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SYNTHESIS OF CONVALLOSIDE

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The known natural diglycoside convalloside — strophanthidin 3β-O-[4-O-β-d-glucopyranosyl-α-L-rhamnopyranoside] — has been synthesized. The synthesis was carried out by the Koenigs-Knorr method via the preparation as intermediates of convallatoxin and its 2,3-isopropylidene derivative. Selectivity of glycosylation was achieved by the preliminary protection of the two OH groups in the cardenolide L-rhamnoside (convallatoxin).

More than 20 cardiac monoglycosides obtained by the glycosylation of cardenolides and bufadienolides by the Koenigs—Knorr method, and also by the orthoester method, are known. The possibilities of the synthesis of glycosides with chain-like carbohydrate units attached as in nature to C-3 of the aglycons has been investigated to a smaller degree. On this level, two synthesized diglycosides are known: K-strophanthin-β [1-3] and erythroside [4]. The synthesis of the first starts with cymarin, which has only one reactive OH group and therefore does not differ basically from the synthesis of monoglycosides. Erythroside is synthesized [4] by using an erysimin monoglycoside having two reactive OH groups in the carbohydrate unit. Definite selectivity of glycosylation at C-4" is achieved because of the conformational differences of the OH group in the D-digitoxose unit.

It appears to us that the use of L-rhamnosides in such reactions is also possible, but with the preliminary protection of two OH groups. In cardenolide L-rhamnosides, which are fairly common monosides, the OH groups at C-2' and C-3' occupy the cis position, which enables them to be protected by the formation of isopropylidene derivatives. We have performed the synthesis of the known natural diglycoside convalloside (III) via the isopropylidene derivative of convallatoxin (II). The convallatoxin necessary for this purpose was synthesized from the aglycon strophanthadin (I) and 2,3,4-tri-O-acetyl-1-bromo-L-rhamnose. The acetonide (II) was obtained by the condensation of convallatoxin with acetone in the presence of copper sulfate.

At both stages, glycosylation was carried out by the Koenigs-Knorr method in boiling dichloroethane [5] with the use of a mixture of silver carbonate and mercury oxide as HBr acceptor. The protective acetyl and isopropylidene groups were removed by controlled alkaline and acid hydrolysis, respectively.

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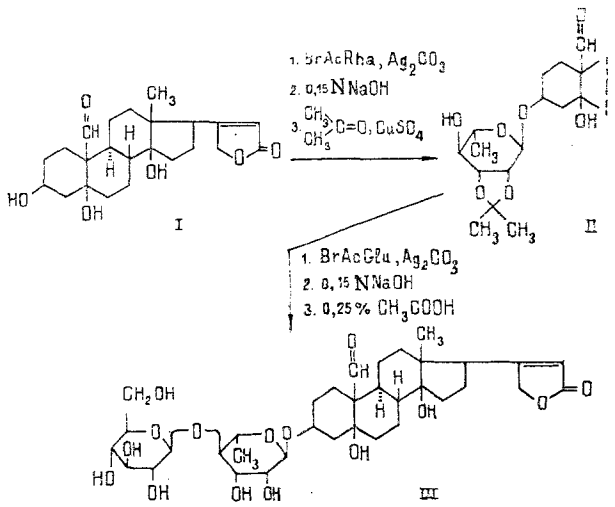

Under the conditions given, convallatoxin was obtained with a yield of 63% calculated on the strophanthidin. The yield of convalloside was 54% calculated on the convallatoxin, or 34% calculated on the strophanthidin.

EXPERIMENTAL

Convallatoxin. In a similar manner to that described below for the glycosylation of convallatoxin acetonide, 10 g of strophanthidin was glycosylated with 2,3,4-tri-O-acetyl-1-bromo-L-rhamnose. The reaction product after alkaline hydrolysis was freed from strophanthidin residues by extraction with hot benzene, and was crystallized from isopropanol. This gave 13.6 g of convallatoxin with mp 208-212/242-246°C; $[\alpha]_D^{20}0 \pm 2°$ (c 1.0; methanol).

2,3-O-Isopropylideneconvallatoxin (II). With continuous stirring, 2 g of convallatoxin was boiled in 30 ml of aetone in the presence of 10 g of anhydrous copper sulfate. The completeness of the reaction was monitored with the aid of chromatography on Silufol in the chloroform—ethanol (9:1) system. The solution was filtered through a filter densified with kieselguhr and with activated carbon, and was evaporated. The amorphous product (1.97 g) had $[\alpha]_D^{20}$ 7.5 ± 3° (c 0.9; methanol) and consisted of an acetonide; the results of its elementary analysis corresponded to those calculated for the composition $C_{32}H_{46}O_{10}$.

Convalloside (III). With heating, 1.95 g of isopropylideneconvallatoxin (II) was dissolved in 0.2 liter of chloroethane, and then 1 g of silver carbonate and 2 g of mercury oxide were added. The mixture was boiled for 1 min, after which, over 3—4 min, a solution of 10 g of 2,3,4,6-tetracetyl-1-bromo-D-glucose in 30 ml of dichloroethane was added with continuous stirring. Boiling and stirring were continued for 30 min. During the reaction, another 50 ml of dichloroethane and, in small portions, 2 g of HgO were added. The solution was filtered, and the precipitate was washed with chloroform. The filtrate was cooled and was purified with a cooled 2 N solution of sodium carbonate (2 × 50 ml) and was washed with water to neutrality (3 × 30 ml), and evaporated. The residue was dissolved in 0.5 liter of ethanol, and the solution was mixed with 0.5 liter of a 0.3 N solution of sodium hydroxide. Controlled alkaline hydrolysis was performed at 18—20°C for 30 min. The solution was neutralized and extracted with chloroform and then with chloroform—ethanol (2:1). The chloroform—ethanol extracts were evaporated.

The residue was dissolved in 40 ml of ethanol, and the solution was treated with 1 ml of 10% acetic acid. The solution was boiled, the hydrolysis of the isopropylidene grouping being monitored with the aid of chromatography on Silufol in the chloroform—methanol (7:3) system. After the end of the reaction, the solution was diluted with 100 ml of chloroform, and 15 ml of a 1% solution of sodium carbonate was added. The organic phase was separated off and the aqueous phase was extracted additionally with chloroform—ethanol (2:1) (4 × 50 ml). The combined ethanol-chloroform solutions were washed with water (2 × 15 ml) and evaporated. The residue (2.1 g) consisted of a light brown powder. Chromatography on paper and on Silufol showed that the product consisted of convalloside contaminated with convallatoxin and a more polar cardenolide. A sample of convalloside was given to us by N. F. Komissarenko.

The glyoside was chromatographed on 80 g of alumina (activity grade III) with elution by mixtures of ethyl acetate and ethanol of increasing polarity. The convalloside was crystallized from ethanol. Melting poing 198–200°C, $[\alpha]_D^{20}$ 9.6 ± 2° (c 1.0; 80% ethanol). Yield 1.4 g (54%, calculated on the convallatoxin).

SUMMARY

The known natural diglycoside convalloside (strophanthidin 3β-O-[4-O-β-D-glucopyranosyl-α-L-rhamnopyranoside]) has been synthesized from strophanthidin, L-rhamnose, and D-glucose. The synthesis was effected by the Koenigs—Knorr method with the formation of convallatoxin and its 2,3-isopropylidene derivative as intermediates. The yield of convallatoxin was 63% calculated on the strophanthidin, and that of convalloside 54% calculated on the convallotoxin or 34% calculated on the strophanthidin.

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DETERMINATION OF SULFUR IN DRUGS OF NATURAL ORIGIN

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The efficacy of the use of Schoniger's method for the quantitative analysis of sulfur in samples of Allium sativum L. and ichthammol has been shown. The relative error of the determination does not exceed 5%.

As a chemical element, sulfur is of great importance in the structural organization of living matter and the regulation of metabolism. Sulfur participates in various biochemical and physicological processes, especially in redox reactions, the synthesis of protein, the regulation of the permeability of membranes, etc [1]. This element is a component of many natural compounds and is responsible for their biological activity (hormones, enzymes, alkaloids, antibiotics, etc.) [1, 2]. In view of this, various methods for the quantitative determination of this element in natural samples have been proposed, which, as a rule, are based on the preliminary prolonged and laborious mineralization of the material under investigation [3, 4].

The method of combustion in a flask with oxygen which is rapid to perform and free from the above-mentioned deficiency, is widely recommended in the analysis of sulfur-containing inorganic substances but it has not found wide use in the analysis of natural materials, [3, 5]. To a certain extent, this is due to a usually low sulfur content of natural materials, their complex chemical composition, and the resulting possible interference of other chemical elements on the results of determinations. However, the generally recognized advantages of this method [3, 5, 6] have impelled us to investigate the possibility of its use in the analysis of natural sulfur-containing compounds.

As the object of investigation we selected natural drugs: garlic (Allium sativum l.) and ichthammol. This choice was due to the following factors:

1. The most important pharmacologically active compounds of garlic are sulfur-containing compounds (alkyl derivatives of cysteine, alkyl polysulfides, etc.) [7,8];

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