STROPHANTHIDIN D- AND L-ARABINOSIDES

I. F. Makarevich, L. N. Kolosok, S. G. Kislichenko, N. A. Kisten, and D. G. Kolesnikov

Khimiya Prirodnykh Soedinenii, Vol. 6, No. 2, pp. 221–224, 1970

UDC 615.711.5+547.92

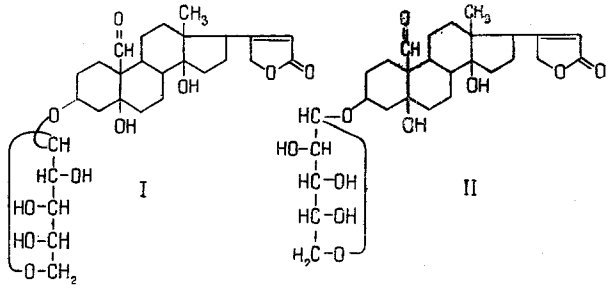
In order to clarify the influence of D- and L-sugars on the biological activity of the cardiac glycosides, we have synthesized strophanthidin arabinosides. The synthesis was effected by the reaction of O-acetylarabinosyl bromides with strophanthidin by the Königs-Knorr method [1] in Chernobai's modification [2]. The reaction products were saponified with ammonia in methanol (removal of the protective acetyl groups). After purification, the glycosides were obtained in the crystalline state.

The arabinosides synthesized differed little on paper chromatography. In the chloroform–tetrahydrofuran (1 : 1)/formamide system, the L-arabinoside is somewhat more polar. Hydrolysis of the glycosides, carried out on the micro scale by the Mannich-Siewert method [3], led to the formation of the aglycone strophanthidin and to D- and L-arabinoses, respectively. The hydrolysis products were identified by paper chromatography.

The synthesis took place stereospecifically. In both cases, 1,2-trans-glycosides with the α-configuration of the glycosidic bond were formed. This is shown by a comparison of molecular rotation according to Klyne's rule [4]:

Substance	$[M]_D$, deg.
Strophanthidin 3-L-arabinoside	+163,3±16
Strophanthidin 3-D-arabinoside	+204,1±16
Strophanthidin	+180,4± 8
Methyl α-L-arabinopyranoside	+ 28,9[5]
Methyl β-L-arabinopyranoside	+404,9[5]
Methyl α-D-arabinopyranoside	— 27,9[6,7]
Methyl β-D-arabinopyranoside	—395,9[6]
$\Delta C_{\text{L-arabinose}}$ in glycoside I	— 17,1±24
$\Delta C_{\text{D-arabinose}}$ in glycoside II	+ 23,7±24
$\Delta C_{\text{L-arabinose}}$ in glycoside I	—17, ±24
$\Delta C_{\text{D-arabinose}}$ in glycoside II	+23,7±24

The dimensions of the oxide ring can be judged from the behavior of the glycosides on hydrolysis with dilute acids. The arabinosides synthesized are not hydrolyzed appreciably by 0.05 N H_2SO_4 at 70° C for 30 min. Such stability of the glycosidic bonds shows the pyranose form of the carbohydrate components [8, 9]. Consequently, the glycosides obtained are strophanthidin 3-α-L-arabinopyranoside (I) and strophanthidin 3-α-D-arabinopyranoside (II).



Results of biological investigations. The determination of biological activity, carried out in both cases on six cats, gave the following results: strophanthidin 3-α-L-arabinoside 0.091 ± 0.004 mg/kg, strophanthidin 3-α-D-arabinoside 0.127 ± 0.007 mg/kg. Consequently, the L-arabinoside is 1.4 times more active than the D-arabinoside.

There is information in the literature on the biological activity of other monotypical pairs of cardiac glycosides. Thus, it is known that the L-rhamnosides, L-diginosides, and L-cymarosides are considerably more active than the corresponding glycosides in which the monosaccharide residues belong to the D-series.

Of the large number of natural cardiac glycosides and those synthesized up to the present time, the highest

cardiotonic activity is possessed by strophanthidin 3-α-L-mannopyranoside, 0.069 mg/kg [10]. It would apparently be premature to give an unambiguous answer to the question of whether the L-sugars regularly impart a greater biological activity to the cardenolides than the corresponding D-sugars, since the four examples of monotypical pairs of glycosides available are inadequate for this purpose.

Glycoside	LD, mg/kg wt of the cat	Literature references
Sarmentogenin 3-α-L-diginoside	0,143	[11]
Sarmentogenin 3-β-D-diginoside	0,328	[11]
Digitoxigenin 3-α-L-rhamnoside	0,278	[12]
Digitoxigenin 3-α-D-rhamnoside	0,615	[13]
Digitoxigenin 3-α-L-cymaroside	0,200	[14, 15]
Digitoxigenin 3-β-D-cymaroside	0,372	[15—17]
Strophanthidin 3-α-L-arabinoside	0,091	Our work
Strophanthidin 3-α-D-arabinoside	0,127	"

The determination of the reason for the greater biological activity of the L-glycosides mentioned as compared with the corresponding D-glycosides is of particular interest. It is possible that the cardiac D-glycosides described are rendered harmless in the organism (by hydrolysis, epimerization, anhydridization, and other transformations) more rapidly. A study of the metabolism of the pairs of compounds mentioned will probably give a correct explanation of the observed difference in biological activity.

EXPERIMENTAL

The substances were analyzed after drying over phosphorus pentoxide in vacuum (0.01 mm Hg) at 110° C for 2 hr. The following systems of solvents were used in the chromatographic studies: chloroform-tetrahydrofuran (1 : 1)/formamide, methyl ethyl ketone–m-xylene (1 : 1)/formamide, benzene/formamide and butan-1-ol–acetic acid–water (4 : 1 : 5). To determine their biological activities, initial solutions of the glycosides at a concentration of 1 : 1000 were prepared, and immediately before investigation they were diluted to a concentration of 1 : 100,000.

Synthesis. A solution of 2 g of anhydrous strophanthidin in 25 ml of absolute dichloroethane was treated with 10 ml of toluene, 15 g of freshly-prepared silver carbonate, 2 g of calcium oxide, and 1 g of activated carbon. The mixture was heated to the boil in an oil bath and, with continuous stirring, 4.5 g of the appropriate O-acetylarabinosyl bromide, dissolved in 15 ml of chloroform, was added over 6 min. The mixture was boiled for another 5 min. After the end of the reaction, the solution was filtered, the precipitate was washed with chloroform, and the filtrate was evaporated in vacuum. The residue was dissolved in 70 ml of methanol, 10 ml of methanol saturated with ammonia was added, and the mixture was left at room temperature (22–25° C) for 20–30 hr. The completeness of the saponification of the acetyl groups was checked by paper chromatography. The methanol and the excess of ammonia were driven off in vacuum. The residue was dissolved in 200 ml of chloroform–ethanol (2 : 1) and 20 ml of water. The aqueous layer was separated off and the ethanolic-chloroformic layer was subjected to additional treatment with water (2 × 10 ml) and evaporated. To separate the strophanthidin, the amorphous powder was dissolved in 40 ml of acetone, 80 ml of benzene was added, and the mixture was heated to 60–70° C. The solution was concentrated to a volume of about 40 ml. The acetone distilled off almost completely. The glycoside synthesized deposited from the benzene solution in the form of a viscous glassy mass. The precipitate was separated off, dissolved in acetone, and again precipitated with benzene. This treatment was repeated four times. The glycoside purified in this way was dissolved in 20 ml of methanol, 10 ml of hot water was added, and the solution was heated in the boiling water bath until the ethanol had been driven off completely. The hot aqueous solution deposited crystals in the form of long prisms.

Strophanthidin 3-α-L-arabinoside. The glycoside was obtained with a yield of 58%. It had mp 170–174° C (from water), $[\alpha]_D^{24}$ +30.44 ± 3° (c 1.00; methanol). It dissolved in conc H_2SO_4, forming a coloration changing with time: 0 min) red; 6 min) orange; 10 min) yellow-brown; 4 hr) brown; 6.5 hr) dark green; 8 hr) green.

Found, %: C 62.52; H 7.90. Mol wt 540.1. Calculated for $C_{28}H_{40}O_{10}$, %; C 62.69; H 7.52. Mol wt 536.6.

Strophanthidin 3-α-D-arabinoside. The yield of finished product was about 55%. The glycoside melted at 211–212° C (from water): $[\alpha]_D^{23}$ +38.03 ± 3° (c 0.94; pyridine). It dissolved in conc H_2SO_4 giving a coloration changing with time: 0 min) orange; 10 min) light brown; 8 hr) lemon yellow.

Found, %: C 62.77; H 7.77. Calculated for $C_{28}H_{40}O_{10}$, %: C 62.69; H 7.52.

CONCLUSIONS

Strophanthidin 3-α-D-arabinopyranoside and strophanthidin 3-α-L-arabinopyranoside have been synthesized from strophanthidin and D- and L-arabinoses. The L-arabinoside possesses a cardiotonic activity 1.4 times greater than that of the D-arabinoside.

REFERENCES

1. W. Königs and E. Knorr, Ber., 34, 957, 1901.
2. V. T. Chernobai, ZhOKh, 34, 1018, 1964.
3. C. Mannich and G. Siewert, Ber., 75, 736, 1942.
4. W. Klyne, Biochem. J., 47, no. 4, xli, 1950.
5. Tollens-Elsner, Kurzes Handbuch der Kohlenhydrate [Russian translation], Leningrad–Moscow, 1938.
6. E. L. Jackson and C. S. Hudson, J. Am. Chem. Soc., 59, 994, 1937.
7. J. Conchie, G. A. Levvy, and C. A. Marsh, Advan. Carbohydr. Chem., 12, 158, 1957.
8. T. Reichstein, Angew. Chem., 63, 412, 1951.
9. A. Hunger and T. Reichstein, Helv. Chim. Acta, 35, 1073, 1952.
10. W. W. Zorbach, S. Saeki, and W. Buehler, J. Med. Chem., 6, 298, 1963.
11. G. Baumgarten, Die herzwirksamen Glykoside, Leipzig, 1963.
12. H. Hauenstein, A. Hunger, and T. Reichstein, Helv. Chim. Acta, 36, 87, 1953.
13. W. W. Zorbach, G. D. Valiaveedan, and D. V. Kashelikar, J. Org. Chem., 27, 1766, 1962.
14. A. F. Krasso, E. Weiss, and T. Reichstein, Helv. Chim. Acta, 46, 1691, 1963.
15. Ch. Tamm, Fortsch. Chem. organ. Naturstoffe, 3, 138, 1956.
16. M. Hartmann and E. Schlitter, Helv. Chim. Acta, 23, 548, 1940.
17. J. C. Hess and T. Reichstein, Helv. Chim. Acta, 36, 85, 1953.

16 May 1969

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