ADAMANTYLIMINO DERIVATIVES OF CARDENOLIDES

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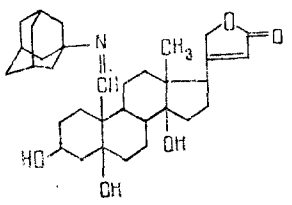
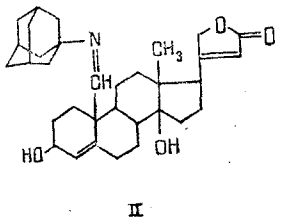
There are statements in the literature that adamantyl derivatives of a number of biologically active substances lower their toxicity and modify their pharmacological properties [1-3].

We set ourselves the task of obtaining a series of adamantyl derivatives of cardenolides. N-tert-adamantyliminostrophanthidin (I) and N-tert-adamantyliminosecurigenin (II) were obtained by the following method.



I



II

Strophanthidin (4 g) was dissolved in 50 ml of chloroform–absolute ethanol (3:1) and the resulting solution was treated dropwise with a solution of 1.5 g of 1-aminoadamantane in the same mixture of solvents. The reaction was performed at the boiling point of the reaction mixture on the water bath. The course of the reaction was monitored by thin-layer chromatography in the methylene chloride–methanol (93:7) system. After the end of the reaction (about 10 h), the mixture of solvents was evaporated off in vacuum, and the residue (4.5 g) was dissolved in methylene chloride and crystallized, giving 3.2 g of N-tert-adamantyliminostrophanthidin (I) with bp 250-256/260°C, $[\alpha]_D^{20}$ +19.7° (c 1.0; methylene chloride–methanol (1:1).

N-tert-Adamantyliminosecurigenin (II) with mp 220-225/230°C was synthesized similarly. However, in contrast to N-tert-adamantyliminostrophanthidin we used additionally for the isolation of N-tert-adamantyliminosecurigenin the chromatography of the reaction products on alumina of activity grade III. The eluants used consisted of mixtures of hexane and ethylene chloride (70:30-10:90) and pure methylene chloride. The N-tert-adamantyliminosecurigenin was crystallized from methanol.

The elementary analyses of the compounds obtained agreed with the calculated figures for the compositions $C_{33}H_{47}O_5N$ and $C_{33}H_{45}O_4N$, respectively.

The IR spectra of the adamantylimino derivatives of strophanthidin and securigenin obtained showed no aldehyde group absorption. There were absorption bands characterizing the following functional groups: an OH group (3460 cm^{-1}), CH and CH_2 groups including the adamantyl nucleus (2850, 2190 cm^{-1}), C=O of a butenolide ring (1787, 1750 cm^{-1}), C=N (1650 cm^{-1}), C=C of a butenolide ring (1620 cm^{-1}), an angular CH_3 group, and a cyclohexane fragment of the adamantyl function (1450 cm^{-1}).

Pharmacological investigations of the adamantylimino derivatives (I) and (II) of the cardenolides obtained have shown that they are less toxic and are cardiotonically less active than the initial cardenolides. Thus, in a study of acute toxicity in experiments on white mice with intraperitoneal administration it was established that the LD_{50} value for N-tert-adamantyliminostrophanthidin was 538 (753.2-384.3) mg/kg, and that for strophanthidin under the same conditions was 174 (212.0-156.1) mg/kg, i.e., N-tert-adamantyliminostrophanthidin is three times less toxic than the initial strophanthidin.

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In experiments on frogs it was established that N-tert-adamantyliminostrophanthidin was approximately four times less cardiotonically active than strophanthidin.

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ALKALOIDS OF *Vinca major* INTRODUCED INTO GEORGIA

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Continuing a study of the alkaloids of the epigeal organs of *Vinca major* L. introduced into an experimental field of the I. G. Kutateladze Institute of Pharmacochemistry of the Academy of Sciences of the Georgian SSR, we have isolated another six bases [1]. The herb was extracted with acidified methanol. After the methanol had been distilled off, the acid solutions were brought to pH 9-10 and the alkaloids were extracted with ethyl ether. The combined material obtained was separated by the usual method into phenolic (A) and nonphenolic (B) fractions [2]. By distributing fraction B according to basicity with the aid of citrate-phosphate buffers having pH 7, 6, 5, 4, 3, and 2.2, five alkaloids were isolated.

Alkaloid B_1, $C_{21}H_{24}N_2O_3$, was obtained from the pH 7 buffer; mp 263-264°C (methanol), $[\alpha]_D$ +14° (c 1.0; methanol). UV spectrum, λ_{max} 243, 294 nm (log ε 3.69, 3.25). IR spectrum, cm^{-1}: 3350, 3060 (—OH, >NH groups); 1720, 1245 (—$COOCH_3$); 750 (disubstituted benzene ring). Alkaloid B_1 was identified as vincarine [3].

Alkaloid B_2, $C_{21}H_{26}N_2O_2$, mp 227-229°C (methanol), was obtained from the pH 6 buffer. Its UV spectrum was characteristic for indoline derivatives. The IR spectrum included the following bands (cm^{-1}): 3340 (—OH), 1620 (indoline ring), 815 (trisubstituted benzene ring). The mass spectrum confirmed the composition of the molecule: M^+ 338. Alkaloid B_2 was assumed to be vincamajorine [4].

Alkaloid B_3, $C_{23}H_{28}N_2O_6$, mp 185-186°C (methanol), $[\alpha]_D$ —150° (c 0.2; chloroform) was obtained from the pH 5 buffer. UV spectrum, λ_{max}: 225 nm (log ε 4.55). IR spectrum (cm^{-1}): 3340 (>NH); 1730, 1275 (—$COOCH_3$); 720, 775, 795 (tetrasubstituted benzene ring). Alkaloid B_3 was majdine [5].

Alkaloid B_4, $C_{21}H_{26}N_2O_3$, mp 233°C (methanol), $[\alpha]_D^{20}$ —5° (c 1.0; chloroform) was isolated from the pH 3 buffer. UV spectrum, λ_{max}: 225, 280 nm (log ε 4.50, 3.95). IR spectrum (cm^{-1}): 3580 (—OH); 1740, 1250 (—$COOCH_3$); 750 (disubstituted benzene ring). Alkaloid B_4 was identified as vincamine [6].

Alkaloid B_4, $C_{22}H_{26}N_2O_3$, mp 215°C (ethyl ether) was obtained from the pH 3 and pH 2.2 buffers. UV spectrum, λ_{max}: 243, 293 nm (log ε 3.93, 3.53). IR spectrum (cm^{-1}): 3100-3200 (—OH); 1740, 1248 (—$COOCH_3$); 760 (disubstituted benzene ring). The mass spectrum confirmed the composition of the molecule: M^+ 366. The alkaloid was identified as vincamajine [7].

Alkaloid A_1, $C_{22}H_{26}N_2O_4$, mp 279-280°C (methanol), $[\alpha]_D$ —140° (c 2.0; chloroform) was isolated from the combined material A by crystallization from ethyl ether. UV spectrum: λ_{max} 244, 312 nm (log ε 3.88, 3.60). IR spectrum (cm^{-1}): 3300 (—OH); 1740, 1640 (—$COOCH_3$), 780, 760, 725 (trisubstituted benzene ring). Alkaloid A_1 was characterized as akuammine [8].

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