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SOME REACTIONS OF COUMESTANS

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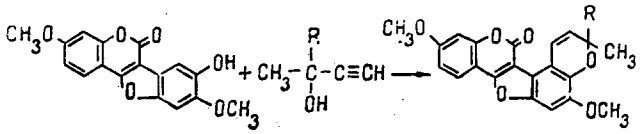
UDC 541.6 + 547.64

Continuing an investigation of coumestans, we have performed their condensation with acetylenic alcohols and their reduction with lithium tetrahydroaluminate.

The reaction of acetylenic alcohols with hydroxycoumarins and hydroxyacetophenones leads to ring closure with the acetylene residue to form dialkylchromenes [1]. The application of this reaction to hydroxycoumestans opens up the possibility of obtaining analogs of the natural coumestan sojagol isolated from soys beans [2]. We have studied the reaction of 11-hydroxy-7,12-dimethoxycoumestan (I) with 3-methylpent-1-yn-3-ol (II) and with 2-methylbut-3-yn-2-ol (III). Condensation took place only with the addition of small amount of zinc chloride to a mixture of equimolar amounts of a carbinol (II) or (III) with the coumestan (I).



I II. $R=C_2H_5$ IV. $R=C_2H_5$
III. $R=CH_3$ V. $R=CH_3$

The structure of the products of the reaction of (I) with the alcohols (II) and (III) as the 7,12-dimethoxy-10,11-(2,2-dialkylchromeno)coumestans (IV) and (V) was confirmed mass spectrometrically. In the mass spectrum of (IV) there is a peak with m/e 392 (12%), which corresponds to the molecular weight of the coumestan (IV), and peaks with m/e 377 ($M^+ - CH_3$) and 363 ($M^+ - C_2H_5$). If the residue of the acetylenic alcohol was bound to the coumestan only by a simple ether bond, it would undergo cleavage with the formation of an ion with m/e 311 ($M^+ - 81$) corresponding to the ejection of an isopentyl residue ($C_5H_6 - CH_3$). However, there is no such peak in the mass spectrum of compound (IV). At the same time, the spectrum does contain the peaks of the doubly charged ions ($M^+ - C_2H_5$)/2 and ($M^+ - CH_3$)/2, which shows the stability of the ($M^+ - 29$) and ($M^+ - 15$) fragments formed. The appearance of such ions is possible in a number of cases, including those in which there is a closed conjugated system. In our case, this system can be produced only by the formation of the 10,12-(2-ethyl-2-methylchromeno)coumestan (IV). Peaks of a doubly charged ion are present in the mass spectrum of the coumestan sojagol [2]. No similar peaks were observed in the mass spectra of esters and ethers of coumestan that we prepared.

Grisebach, studying the biogenesis of coumestrol, put forward a hypothesis of a possible route of its formation in plants via pterocarpans [3]. A number of workers have shown the possibility of the synthetic passage from pterocarpan to coumestans and conversely [4, 5]. The reaction of coumestans with lithium tetrahydroaluminate is the first step of the transition from coumestans to pterocarpans, which confirms a possible biogenetic link between these compounds. The reduction of 7,11-12-tribenzyloxycoumestan (VII) with

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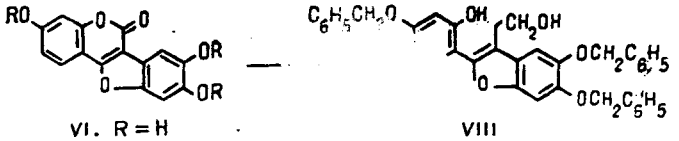
lithium tetrahydroaluminate in tetrahydrofuran led to the coumarone (VIII). 5,6-Dibenzyloxy-2-(4-benzyloxy-2-hydroxyphenyl)-3-hydroxymethylcoumarone (VIII) was identified by IR spectroscopy and thin-layer chromatography. In the IR spectrum of (VIII) there are no absorption bands in the 1690-1760 cm^{-1} region, but the absorption band of a hydroxyl does appear. The R_f values on silica gel are 0.76 for (VII) and 0.28 for (VIII). The coumarone obtained does not fluoresce in chloroform solution, unlike 7,11,12-tribenzyloxycoumestan; the melting point of a mixture of compounds (VII) and (VIII) gives a depression. This reaction has also been studied on medicagol [6] and methoxycoumestan [7].



VI. R = H
VII. R = $C_6H_5CH_2$

VIII

EXPERIMENTAL

7,12-Dimethoxy-10,11-(2-ethyl-2-methylchromeno)coumestan (IV), $C_{22}H_{20}O_6$. A mixture of 5.5 g of 11-hydroxy-7,12-dimethoxycoumestan (I), 3.2 g of freshly fused zinc chloride, and 10 ml of 3-methylpent-1-yn-3-ol (II) was stirred at 100°C for 30 min and then 130°C for another 30 min. At the end of the heating period, the semiliquid mass solidified. After cooling, it was extracted with ether, and the ethereal extract was washed with dilute acid, 10% sodium carbonate solution, and water, and was dried over sodium sulfate. Then it was evaporated, the residue was dissolved in 50 ml of methanol, and 100 ml of petroleum ether was added. The solution was washed several times with water, dried, and evaporated. On cooling, the resinous residue formed crystals with mp 195°C (petroleum ether–benzene; 1 :1). R_f 0.82 (benzene–acetone; 9 :1).

Mass spectrum (m/e, %): M^+ 392 (12); 377 (8); 364 (21); 363 (100); 348 (8); 333 (7); (m/2e, %): 188.5 (1); 181.5 (8).

7,12-Dimethoxy-10,11-(2,2-dimethylchromeno)coumestan (V), $C_{22}H_{16}O_6$. A mixture of 4.5 g of 11-hydroxy-7,12-dimethoxycoumestan (I), 3.5 g of freshly fused zinc chloride, and 10 ml of 2-methylbut-3-yn-2-ol (III) was stirred at 60°C for 30 min and at 100°C for another 30 min, and was then treated as described above. The crystals that formed were recrystallized from benzene–petroleum ether, mp 248°C. The substance did not fluoresce in ethanol.

7,11,12-Tribenzyloxycoumestan (VII), $C_{36}H_{26}O_6$. A mixture of 1 g of 7,11,12-trihydroxycoumestan (VI), 0.5 g of potassium iodide, 15 ml of benzyl chloride, and 2 g of calcined potassium carbonate in 150 ml of acetone was boiled under reflux for 10 h. Then it was cooled, filtered, and evaporated under vacuum, and the residue was poured into water containing ice. The resinous deposit that formed crystallized on prolonged cooling. It was recrystallized from ethanol–chloroform (4 :1); the solution fluoresced, and the product had mp 175°C. Yield 0.8 g (42%), R_f 0.76 (benzene–methanol; 9 :1; UV light). UV spectrum (λ_{max}, mμ): 251, 308, 349. IR spectrum (cm^{-1}): 1600, 1625, 1743.

5,6-Dibenzyloxy-2-(4-benzyloxy-2-hydroxyphenyl)-3-hydroxymethylcoumarone (VIII), $C_{36}H_{30}O_6$. A solution of 1.5 g of 7,11,12-tribenzyloxycoumestan (VII) in tetrahydrofuran was added dropwise over an hour to a suspension of 0.9 g of lithium tetrahydroaluminate in absolute tetrahydrofuran. Then the reaction mixture was boiled under reflux for 1.5 h. After cooling, the unchanged lithium tetrahydroaluminate was decomposed, and the reaction product was extracted with ether. The extract was washed with sodium carbonate solution and with water and was dried. After evaporation of the solvent, the resinous residue was dissolved in a small amount of ether and the solution was passed through a column of carbon. On evaporation, the purified ethereal solution deposited white crystals with mp 170°C. Yield 0.42 g (28%), R_f 0.28 (SiO_2; benzene–methanol, 9 :1; UV). UV spectrum (λ_{max}, mμ): 244, 278, 320. IR spectrum (cm^{-1}): 1610, 1630, 3550.

The results of the elementary analyses of compounds (IV), (V), (VII), and (VIII) corresponded to the calculated figures.

SUMMARY

1. 11-Hydroxy-7,12-dimethoxycoumestan has been condensed with acetylenic alcohols, and it has been shown that the reaction products are 7,12-dimethoxy-10,11-(2,2-dialkylchromemo)coumestans.

2. 7,11,12-Tribenzyloxycoumestan has been reduced with lithium tetrahydroaluminate, giving 5,6-dibenzyloxy-2-(4-benzyloxy-2-hydroxyphenyl-3-hydroxymethylcoumarone.

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ULTRAVIOLET ABSORPTION OF FLAVONOIDS

VIII. IONIZATION CONSTANTS OF KAEMPFEROL AND QUERCETIN

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We have previously studied the acid properties of a series of mono- and disubstituted flavones [1-3]. Considerable interest is presented by an investigation of the acid properties of more highly hydroxylated flavonoid derivatives, many of which are widely used as complex-forming agents in analytical chemistry. There is little information in the literature on this question. Of the large number of natural flavonoids, ionization constants have been determined only for quercetin [4] and morin [5-7], without the assignments of the values obtained to particular hydroxy groups.

The present paper gives the results of a determination of the ionization constants of tetra- and pentahydroxy-substituted natural flavones (kaempferol and quercetin) (Table 1). The assignment of the values of the constants to particular hydroxy groups was made on the basis of the results of a comparative analysis of the constants obtained for kaempferol and quercetin with similar results for mono- and dihydroxyflavones with a corresponding type of substitution. It can be seen from this that both in kaempferol and in quercetin the most highly acidic properties are possessed by the hydroxy group in position 7. The 4'-OH group will undergo dissociation next.

It is possible that the two constants in kaempferol are due to the 3-OH and 5-OH groups, in the sequence given in Table 1. But since the capacity for ionization of the 3- and 5-hydroxy groups is considerable and changes differently under the influence of substituents in positions 7 or 4', we cannot definitely affirm the assignment of the two latter constants that we have made. For this purpose the ionization constants of trihydroxyflavones with a related type of substitution must be determined.

As can be seen from Table 1, for quercetin we found the ionization only of the two hydroxy groups possessing the highest acidity. The ionization of the remaining hydroxyls takes place in a fairly strong alkaline medium (pH > 9.6) in which quercetin undergoes irreversible changes. Consequently, it did not appear possible to determine the ionization constants of these groups.

TABLE 1. Ionization Constants ($pK_a \pm \Delta x$) of Kaempferol and Quercetin

Compound	pK_{a1}	pK_{a2}	pK_{a3}	pK_{a4}
	7-OH	4'-OH	3-OH	5-OH
3,4',5,7-Tetrahydroxyflavone (kaempferol)	8,2±0,2	9,5±0,1	(10,5)	(12,5)
3,3',4',5,7-Tetrahydroxyflavone (quercetin)	7,3±0,1	8,4±0,1	—	—

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