UDC 547.7

PHYTOESTROGENS*

III. Synthesis of the Flavylium Salt 7, 11-Dihydroxycoumestanevia

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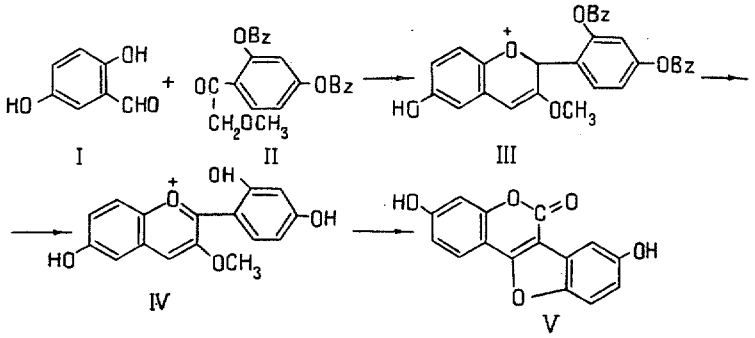
It has been reported previously [1] that some of the phytoestrogens forming hydroxy derivatives of coumestane exhibit not only an estrogenic but also an anabolic effect. Consequently, they are regarded as growth stimulators for animals [2]. It is stated [3] that the estrogenic activity of coumestrol (7, 12-dihydroxycoumestane) falls or disappears completely if either of the phenolic hydroxyls in the 7 and 12 positions is removed or, conversely, if an additional phenolic hydroxyl is introduced into any position of the coumestane skeleton. However, at the present time there is no information on the influence of the number and position of hydroxy groups in the coumestrane ring on its anabolic activity.

In a study of hydroxycoumestanes in connection with the relationship between their structure and activity, we have synthesized 11-coumestrol, or 7, 11, 12-trihydroxycoumestane [4]. It was found that when an additional (third) hydroxy group was introduced into position 11 of coumestrol, the anabolic effect was retained. In the present paper we report the synthesis of an isomer of natural coumestrol, namely 7, 11-dihydroxycoumestane (V). To obtain it we made successful use of the elegant method that Jurd has employed in the synthesis of coumestrol [5] and medicagol [6].

The condensation of 2, 5-dihydroxybenzaldehyde (I) with ω-methoxy-2, 4-dibenzyloxyacetophenone in an ethereal solution of hydrogen chloride gave the corresponding dibenzyloxyflavylium chloride (III), which was debenzylated with a mixture of concentrated acetic and hydrochloric acids to 2', 4', 6-trihydroxy-3-methoxyflavylium chloride (IV). By oxidation with hydrogen peroxide in aqueous ethanolic solution, the latter was converted into 7, 11-dihydroxycoumestane (V) by the following route:



Because of the difficulty of purifying 7, 11-dihydroxycoumestane, it was identified in the form of the diacetate.

The IR spectra were taken on a UR-10 instrument, and the UV spectra on a SF-4 instrument. The thin-layer chromatography was carried out on plates with a fixed layer of KSK silica gel.

Experimental

ω-Methoxy-2, 4-dibenzyloxyacetophenone (II). A mixture of 2.7 g of ω-methoxy-2, 4-dihydroxyacetophenone [7], 6.3 g of benzyl chloride, 1.35 g of potassium iodide, and 5.4 g of potassium carbonate in 36 ml of dry acetone was heated for 6 hr. After the acetone had been distilled off, a yellow oil remained which crystallized in the cold. The crystals were washed with small portions of cold methanol. Yield 3.26 g (61%), mp 90-92° C.

2', 4'-Dibenzyloxy-3-methoxy-6-hydroxyflavylium chloride (III). A solution of 2.6 g of II and 1 g of 2, 5-dihydroxybenzaldehyde [8] in 17 ml of ethyl acetate was treated with 50 ml of dry ether. The reaction mixture was saturated with hydrogen chloride at +5-8° C for 5 hr. A precipitate deposited from the red mass. It was recrystallized from glacial acetic acid. Yield 3.5 g (74%), mp 154-156° C, UV spectrum: λ_{max} (0.5% solution of HCl in ethanol) 265, 490 mμ (log ε 3.968; 3.93).

Found, %: C 68.22, H 5.34, Cl 6.71. Calculated for $C_{30}H_{25}O_5Cl \cdot 1.5H_2O$, %: C 68.1, H 5.34, Cl 6.77.

*For Communication II, see [4].

2', 4', 6-Trihydroxy-3-methoxyflavylium chloride (IV). A mixture of 2.7 g of III, 18 ml of glacial acetic acid, and 18 ml of concentrated hydrochloric acid was heated at 80° C for 1 hr and then at 100° C for another 1 hr. The cooled solution was treated with 107 ml of 10% hydrochloric acid. To the suspension of red flavylium salt that separated out 10 ml of benzene was added in order to extract the benzyl chloride. The flavylium chloride was recrystallized from an aqueous methanolic solution of HCl (150 ml of methanol and 30 ml of 10% hydrochloric acid). Yield 1.1 g (64%). UV spectrum: λ_{max} (0.5% solution of HCl in ethanol) 263, 280, 369, 493 mμ (log ε 3.968, 3.889, 5.414, 4.375).

Found, %: C 60.06, H 4.42, Cl 11.08%. Calculated for $C_{16}H_{13}O_5Cl$, %: C 59.89, H 4.08, Cl 11.05.

7,11-Dihydroxycoumestane (diacetate). A suspension of 1.35 g of IV in 28 ml of methanol was treated with 14 ml of water and then 4.2 ml of 30% hydrogen peroxide was added to the reaction mixture in drops. The solution was stirred for 10–15 min until a clear dark yellow solution had been formed. Then 5.6 ml of concentrated sulfuric acid was carefully added. The mass, which became warm, was heated additionally in the water bath for another 20 min. After 3–4 hr at room temperature, 1 g of crude product was deposited.

The crude 7,11-dihydroxycoumestane isolated was chromatographed on a column of silica gel. Benzene–ether (4:1) eluted other products of the oxidation of the flavylium salt, but the 7,11-dihydroxycoumestane itself was not eluted. The 7,11-dihydroxycoumestane extracted from the column was acetylated, mp 243–245° C (from acetic acid). IR spectrum of V: 3300 cm^{-1}, 7,11-diacetoxycoumestane, 1210 cm^{-1}; R_f of coumestrol diacetate and 7,11-diacetoxycoumestane 0.84 [benzene–ether (4:1), revealing agent iodine vapor].

Found, %: C 64.84, H 3.47. Calculated for $C_{19}H_{12}O_7$, %: C 64.75, H 3.43.

Summary

The synthesis of an isomer of the natural phytoestrogen coumestrol, 7,11-dihydroxycoumestane, by the oxidation of the corresponding flavylium chloride has been described. 7,11-Dihydroxycoumestane was identified as the diacetate.

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