Chemistry of Natural Compounds, Vol. 42, No. 4, 2006

NEW AZOMETHINE CARDENOLIDE GLYCOSIDES

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UDC 547.92/93+615.224:547.918

New azomethines (aldimines) were synthesized from cardiac glycosides erysimin and cymarin. The structures of the new compounds were confirmed by PMR spectra and elemental analysis.

Key words: azomethines, aldimines, cardenolide glycosides, erysimin, cymarin, amines.

Azomethines are comparatively nontoxic compounds [1]. Therefore, the toxicity of natural cardiac glycosides may possibly be reduced by preparing them. In continuation of this research [1, 2], we prepared new azomethines of the cardiac glycosides erysimin and cymarin (**1**, **2**, **5-10**, **12**, **14**) and semicarbazones (**3** and **11**) and hydrazones (**4** and **13**) related to them.

The synthesis was performed mainly using the literature method [1-3] of direct reaction of aldehydeglycosides and primary amines with boiling in solvents that enable the removal of water as an azeotrope. Of all reagents used, aminoalkylpyridines formed the azomethines most completely and quickly, which led to the use of pyridine as a catalyst, the use of which for these purposes was first proposed by Gubin and Makarevich [4].

In fact, small additions of pyridine (see Experimental) accelerated the reaction. A second factor that increased the rate of the reaction and the yield of the target azomethines was performing the synthesis at high concentrations of reagents, according to recommendations in the literature [5].

In some instances the reaction products could be crystallized directly after the synthesis. However, chromatographic purification over columns of Al_2O_3 or SiO_2 was required more often than not.

Only one of the two geometric isomers that are possible in principle based on the different location of the functional groups around the C=N double bond was obtained in practice. We believe as before [3] that this is the *trans*-isomer. This is consistent with the PMR spectra and the ability of the obtained azomethines to form complexes with Cu ions. Only the *trans*-isomer with the chelating structure consisting of the 5β-OH, the C-3 O atom, and the unshared electron pair on N that is oriented toward the first two groups can form a complex with Cu ions.

The PMR spectra of the obtained azomethines have the signal for the angular methyl 18-CH_3 at 0.66-0.73 ppm, i.e., shifted to strong field due to the steric effect on it of the 19C–H proton, i.e., the 19C–H proton is oriented toward this methyl. These data agree with the literature [3] relative to the stereochemistry of aldimines of cardenolides. Figure 1 shows the PMR spectrum.

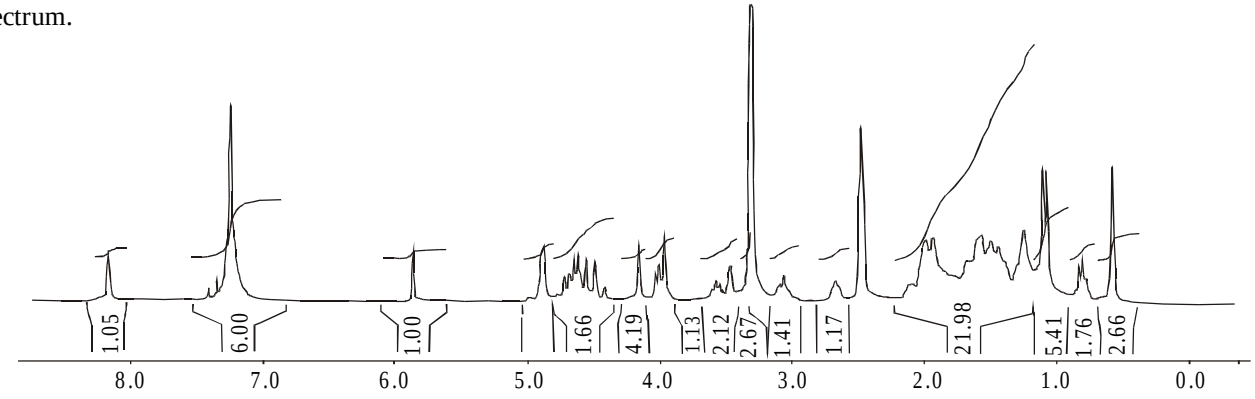

Fig. 1. PMR spectrum of benzyliminocymarin.

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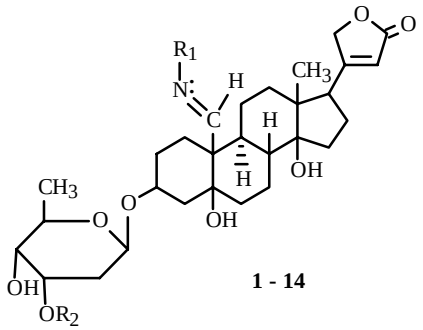
Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 362-363, July-August, 2006. Original article submitted April 13, 2006.

0009-3130/06/4204-0449

TABLE 1. Azomethines of Erysimin and Cymarin

Compound	R_2	Molecular formula	mp, °C	$[\alpha]_D^{20}$ in MeOH
1	CH_3	$C_{36}H_{48}N_2O_8$	132-134	+51.8±2
2	CH_3	$C_{36}H_{48}N_2O_8$	142-144	+49.9±2
3	CH_3	$C_{31}H_{44}N_3O_9$	147-150/172-174	+42.4±2
4	CH_3	$C_{36}H_{48}N_2O_8$	111-114	+78.1±3
5	CH_3	$C_{37}H_{49}NO_8$	109-110/127-129	+65.3±2
6	CH_3	$C_{32}H_{46}NO_9$	139-142	+47.7±2
7	CH_3	$C_{33}H_{48}NO_9$	135-138	+36.9±3
8	CH_3	$C_{36}H_{48}N_2O_8$	118-121	+66.7±3
9	CH_3	$C_{34}H_{45}NO_9$	130-132	+60.1±3
10	CH_3	$C_{36}H_{49}N_2O_9$	107-109	+44.3±3
11	H	$C_{30}H_{42}N_3O_9$	273-275	+54.8±3
12	H	$C_{36}H_{49}NO_9$	120-122	+20.2±3
13	H	$C_{33}H_{43}N_2O_9$	115-117	+26.3±3
14	H	$C_{35}H_{50}NO_9$	140-142	+27.5±3



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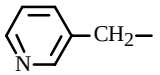
R_1 =



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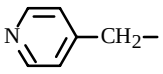

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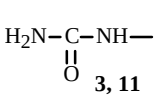

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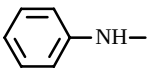

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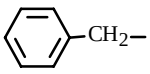

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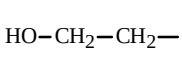

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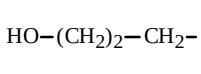

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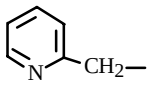

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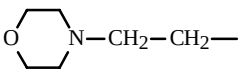

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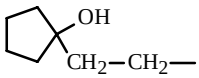

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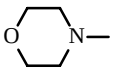

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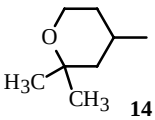

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EXPERIMENTAL

The course of reactions and purity of compounds were monitored using TLC on Sorbfil plates and $CHCl_3$:CH_3OH:H_2O (85:15:0.7) with development by Raymond reagent. Melting points were determined on a Kofler block. PMR spectra were recorded on a Varian VX-200. Elemental analyses were measured on an automated C—H—N—S analyzer and agreed with those calculated.

Benzyliminocymarin (5). Cymarin (1.5 g) was dissolved in benzene:isopropanol (3:1, 25 mL) and treated with benzylamine ($C_6H_5CH_2NH_2$, 0.44 g, 1.5-fold excess of calc.). The mixture was boiled for 2 h in a long-necked flask, periodically adding evaporating solvent. The solution was concentrated to about 3 mL and treated with anhydrous pyridine (5 drops). The reaction was continued, adding benzene (1 mL) every 10-15 min. After the reaction was completed and the solution was cooled to room temperature, nefras (35 mL, bp 170-195°C) was added. The mixture was stirred. The nefras solution was decanted. The thick mass was ground three times with nefras (15 mL) until it turned into a powder. This transferred the benzylamine into the nefras. The resulting crude benzyloiminocymarin (1.7 g) was chromatographed over an Al_2O_3 column (50.0 g Al_2O_3, Brockmann activity III).

The eluents were $CHCl_3$ and $CHCl_3$:CH_3OH of increasing polarity. Fractions containing pure cymarin azomethine were crystallized from CH_2Cl_2:nefras to afford **5** (1.04 g, 60% of calc.), $C_{37}H_{49}NO_8$, mp 109-110/127-129°C, $[\alpha]_D$ +65.3 ± 2° (*c* 0.8, CH_3OH).

The remaining azomethines of cymarin and erysimin were synthesized analogously. Table 1 gives their properties.

REFERENCES

1. I. F. Makarevich and S. V. Kovalev, *Khim. Prir. Soedin.*, 185 (1998).
2. I. F. Makarevich, Yu. I. Gubin, M. V. Mokrouz, S. V. Kovalev, T. V. Slyusarskaya, and K. V. Zhernoklev, *Farmakom*, No. 2, 36 (2001).
3. I. F. Makarevich, Yu. I. Gubin, and R. Megges, *Khim. Prir. Soedin.*, 332 (2005).
4. Yu. I. Gubin and I. F. Makarevich, *Khim. Prir. Soedin.*, 381 (2006).
5. I. F. Makarevich, Yu. I. Gubin, and R. Megges, *Khim. Prir. Soedin.*, 42 (2005).