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PARTIAL SYNTHESIS OF EVONOLOSIDE

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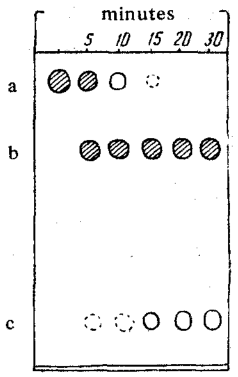
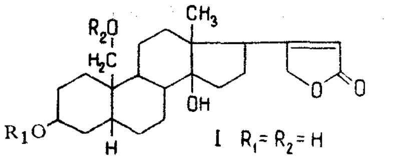
Natural evonoloside (IV) was first obtained from Evonymus europaea (European euonymus) and was characterized by us as cannogenol 3-α-L-rhamnopyranoside [1, 2].

This glycoside has also been obtained [3] by the reduction of cannogenin rhamnoside. In the present work the partial synthesis of evonoloside is described, confirming its structure and the possibility of introducing the sugar component into the aglycone when a primary alcohol group is present in the latter.

It is impossible to synthesize evonoloside by the direct condensation of acetylrhamnosyl bromide with cannogenol (I), since the reaction takes place at both hydroxy groups (at C_3 and C_{19}), but preferentially at the primary hydroxyl (at C_{19}). Consequently, making use of the method of protecting primary and secondary e-hydroxyls [4, 5], we partially acetylated cannogenol, introducing the protective substituent at C_{19}. It was established by paper chromatography (figure) that in the action on cannogenol of acetic anhydride in pyridine for 15 min, the initial aglycone was almost completely converted into acetates. The main product was 19-acetylcannogenol (II), with about 10% of 3,19-diacetylcannogenol. The acetyl derivatives of cannogenol, without being separated into the individual substances, were condensed with acetylrhamnosyl bromide by the Konigs-Knorr method [7]. The reaction products, including the acetate (III), were saponified with ammonia, giving a mixture of cardenolides consisting predominantly of evonoloside (IV), a small amount of cannogenol (I), and, as impurity, a third, unidentified, cardenolide. By the successive extraction of an aqueous solution of the mixture of cardenolides with chloroform and ethanol–chloroform (1 : 3) and crystallization, the evonoloside (IV) was obtained in the pure state (350 mg). From its melting point, mixed melting point, color reaction with sulfuric acid, and IR spectrum, the glycoside obtained was identical with natural evonoloside.

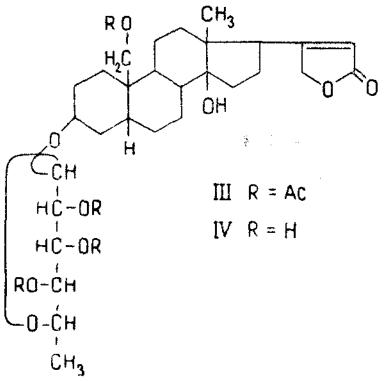


Chromatogram of cannogenol (a); 19-acetylcannogenol (b); and 3, 19-diacetylcannogenol (c) [methyl ethyl ketone–m-xylene (1 : 1)/formamide system [6].



I $R_1 = R_2 = H$

II $R_1 = H$; $R_2 = Ac$



III R = Ac

IV R = H

Experimental

The substances were analyzed after drying for 3 hr in vacuum (0.01 mm Hg) over phosphorus anhydride at 80° C. The cardenolides were chromatographed on paper of the Goznak Leningrad paper mill in the solvent systems chloroform–tetrahydrofuran (1 : 1)/formamide and m-xylene–methyl ethyl ketone (1 : 1)/formamide.

Acetylation of cannogenol. A solution of 730 mg of cannogenol in 10 ml of absolute pyridine was treated with 5 ml of acetic anhydride, and the mixture was left at 24–25° C for 15 min. Then it was brought into a separating funnel containing 0.5 *l* of ice water and stirred for 30 min. The acetates of the cardenolides were extracted with chloroform (150 ml × 3). The chloroformic extract was treated with 10 ml of 2 N sodium carbonate solution and with water (15 ml × × 4); then it was dried with anhydrous sodium sulfate and evaporated in vacuum. The still residue (800 mg) consisted of a yellowish amorphous powder.

Synthesis of evonoloside. A reaction flask was charged with 800 mg of cannogenol acetates, 40 ml of dichloroethane, and 15 g of silver carbonate. With continuous stirring and boiling of the reaction mixture, 7 g of acetylrhamnosyl bromide dissolved in 25 ml of toluene was added over an hour. Then the reaction mixture was boiled additionally for 30 min. During the reaction, toluene was added to the flask from time to time. At the end of the reaction the solution was filtered and the residue was washed with chloroform. The filtrate was evaporated in vacuum. The residue was dissolved in 150 ml of methanol saturated with gaseous ammonia, and the solution was left at 20–25° C for 3 days. The completeness of the saponification of the acetyl groups was checked by paper chromatography. The methanolic solution was evaporated in vacuum to dryness. Water (150 ml) and chloroform (200 ml) were added to the flask containing a still residue and stirred until the cardenolides had dissolved. The chloroform layer was separated off and the aqueous layer was treated with chloroform (100 ml × 4) and with a mixture of ethanol and chloroform (1 : 2, 150 ml × 4). The chloroformic extract, which did not contain evonoloside, was discarded. The alcoholic-chloroformic solution was dried with anhydrous sodium sulfate and evaporated in vacuum. The glycoside was crystallized from acetone to give 350 mg of evonoloside with mp 159–162° C $[\alpha]_D^{26}$ −15.5 ± 4° (c 0.55; methanol). This substance dissolves in concentrated sulfuric acid, changing colors in the same intervals time, as does natural evonoloside: 1 min—yellow, 45 min—pink-violet, 75 min—violet. The IR spectrum, taken by I. P. Kovalev on a UR-10 spectrophotometer, was identical with that of natural evonoloside. A mixture of the glycoside synthesized and the natural glycoside gave no depression of the melting point.

Conclusions

The synthesis of evonoloside has been effected from cannogenol and L-rhamnose with a yield of 35%. It has been shown that when a primary alcohol group (at C_{19}) and a secondary axial hydroxy group (at C_3) are present in the aglycone, to introduce the sugar component at C_3 it is desirable first to protect the primary OH group by the partial acetylation of the aglycone.

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