzene was boiled for 18 h. This gave 0.75 g of the bismethiodide (**3**), with mp 215-217°C, R_f 0.38 (system 2).

Bismethochloride (4). A solution of 0.58 g of the bismethiodide (**3**) in 100 ml of ethanol was treated with 0.31 g of silver chloride, and the mixture was shaken for 9 h. After the complete replacement of the iodine by chlorine, the reaction product was filtered and the filtrate was evaporated, leading to the precipitation of 0.41 g of the bismethochloride (**4**) with mp 258-260°C, R_f 0.40 (system 2).

Bisethiodide (5). A solution of 0.61 g of N,N′-dimethylcyclobuxine-D in 30 ml of anhydrous benzene was treated with 0.51 ml of ethyl iodide, and the mixture was boiled for 32 h. This gave 0.96 g of bisethiodide with mp 216-218°C, R_f 0.42 (system 3).

Bisethochloride (6). A solution of 0.68 g of the bisethiodide (**5**) in 120 ml of ethanol was treated with 0.68 g of silver chloride, and the mixture was shaken for 9 h, with the complete replacement of iodine by chlorine. Thus gave 0.49 g of the bisethochloride (**6**) with mp 249-251°C, R_f 0.45 (system 2, TLC on alumina).

Bispropiodate (7). A mixture of 0.42 g of N,N′-dimethylcyclobuxine-D (**2**), 0.44 ml of propyl iodide and 25 ml of anhydrous benzene was boiled for 41 h. This gave 0.55 g of the bispropiodide (**7**) with mp 249-251°C, R_f 0.45 (system 2, TLC on alumina).

Bispropochloride (8). A solution of 0.41 g of the bispropiodide (**7**) in 100 ml of ethanol was treated with 0.35 g of silver chloride, and the mixture was shaken for 10 h, with the complete replacement of iodine by chlorine. This gave 0.27 g of the bispropochloride (**8**), with mp 229-231°C, R_f 0.57 (system 4).

The influence of the compounds on the arterial pressure (AP), respiration, neuromuscular transmission, sympathetic ganglia (from their effect on the contraction of the third eyelid), and parasympathetic ganglia (from their effect on the depressor reaction of the AP on the stimulation of the peripheral section of the vagus nerve) was studied under the conditions of an acute experiment on urethane-anesthetized cats. The results of the experiments showed that all the compounds studied affected the AP. The initial hypotensive dose was 0.5 mg/kg. Compounds (**4**) and (**8**) in a dose of 1 mg/kg (duration 10-15 min) and (**6**) in a dose of 2 mg/kg (duration 20-30 min) caused a fall in the AP by an average of 30%. Beginning from a dose of 0.3-0.5 mg/kg, all the compounds studied suppressed neuromuscular transmission. An increase to 1 mg/kg led to complete blockage of neuromuscular transmission. In these doses the duration of the myorelaxant effect amounted to 5-10 min for substances (**4**) and (**8**) and 20-40 min for (**6**). At these doses suppression of respiration also set in, but complete apnea was achieved only when the doses administered were increased to 2 mg/kg.

In doses of 1-2 mg/kg, the compounds suppressed contraction of the tonified third eyelid of a cat by approximately 50-100%, respectively, for 15-20 min. The cardiac ganglia of the vagus nerve proved to be more sensitive to the compounds studied; i.e., complete blockage of the latter was observed on the injection of compound (**4**) in a dose of 0.5 mg/kg, of (**6**) at 0.3 mg/kg, and of (**8**) at 0.2 mg/kg. In these doses the duration of the effect was 15-20 min for compound (**4**), 20-30 for (**6**), and 45-90 min for (**8**). In concentrations of $1 \cdot 10^{-6}$-$1 \cdot 10^{-4}$ g/ml the compounds had no effect on an acetylcholine spasm of an isolated rat intestine and, consequently possessed no M-cholinolytic effect, while the blockage of the AP depressor reactions on the electric stimulation of the vagus nerve is a manifestation of a ganglioblocking action in relation to parasympathetic ganglia.

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