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ALDIMINES OF CARDENOLIDES AND CARDENOLIDE-GLYCOSIDES

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New aldimines were synthesized from the cardenolide strophantidin and cardenolide-glycosides erysimin and cymarin and included morpholine, nitrile, pyridine, furan, hydroxy- and methoxyphenyl, piperidine, and other derivatives. An effective modified method for synthesizing aldimines was proposed. 52 new compounds were synthesized. Their structures were confirmed by IR and PMR spectra and elemental analysis.

Key words: aldimines, strophantidin, erysimin, cymarin.

We previously reported [1, 2] the synthesis of eight aldimines of strophantidin, some of which were slightly toxic cardiotonics, for example, adamantyliminostrophantidin [2].

Therefore, it seemed advisable to continue research on the preparation of a broader set of new compounds with subsequent pharmacological screening. For this, we used amines of various structures.

The starting natural compounds were the cardenolide strophantidin and the cardenolide-glycosides erysimin and cymarin, which have angular aldehydes [3]. These were synthesized by two methods. Organic compounds containing a free primary amine were reacted directly with the natural aldehydes by boiling in appropriate solvents and removing the water formed during the reaction by azeotropic distillation. It was found that the imines formed most rapidly and completely at the highest possible concentrations of the reactants, when the reaction mixture was like a melt. From the time such a state was reached, the reaction was finished usually within an hour.

The second method was necessitated by the fact that primary amines are commonly sold as salts, more often as hydrochlorides. In these instances, the reaction was carried out in boiling solutions with sodium acetate.

For both methods the course of the reactions was monitored by TLC or paper chromatography.

The yields of the desired products were 60-80% of those calculated.

The structures of products **1**-**52** were confirmed by elemental analysis and IR and PMR spectra. The IR spectra typically lacked absorption bands for aldehyde and contained absorption bands for C=N groups (1650 cm^{-1}).

During the synthesis of the cardenolide aldoximes we observed the rare case where two types of isomers, conformational (conformers) and geometrical (*cis—trans* or *syn—anti*), were formed simultaneously. The conformational isomers formed because free rotation around the C10–C19 single bond is restricted for steric reasons. We have previously reported this during the synthesis of cardenolide oximes [4] and demonstrated that the most stable of the two possible conformers is that in which the H atom of C19–H is oriented toward the angular methyl of the 18-CH_3. This is completely consistent with the cardenolide aldimines and is confirmed by the following data. Strophantidin aldimines form complexes (green colored) with Cu ions that are soluble in organic solvents. The unshared pair of the N atom and the C3 and C5 OH groups (**5**) are involved in the complexation. The PMR spectra of the aldimines have signals for the angular 18-CH_3 methyl near 0.66-0.74 ppm, i.e., shifted to strong field. This is due to steric shielding of this group by the 19C–H proton. The steric proximity of the 19C–H and 18-CH_3 protons is clearly visible in 3D-models of these molecules.

This orientation of the 19C–H proton affects directly the geometric isomerism due to the steric placement of the functional groups around the C=N double bond. Of the geometric isomers (**3**, **4**), the *anti* (*E*)-isomers (**3**) are most probable. Just this *E*-isomer can easily form complexes with Cu ions (**5**), which was observed in this instance.

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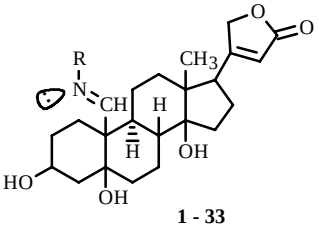
TABLE 1. Strophantidin Imines

Compound	Empirical formula	mp, °C	$[\alpha]_D^{20}$, deg (MeOH)	Compound	Empirical formula	mp, °C	$[\alpha]_D^{20}$, deg (MeOH)
1	$C_{31}H_{41}NO_5$	157-160	+28.9±4	**18**	$C_{27}H_{41}NO_6$	154-157	+29.5±2
2	$C_{28}H_{37}NO_6$	109-112	+91.6±3	**19**	$C_{27}H_{41}NO_6$	154-157	+30.2±3
3	$C_{29}H_{38}N_2O_5$	128-133	+72.0±4	**20**	$C_{27}H_{41}NO_7$	141-145	+30.6±3
4	$C_{33}H_{45}NO_7$	103-105	+35.2±3	**21**	$C_{30}H_{45}NO_6$	146-149	+35.7±2
5	$C_{31}H_{45}NO_5$	110-114	+35.3±2	**22**	$C_{31}H_{41}NO_7$	217-221	+48.3±3
6	$C_{29}H_{45}N_3O_5$	104-107	+45.0±3	**23**	$C_{31}H_{41}NO_6$	231-234	+37.7±2
7	$C_{29}H_{38}N_2O_5$	125-129	+66.7±2	**24**	$C_{26}H_{37}NO_7$	110-112	+73.7±3
8	$C_{29}H_{38}N_2O_5$	120-123	+62.1±3	**25**	$C_{27}H_{41}NO_7$	144-146	+49.8±3
9	$C_{31}H_{39}NO_7$	129-134	+73.0±3	**26**	$C_{27}H_{41}N_2O_6$	145-149	+37.3±2
10	$C_{26}H_{37}NO_5$	177-178	+62.3±3	**27**	$C_{29}H_{44}N_2O_6$	105-107	+42.6±3
11	$C_{32}H_{43}NO_7$	116-119/125-127	+54.0±2	**28**	$C_{30}H_{46}N_2O_5$	162-166	+37.3±2
12	$C_{30}H_{45}NO_6$	141-144	+32.1±3	**29**	$C_{30}H_{48}N_2O_7$	140-144	+28.4±3
13	$C_{33}H_{45}NO_8$	138-142	+48.0±3	**30**	$C_{25}H_{35}N_2O_5$	137-140	+52.1±3
14	$C_{32}H_{43}NO_7$	127-130	+57.3±3	**31**	$C_{31}H_{40}NFO_5$	172-176	+57.5±2
15	$C_{27}H_{41}NO_5$	205-207	+36.9±3	**32**	$C_{33}H_{53}NO_5$	88-92	+39.3±2
16	$C_{31}H_{43}NO_6$	100-104	+36.8±3	**33**	$C_{30}H_{37}NO_8$	120-124	+28.5±2
17	$C_{32}H_{43}NO_7$	114-117	+57.1±3				



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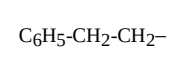

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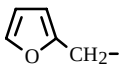

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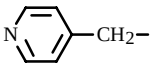

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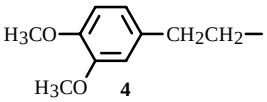

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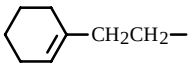

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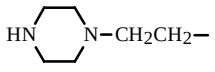

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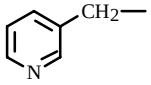

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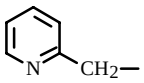

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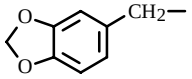

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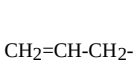

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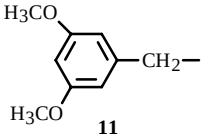

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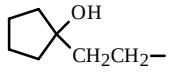

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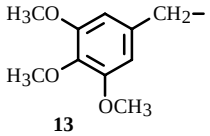

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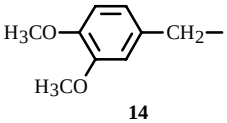

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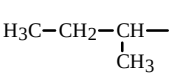

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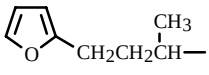

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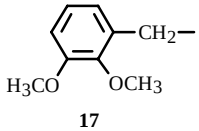

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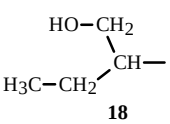

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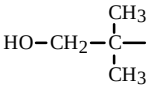

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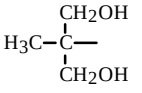

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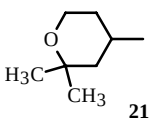

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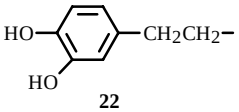

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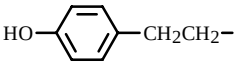

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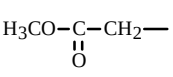

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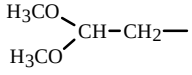

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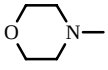

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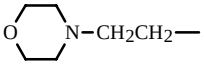

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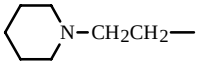

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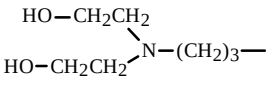

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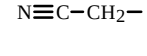

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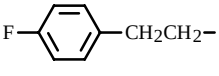

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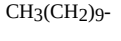

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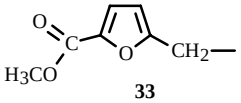

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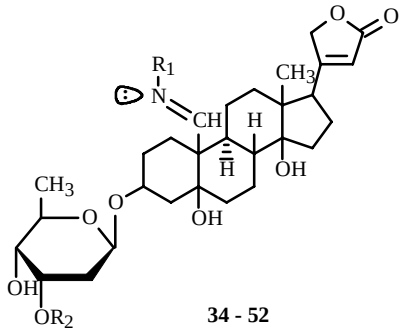
TABLE 2. Erysimin and Cymarin Imines

Compound	R_2	Empirical formula	mp, °C	$[\alpha]_D^{20}$, deg (MeOH)	Compound	R_2	Empirical formula	mp, °C	$[\alpha]_D^{20}$, deg (MeOH)
34	H	$C_{34}H_{47}NO_9$	139-143	+72.7±3	**44**	CH_3	$C_{32}H_{46}N_2O_8$	144-146/164-167	+44.9±2
35	H	$C_{37}H_{51}NO_8$	123-126/162-165	+35.7±3	**45**	H	$C_{37}H_{55}NO_8$	105-109	+21.4±3
36	H	$C_{37}H_{51}NO_9$	Amorph.	+29.6±3	**46**	H	$C_{32}H_{49}NO_9$	Amorph.	+38.5±3
37	H	$C_{35}H_{48}N_2O_8$	159-164	+25.7±2	**47**	H	$C_{39}H_{63}NO_8$	97-100/112-114	+41.7±2
38	H	$C_{35}H_{48}N_2O_8$	150-152	+60.2±2	**48**	H	$C_{41}H_{67}NO_8$	87-91	+41.3±2
39	H	$C_{35}H_{48}N_2O_8$	142-147	+70.8±3	**49**	H	$C_{30}H_{45}N_3O_9$	182-185	+47.0±3
40	H	$C_{37}H_{50}FNO_8$	137-138/143-144	+23.6±3	**50**	H	$C_{31}H_{47}NO_9$	Amorph.	+39.3±3
41	H	$C_{32}H_{47}NO_8$	150-154	+40.2±3	**51**	CH_3	$C_{34}H_{53}NO_8$	Amorph.	+26.0±3
42	H	$C_{31}H_{44}N_2O_8$	118-121	+36.3±2	**52**	CH_3	$C_{31}H_{47}N_3O_8S$	186-188	+16.3±3
43	H	$C_{36}H_{56}N_2O_8$	132-135	+38.3±3					



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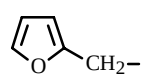

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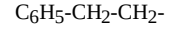

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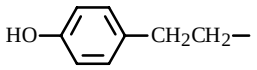

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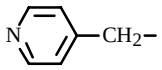

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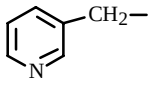

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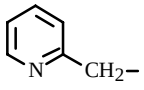

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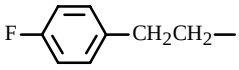

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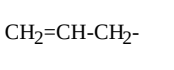
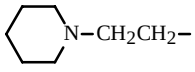


41

42, 44



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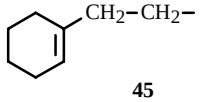

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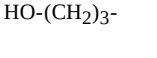

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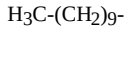

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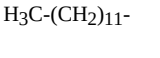

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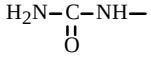

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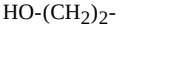

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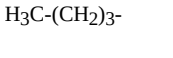

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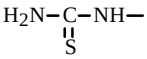


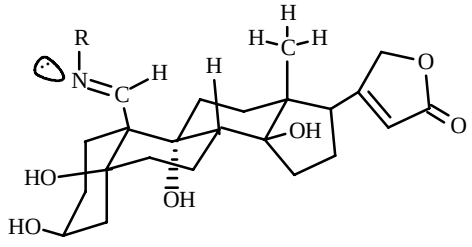
52

34 - 43, 45 - 50: R_2 = H; **44, 51, 52:** R_2 = CH_3

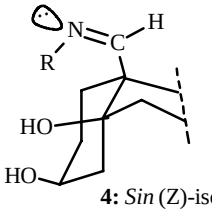
The *syn* (*Z*)-isomer (**4**) cannot form such complexes.

Computer modeling of the stereoisomers confirmed that the *anti* (*E*)-isomers (**3**) are more stable. The *syn* (*Z*)-isomers are less stable owing to steric hindrance arising, on one hand, between the functional group on the N atom and, on the other, from the 1β H, 5β OH, and 3β OH steroid part of the molecule.

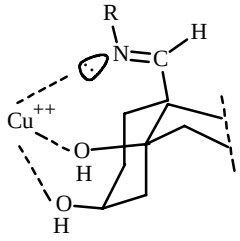
The research resulted in the synthesis of a rather broad set of new strophantidin, erysimin, and cymarin aldimines (**1**-**52**). Pharmacological screening of the new compounds will be reported elsewhere.



3: *Anti* (E)-isomer



4: *Sin* (Z)-isomer



5

EXPERIMENTAL

Paper chromatography was performed using MEK:*m*-xylene(1:1)/formamide. TLC was performed on Silufol-254 plates using $CHCl_3$:CH_3OH (85:15) with Raymond developer. IR spectra were recorded on a Specord-75 IR spectrometer (KBr disks); PMR spectra, on a Varian VX-200. Elemental analysis was performed on a Model 1106 automated C-H-N-S analyzer. Elemental analyses of all compounds agreed with those calculated. Melting points were determined on a Kofler block.

Compounds **11** and **42** are used as examples of the two synthetic methods.

Preparation of 11. Strophantidin (3 g) was dissolved with heating in isopropanol:benzene (1:3, 30 mL) and treated with 3,5-dimethoxybenzylamine (1.65 g, 1.5-fold calculated excess). The reaction mixture was boiled in a long-necked flask on a water bath and treated with small portions of the evaporating solvent. At the time when, according to chromatographic analysis, the content of the desired product was greater than that of starting strophantidin, the reaction mixture was condensed to a syrupy consistency. Heating was continued, adding anhydrous benzene (1-2 mL) every 7-10 min. When the reaction was complete, the flask was removed from the water bath, treated with petroleum ether (30 mL), and thoroughly mixed. The petroleum-ether solution, into which the remaining reagent had transfered, was decanted. The thick mass was treated another four times with petroleum ether in a similar fashion, converting it to a powder. The amorphous powder was separated on a Buchner funnel and dried in vacuo. It was crystallized from methanol. For this, the amorphous powder was dissolved in CH_2Cl_2 (10 mL) and treated with methanol (20 mL). The solution was concentrated with heating to a small volume (~10 mL) and left at room temperature. The resulting crystals were separated and washed with methanol to afford chromatographically pure **11**, 2.8 g, mp 116-119/125-127°C, $[\alpha]_D$ +54.0 ± 2° (*c* 1.1, MeOH).

Compound 42. Erysimin glycoside (3 g) was dissolved with heating in benzene:isopropanol (1:1, 30 mL). Acetonitrileamine hydrochloride ($N{\equiv}C–CH_2–NH_2 \cdot HCl$, 0.9 g) and anhydrous NaOAc (0.78 g) ground into a fine powder were added with stirring. The solution was boiled in a long-necked flask, periodically adding solvent (2-3 mL). Chromatographic analysis showed that the reaction was complete in 1 h 40 min and that all erysimin had reacted with the amine. The solution was concentrated to a small volume (7 mL). Petroleum ether (25 mL) was added. A thick mass precipitated. The petroleum-ether layer was separated and discarded. The thick mass was dissolved in $CHCl_3$ (5 mL) and again treated with petroleum ether. This operation was repeated another four times to afford a pink amorphous powder (3.1 g). Then, the desired product was purified by column chromatography over Al_2O_3 (90 g, Brockmann activity grade III, activated for 2 h at 110°C). The eluent was $CHCl_3$:isopropanol (95:5) of increasing polarity (to 80:20). Fractions (3 mL) were collected using an automated collector.

Fractions **6-40** were combined and evaporated in vacuo to afford a chromatographically pure white amorphous powder (2.38 g).

Crystallization. The amorphous powder was dissolved in methanol (5 mL), heated, and left at room temperature for 17 h. The resulting crystals were separated and dried to afford final product (**42**), 1.75 g, mp 118-121°C, $[\alpha]_D^{20}$ +36.3 ± 2° (*c* 1.2, MeOH).

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