CARDENOLIDE AND BUFADIENOLIDE DERIVATIVES OF AJMALINE

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A description is given of the synthesis of new compounds — 3-O-(ajmalin-N(b)-ioacetyl)strophanthidin and 3-O-(ajmalin-N(b)-ioacetyl)hellebrigenin bromides — possessing antiarrhythmic and cardiotonic activity. The synthesis was performed in two stages: 1) a preparation of halogen derivatives of the cardiac aglycones by acylating them with bromoacetyl bromide; and 2) the reaction of the alkaloid ajmaline with the halogen derivatives of the cardiac aglycones to quaternary salts.

The search for substances possessing an effective antiarrhythmic action is being carried on in many countries, since the majority of existing drugs do not satisfy clinicians because of their serious side effects. The main defect of many antiarrhythmic drugs that have been created that limits their use is the fact that they possess a depressing action on the myocardium and lower the arterial pressure [1, 2].

Having set ourselves the aim of obtaining compounds that could effectively normalize the rhythm of cardiac contractions and simultaneously tone up the work of the myocardium and the blood vessels, we have taken the path of semisynthesis using natural compounds with known biological effects. As such initial substances we have selected cardenolides and bufadienolides possessing a cartiotonic action [3] and the alkaloid ajmaline, which possesses an antiarrhythmic activity and has been suggested by us previously [4] as a drug. The combination of these substances in a single molecule, so it appears to us, should lead to the achievement of the aim set.

In the selection of methods of synthesis, we took into account the fact that the alkaloid ajmaline readily reacts with halogen derivatives of hydrocarbons to form quaternary salts, and this leads to a considerable enhancement of the antiarrhythmic activity; for example, N(b)-propylajmalinium bromide is 7-10 times more active than the initial amjaline [5]. Consequently, the synthesis could be carried out by obtaining intermediate halogen derivatives of cardenolides and bufadienolides.

The increase in the antiarrhythmic activity of ajmaline on the formation of quaternary salts was an important factor, since this enabled us to obtain a correlation in the biological activity of the two parts of the molecule of the "planned" compound. In order to obtain a still better correspondence it was necessary to reduce the cardiotonic activity of the cardenolide or bufadienolide member consisting, in particular, of such highly active aglycones as strophanthidin and hellebrigenin by a factor of 5-7. It is possible to reduce the biological activity of the cardiac aglycones within these limits by several methods. The simplest of them is the addition of a substituent containing an aromatic system. Since the alkaloid ajmaline contains such a system the task was simplified — the synthesis could be effected in two stages.

The acylation of the cardiac aglycones strophanthidin [3] and hellebrigenin [3] with monobromoacetyl bromide yielded 3β-O-bromoacetylstrophanthidin and 3β-O-bromoacetylhellebrigenin. These halogen derivatives of the agylcones were then subjected to direct interaction with the alkaloid ajmaline. The reaction was performed in a polar organic solvent — acetonitrile — at room temperature. The completeness of the reaction was checked by paper chromatography. Quaternary salts formed were isolated in the pure form by repeated crystallization. In this way we obtained 3-O-(ajmalin-N(b)-ioacetyl)strophanthidin bromide (I) and 3-O-(ajmalin-N(b)-ioacetyl)hellebrigenin bromide (II).

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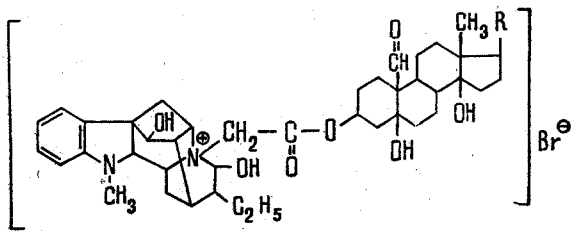
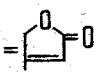
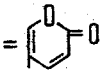


I. R = 

II. R = 

Of the two nitrogen atoms present in the alkaloid ajmaline, only one — the N(b) atom — took part in the reaction. This possesses a greater reactivity than ordinary tertiary nitrogen atoms apparently because of the influence of the neighboring OH group. The N(a) atom, which is connected with a benzene ring, is unreactive and under the given conditions does not form quaternary salts with halogen derivatives of hydrocarbons.

A confirmation of the fact that the addition reaction takes place at the N(b) atom is given by IR spectroscopy. The IR spectrum of 3-O-(ajmalin-N(b)-ioacetyl)strophanidin bromide (I), recorded against the background of the spectrum of ajmaline, is characterized by absorption bands with frequencies of 1738, 1700, 1622 cm^{-1}, and others, which belong to the strophanthidin part of the molecule, and of 1610, 1300, 1200, 760 cm^{-1} and others, which belong to the ajmaline part. The spectrum retains the absorption at 1300 cm^{-1} belonging to the aromatic tertiary amine group, i.e., the N(a) grouping. At the same time, the bands of stretching vibrations with frequencies of 1053 and 1040 cm^{-1} belonging to the nonaromatic (N(b)) atom have disappeared (these bands are present in the spectrum of the initial ajmaline). The disappearance of these bands is due to the formation of a quaternary ammonium salt, which has no characteristic absorptions.

Compound (I) gave positive reactions for cardenolides (Legal, Raymond) and also for bound ajmaline (with concentrated nitric acid — red coloration with blue fluorescence in UV light). The results of the elementary analysis of substances (I) and (II) agreed with the calculated figures. All this in combination with the directed nature of the synthesis performed confirmed the correctness of the proposed structures of (I) and (II).

Pharmacological investigations of substances (I) and (II) have confirmed the aim of the synthesis. The substances obtained possess a pronounced antiarrhythmic and cardiotonic activity. We investigated 3-O-(ajmalin-N(b)-ioacetyl)strophanthidin bromide (I) in most detail. In experiments on rats, guinea-pigs, and rabbits it showed a protective and arresting action in precardiac and gastric arrhythmias of various origins and increased the contractile capacity of the heart. In therapeutic doses having an antiarrhythmic action no fall in the arterial pressure was observed. As compared with a mechanical mixture of ajmaline and strophanthidin the synthesized substance (I) had the advantage that it possessed a considerably lower toxicity. The LD_{100} values for (I) were 2.5 mg/kg and 5.9 mg/kg in experiments on cats and guinea-pigs, respectively.

EXPERIMENTAL

The IR spectra were taken on an IR-27G spectrometer. Elementary analyses were performed on a Hewlett-Packard automatic C—H—N analyzer, and the analyses of all the compounds corresponded to the calculated figures. The melting points were determined on a Kofler block. The purities of the substances and the course of the reactions were checked by paper chromatography using the following systems: methyl ethyl ketone—m-xylene (1:1)/formamide and chloroform—tetrahydrofuran (1:1)/formamide.

3-O-Bromoacetylstrophanthidin. A solution of 32 g of strophanthidin in 75 ml of absolute pyridine was cooled to 0.3°C, and 10 ml (1.7 times the calculated amount) of monobromoacetyl bromide diluted with 45 ml of absolute dioxane was slowly, over 10-15 min, added to it from a separatory funnel. After 1 h, 600 g of ice was added to the reaction mixture and it was stirred and was left for crystallization at 0-3°C for 17-20 h. The crystals that deposited were separated off by filtration and washed with water (100-120 ml). Then they were dissolved with heating in 2 liters of ethanol, the solution was treated with 0.5 g of activated carbon and filtered, and the filtrate was evaporated in vacuum to a volume of

about 200 ml. Rapid crystallization of the bromoacetylstrophanthidin then took place. The crystals were separated off and washed with ethanol. The yield was 26 g, $C_{25}H_{33}O_7Br$, mp 217-219°C, $[\alpha]_D^{22}$ +44.0 ± 2°, $[M]_D$ +231 ± 10° (c 1.11; chloroform–methanol (7:1)).

3-O-Bromoacetylhellebrigenin. Hellebrigenine was acylated with monobromacetyl bromide as described above. This gave 3-O-bromoacetylhellebrigenin with the composition $C_{26}H_{33}O_7Br$, mp 204-206°C, $[\alpha]_D^{21}$ +30.0 ± 2°, $[M]_D$ +161 ± 11° (c 1.00; chloroform).

3-O-(Ajmalin-N(b)-ioacetyl)strophanthidin Bromide (I). A solution of 12.3 g of ajmaline and 19.8 g of bromoacetylstrophanthidin (equimolar ratio) in 190 ml of acetonitrile was left at room temperature (20-22°C) for 40 h. After this time, as the results of a chromatographic analysis showed, the reaction was complete and substance (I) had deposited as a precipitate. To complete the precipitation of (I) a double volume of ether was added to the flask containing the reaction mixture. The reaction product was separated off by filtration and was washed with water. Then it was dissolved in 320 ml of 96% ethanol, and 1.5 liters of diethyl ether was slowly added and the mixture was left at room temperature for 2 h. The resulting crystals were separated off, washed with ether, and dried in the vacuum desiccator. This gave 22-24 g of substance (I) with the composition $C_{45}H_{59}O_9N_2Br$, mp 210-212°C, $[\alpha]_D^{24}$ +41.5 ± 2°, $[M]_D$ +353 ± 17° (c 2.00; pyridine). Compound (I) was soluble in ethanol, pyridine, and dimethylformamide, sparingly soluble in water, and insoluble in ethers and benzene.

3-O-(Ajmalin-N(b)-ioacetyl)hellebrigenin Bromide (II). The reaction of 3-O-bromoacetylhellebrigenin with the alkaloid ajmaline was carried out in the same way as in the synthesis of substance (I). The desired product (II) obtained had the composition $C_{46}H_{59}O_9N_2Br$, mp 238-241°C, $[\alpha]_D^{20}$ +28.3 ± 2°, $[M]_D$ +244 ± 17° (c 1.80; pyridine).

SUMMARY

The following compounds have been synthesized from cardiac aglycones and the alkaloid ajmaline: 3-O-(ajmalin-N(b)-ioacetyl)strophanthidin bromide (I) and 3-O-(ajmalin-N(b)-ioacetyl)hellebrigenin bromide (II); they possess two therapeutically important properties — the capacity for normalizing the rhythm of cardiac contractions and for toning up the work of the myocardium.

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