SYNTHESIS OF 3-EPISTROPHANTHIDIN AND 3-EPISTROPHANTHIDOL

I. F. Makarevich

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In a preceding communication, the isolation from the seeds of Strophanthus kombe Oliv. (strophanthus) [1] of two new cardiac aglycones was reported. They were characterized provisionally as 3-epistrophanthidin and 3-epistrophanthidol. To answer the question of the structure of the substances more fully, we have carried out an independent synthesis of 3-epistrophanthidin (XII) and 3-epistrophanthidol (V).

The cardenolides V and XII were synthesized (see Scheme) from strophanthidin (VI) and strophanthidol (I) by oxidation of the alcoholic group at $C_{(3)}$, reduction of the oxo compounds so produced, and chromatographic separation of the isomeric reduction products. The primary hydroxyl group of strophanthidol (I) and the aldehyde group of strophanthidin (VI) were previously protected in a suitable manner. For the protection of the OH group at $C_{(19)}$, strophanthidol was subjected to partial acetylation [2, 3].

From strophanthidol (I), 19-O-acetylstrophanthidol (II) was obtained. Substance II, containing as impurities the initial cardenolide I and the 3-mono- and 3, 19-di-O-acetates of strophanthidol, was oxidized with chromic anhydride without purification. The oxidation product (III), also contaminated with other cardenolides, was reduced with sodium borohydride. The mixture of substances IV and II was saponified with ammonia in methanol. The 3-epistrophanthidol (V) and strophanthidol (I) formed were separation by absorption chromatography on alumina. The yield of the pure cardenolide V was 40% (on the starting material).

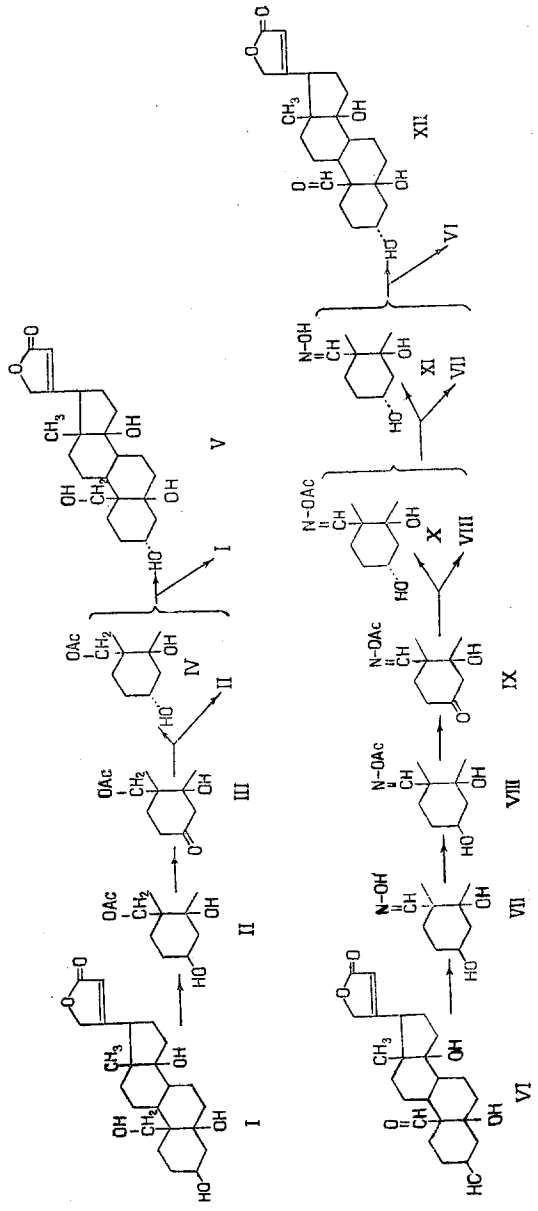
3-Epistrophanthidin (XII) was synthesized with a yield of only about 10%. To protect the aldehyde group it was insufficient to obtain the oxime of strophanthidin (VII) since the oxime group is capable of being oxidized by chromic anhydride. Consequently, VII was selectively acetylated, giving the acetoxime VIII. Then, by oxidizing the alcohol group at $C_{(3)}$ and reducing the oxo group with sodium borohydride, a mixture was obtained which consisted of the acetoxime of 3-epistrophanthidin (X) and the acetoxime of strophanthidin (VIII). To remove the protective groups, substances X and VIII were saponified with methanolic ammonia solution. The saponification products, the oximes XI and VII, were hydrolyzed with dilute acid. At this stage of the synthesis, because the hydrolysis required relatively severe conditions, a considerable amount of anhydrocardenolides was formed. The 3-epistrophanthidin (XII) was isolated in the pure state after the chromatographic separation of the mixture of substances on alumina.

The results of a comparison of the properties of the 3-epistrophanthidin and 3-epistrophanthidol synthesized with those of the natural cardenolides IM-38 and IM-40 [1] shows that the respective pairs are identical (IM-38 = XII and IM-40 = V). Thus, the hypothesis put forward previously [1] on the structure of the new cardenolides has been shown to be correct.

EXPERIMENTAL

Synthesis of 3-epistrophanthidol (V). A solution of 2 g of strophanthidol in 10 ml of pyridine was treated with 5 ml of acetic anhydride, and the mixture was left at 22° C for 20 min. Then, about 10 g of ice was added to the reaction mixture. After 20 min, the solution was evaporated to dryness in vacuum. The residue, consisting predominantly of substance II, was dissolved in 5 ml of glacial acetic acid, and 5 ml of a saturated acetic acid solution of chromic anhydride was added. Oxidation was carried out at 23° C for 30 min. After the end of the reaction, the mixture was transferred to a separating funnel containing 200 ml of chloroform and 20 ml of 1 N H_2SO_4. The chloroform layer was separated off, treated with water (2 × 20 ml), with saturated sodium carbonate solution until the acetic acid had been completely neutralized, and again with water (3 × 20 ml).

The purified chloroform layer was evaporated in vacuum. The residue, consisting mainly of substance III was dissolved in 20 ml of 80% dioxane. To the solution 0.5 g of sodium borohydride was added during 15 min. The reaction mixture was transferred to a separating funnel containing 150 ml of chloroform–ethanol (4 : 1). The ethanolic



chloroform layer was treated with water (4 × 10 ml) and evaporated. The residue was dissolved in 50 ml of methanol, 10 ml of methanol saturated with gaseous ammonia were added, and the mixture was left at 22–26° C for 18 hr. The solvent and the excess of ammonia were driven off in vacuum. The mixture of cardenolides V and I so obtained were separated by chromatography on 100 g of alumina (activity grade III). Elution was carried out with chloroform–ethanol (98 : 2–92 : 5). The strophanthidol (I) and 3-epistrophanthidol (V) were crystallized from acetone.

The strophanthidol (I) melted at 139–143° C; $[\alpha]_D^{24}$ +36.7 ± 2° (c 0.92; methanol); on paper chromatography, it had the same "mobility" as an authentic sample of strophanthidol.

The 3-epistrophanthidol (V) melted at 263–267° C; $[\alpha]_D^{23}$ +29.4 ± 2° (c 0.70; methanol). It dissolved in conc H_2SO_4 forming a coloration changing with time: 0 min) yellow-brown; 1 min) red; 5 min) red-orange; 150 min) pale pink; and 220 min) light brown. The reaction with tetranitromethane was negative.

Found, %: C 67.69; H 8.56. Mol. wt. 408.2. Calculated for $C_{23}H_{34}O_6$, %: C 67.95; H 8.43. Mol. wt. 406.5.

From these results and also those of paper chromatography and the melting point of a mixture (263–267° C), the cardenolide was shown to be identical with the substance IM-40 obtained from strophanthus.

Synthesis of 3-epistrophanthidin (XII). A solution of 5 g of strophanthidin in 300 ml of methanol was treated with 1.4 g of hydroxylamine hydrochloride and 1 g of potassium acetate dissolved in 2 ml of water. The flask was attached to a reflux condenser and was heated at 100° C for 2 hr. The solution was concentrated to a volume of about 100 ml, 50 ml of water was added, and the mixture was heated until the methanol had been driven off completely. The aqueous solution deposited a crystalline residue of strophanthidin oxime (VII) which was filtered off and washed with water. This gave 4.95 g of VII with mp 257–265° C; $[\alpha]_D^{25}$ +54.2 ± 4° (c 0.5; methanol).

A solution of 4.9 g of strophanthidin oxime (VII) in 26 ml of pyridine was treated with 13 ml of acetic anhydride and acetylation was carried out at 25° C for 12 min. The reaction was stopped by adding about 20 g of ice. After 20 min, the solution was evaporated to dryness in vacuum.

The oxidation of the acetoxime VIII, the reduction of the oxidation product IX, and the saponification of substances X and VIII were carried out as described above.

The cardenolides XI and VII were hydrolyzed with 0.26 N HCl prepared in 50% ethanol by boiling the reaction mixture in a flask with a reflux condenser for 2.5 hr. After the end of hydrolysis and the usual elimination of the acid, the mixture of the aglycones XII and VII and anhydro compounds was chromatographed on 250 g of alumina (activity grade III). Elution was performed with chloroform–ethanol (98 : 2–95 : 5). The strophanthidin (VI) and 3-epistrophanthidin (XII) obtained in the individual state were crystallized from ethanol.

The strophanthidin (VI) melted at 169–175° C; $[\alpha]_D^{24}$ +44.3 ± 3° (c 0.62; methanol).

The amount of 3-epistrophanthidin (XII) obtained was 496 mg. Its melting point was 238–256° C; $[\alpha]_D^{25}$ +42.4 ± 2° (c 1.10; methanol). It dissolved in conc H_2SO_4 forming a coloration changing with time: 0 min) red; 2 min) yellow; and 60 min) lemon-yellow. The reaction with tetranitromethane was negative.

Found, %: C 68.01; H 8.09. Mol. wt. 406.6. Calculated for $C_{23}H_{32}O_6$, %: C 68.29; H 7.97. Mol. wt. 404.5.

The characteristics given and also the results of paper chromatography coincide completely with the properties of the cardenolide IM-38 obtained from strophanthus.

CONCLUSIONS

3-Epistrophanthidin and 3-epistrophanthidol have been synthesized from strophanthidin and strophanthidol with yields of 10 and 40%, respectively. The substances synthesized proved to be identical with the new natural aglycones isolated from the seeds of Strophanthus kombe Oliv.

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