Chemistry of Natural Compounds, Vol. 34, No. 2, 1998

STROPHANTHIDIN AZOMETHINES

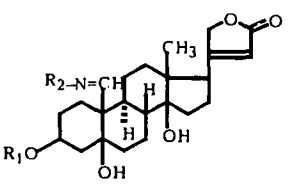
I. F. Makarevich and S. V. Kovalev

UDC 547.92/93

From the cardenolide strophanthidin have been synthesized its semicarbazone, thiosemicarbazone, and phenylhydrazone, benzyliminostrophanthidin, cyclohexyliminostrophanthidin, hydroxyethyliminostrophanthidin, and hydroxypropyliminostrophanthidin.

We have previously obtained a number of aldoximes of cardenolides and their glycosides and have investigated their biological activity [1, 2]. It was shown that the introduction of an oxime group into an aglycon increases its biological activity 2.5- to 3-fold. Compound (**1**) has proved to be even more sensitive, its activity being 5 times higher than that of the initial strophanthidin derivative and amounting to 0.06 mg/kg body weight of a cat (by Hatcher's method).

With the aim of a fuller study of the relationship between chemical structure and biological activity, we have synthesized a series of new azomethines from strophanthidin: strophanthidin semicarbazone (**2**), strophanthidin thiosemicarbazone (**3**), strophanthidin phenylhydrazone (**4**), benzyliminostrophanthidin (**5**), cyclohexyliminostrophanthidin (**6**), hyroxyethyliminostrophanthidin (**7**), and hydroxypropyliminostrophanthidin (**8**).



1. R_1=Ac. R_2= OH
2. R_1= H. R_2= H_2NCONH-
3. R_1= H. R_2= H_2NCSNH-
4. R_1= H. R_2= C_6H_5NH-
5. R_1= H. R_2= $C_6H_5CH_2$-
6. R_1= H. R_2= 
7. R_1= H. R_2= $HOCH_2CH_2$-
8. R_1= H. R_2= $HO(CH_2)_3$-

The syntheses were carried out by heating strophanthidin with the appropriate amines. It must be mentioned that, while the production of substances (**2**, **4**, **5**, and **6**) was a simple process in each case, substantial difficulties arose in the synthesis of the others (**3**, **7**, and **8**). In these cases the reactions were only 40-60% complete, so that chromatographic isolation of the desired substances was necessary.

The authenticity of the proposed structures (**1-8**) was confirmed by directed synthesis, elementary analysis, and PMR spectra. Each PMR spectrum contained a one-proton singlet with a chemical shift in the region of 7.60-8.03 ppm belonging to a $^{19}CH{=}N-$ grouping.

EXPERIMENTAL

Elementary analyses were performed on a Hewlett-Packard automatic C–H–N–S analyzer; the results corresponded to the calculated figures. The purity of the substances and the course of the reactions were monitored by paper chromatography using the following solvent systems: methyl ethyl ketone–*m*-xylene (1:1)/formamide, toluene–butan-1-ol (1:2)/water, and benzene/formamide, and by thin-layer chromatography using the solvent system chloroform–methanol–water (85:15:0.7).

State Scientific Center for Drugs, Kharkov-85, 33 Astronomicheskaya ul. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 185-187, March-April, 1998. Original article submitted December 1, 1997.

 0009-3130/98/3402-0148$20.00

Strophanthidin Semicarbazone (2). A solution of 3 g of strophanthidin in 300 ml of methanol was treated with 5.9 g of semicarbazide hydrochloride and 7.2 g of sodium acetate dissolved in 40 ml of water. The mixture was boiled for 4 h in a flask fitted with a reflux condenser. After the end of the reaction, 50 ml of water was added to the flask, the solution was concentrated to an aqueous residue, and the crystals that deposited were separated off. The technical product so obtained was recrystallized from benzene and, twice, from ethanol. This gave the chromatographically pure semicarbazone (2), mp 268-275°C, $[\alpha]_D^{20}$ +68.0 ± 2° (*c* 0.5; chloroform–ethanol–pyridine), $C_{24}H_{35}N_3O_6$.

Compounds (4), (5), and (6) were obtained analogously.

Strophanthidin phenylhydrazone (4) was crystallized from ethanol, mp 242-246°; $[\alpha]_D^{20}$ +52.0 ± 2° (*c* 0.5 chloroform), $C_{29}H_{38}N_2O_5$.

Benzyliminostrophanthidin (5) was crystallized from methanol, mp 185-190°; $[\alpha]_D^{20}$ +26.4 ± 3° (*c* 0.4; chloroform), $C_{30}H_{39}NO_5$.

Cyclohexyliminostrophanthidin (6) was crystallized from a mixture of acetone and water, mp 130-140°; $[\alpha]_D^{20}$ +8.9 ± 2°(*c* 0.6; chloroform), $C_{29}H_{43}NO_5$.

Strophanthidin Semicarbazone (3). A solution of 7.5 g of thiosemicarbazide in 100 ml of 60% ethanol was added to a solution of 5 g of strophanthidin in 230 ml of ethyl alcohol. The mixture was boiled in a flask fitted with a reflux condenser for 30 h. Two further 3-g portions of thiosemicarbazide were added during the reaction. Judging from the results of chromatographic analysis, after this time the synthesis had proceeded by approximately 60%. The cardenolides were extracted from the reaction mixture with chloroform (400 ml). The alcohol–chloroform mixture was evaporated, and the residue was chromatographed on a column containing 200 g of alumina (activity grade III), the eluents being chloroform–ethanol–ethyl acetate mixtures of increasing polarity. The fractions containing the individual strophanthidin thiosemicarbazone that were obtained were combined and crystallized from methanol–ethyl acetate–water–hexane (two-phase system), mp 190-195°; $[\alpha]_D^{20}$ +62.4 ± 2° (*c* 0.6; chloroform–ethanol), $C_{24}H_{35}NO_5S$.

Hydroxyethyliminostrophanthidin (7). The synthesis was conducted in a similar manner to that of (3), including the adsorption-chromatic separation of the mixture of products. Compound (7) was crystallized from acetone, mp 140-145°; $[\alpha]_D^{20}$ +31.0 ± 3° (*c* 0.5; chloroform–ethanol), $C_{25}H_{37}NO_6$.

Hydroxypropyliminostrophanthidin (8). The synthesis and chromatographic purification were analogous to those for substance (3). The desired product (8) had mp 115-120°; $[\alpha]_D^{20}$ +30.1 ± 3° (*c* 0.5 chloroform–ethanol).

REFERENCES

1. I. F. Makarevich, in: Modern Problems of Pharmaceutical Science and Practice [in Russian], Kiev (1972), p. 508.
2. I. F. Makarevich, M. V. Mokrouz, and L. Ya. Topchii, Khim. Prir. Soedin., 608 (1983).
3. I. F. Makarevich, M. V. Mokrouz, V. F. Konev, and L. Ya. Topchii, Inventors' Certificate No. 1088347.