PHYTOESTROGENS

V. Synthesis of Coumestans by the Wanzlik Reaction*

L. L. Simonova and A. A. Shamshurin

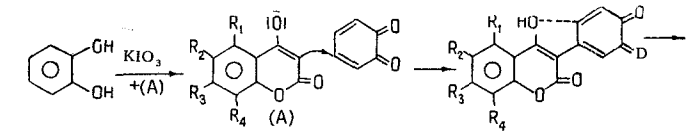
Khimiya Prirodnykh Soedinenii, Vol. 6, No. 3, pp. 355–358, 1970.

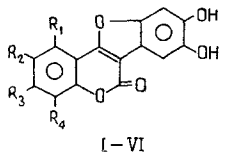
UDC 547.7

At the present [1], 12 coumestan phytoestrogens have been isolated from lucerne and clover, and of these six contain methoxyl groups. It is an interesting fact that among the natural coumestans no C-methyl derivatives have yet been detected.

Continuing our work on the chemistry of the coumestans [2–4], we synthesized new representatives of this group: methyl- and methoxycoumestans.

In the syntheses we made successful use of the chemically interesting Wanzlik reaction [5]. Its mechanism consists in the reaction of an o-quinone, obtained by dehydrogenation in situ, with a nucleophilic partner (coumarin). The coumestan system (I–VI) arises as a result of C—C coupling and the subsequent formation of a C—O bond.





I–VI

I. $R_1 = CH_3$; $R_2 = R_4 = H$; $R_3 = OH$

II. $R_1 = OCH_3$; $R_2 = R_4 = H$; $R_3 = OH$

III. $R_1 = CH_3$; $R_2 = R_4 = H$; $R_3 = OCH_3$

IV. $R_1 = R_3 = R_4 = H$; $R_2 = CH_3$

V $R_1 = R_2 = R_3 = H$, $R_4 = CH_3$

VI $R_1 = R_4 = H$; $R_2 = R_3 = CH_3$

7, 11, 12-Trimethoxy-5-methylcoumestan (VII) was obtained by the methylation of I with dimethyl sulfate. The methylenation of compound III gave 7-methoxy-5-methyl-11,12-methylenedioxycoumestan (VIII).

Compounds I–VI were synthesized from the 4-hydroxycoumarin derivatives given in Table 1.

Table 1

Coumarin	R_1	R_2	R_3	R_4
IX	CH_3	H	OH	H
X	OCH_3	H	OH	H
XI	CH_3	H	OCH_3	H
XII	H	CH_3	H	H
XIII	H	H	H	CH_3
XIV	H	CH_3	CH_3	H

Compound IX was obtained by condensing orcin, and X by condensing 1, 3-dihydroxy-5-methoxybenzene, with malonic acid in the presence of phosphorous oxychloride and zinc chloride; XI was obtained by the partial methylation of compound IX with dimethyl sulfate; and XII, XIII, and XIV were obtained by published methods [6, 7].

All the alkoxy- and alkylcoumestans, except VII and VIII, were identified in the acetate form.

*For part IV, see [4].

We followed the change in frequency of the vibrations of the carbonyl group of δ-lactones in eight coumarins and two coumestans, VII and VIII, by means of their IR spectra. The last two compounds can be considered as derivatives of benzofurocoumarin: VII is 5', 6', 7-trimethoxy-5-methylbenzofuro(3', 2'-3, 4)coumarin and VIII is 7-methoxy-5-methyl-5', 6'-methylenedioxybenzofuro(3', 2'-3, 4)coumarin. The frequency of the vibrations of these compounds in the 1600–1750- and 3000–3600-cm^{-1} regions are given below (the IR spectra were recorded on a UR-10 instrument with the substances in the form of mulls in paraffin oil).

Substance	ν cm^{-1}
4,7-Dihydroxycoumarin	1635, 1665—1670
4,7-Dihydroxy-5-methylcoumarin	1620, 1665 · 1670, 3100—3300
4,7-Dihydroxy-5-methoxycoumarin	1635, 1640, 1695, 3300
4-Hydroxy-7-methoxycoumarin	1615, 1640, 1705, 3350
4-Hydroxy-8-methylcoumarin	1610, 1660, 1690, 1705, 3450
4-Hydroxy-6-methylcoumarin	1610, 1635, 1690—1695
4-Hydroxy-7-methoxy-5-methylcoumarin	1615, 1650, 1700, 1705, 3150
4,5,7-Trimethoxycoumarin	1615, 1720
7,11,12-Trimethoxy-5-methylcoumestan	1630, 1740
7-methoxy-5-methyl-11,12-methylenedroxycoumestan	1610, 1735

The introduction of a substituent into the benzene ring of a 4-hydroxycoumarin derivative leads to a small decrease in the frequency of the vibrations of the carbonyl group compared with 4-hydroxycoumarin The introduction of a hydroxyl group, even into position 7 of coumarin, sharply changes the spectrum in the 1600–1750-cm^{-1} region. It is obvious that in the hydroxylated coumarins the possible formation of strong intermolecular hydrogen bonds, which tend to decrease the frequency of the vibrations of the C=O group, appears.

In all the hydroxycoumarins, the hydroxyl group appears in the form of low-intensity peaks or in the form of a broad band in the 3100–3300-cm^{-1} region.

EXPERIMENTAL

1, 3-Dihydroxy-5-methoxybenzene. The substance was obtained by a published method [8]. It was purified on a column of silica gel, being eluted with a benzene—ether mixture (8 : 2), after which it was distilled at 145–146° C (1–1.5 mm).

4, 7-Dihydroxy-5-methylcoumarin (IX). In drops, 7 ml of phosphorus oxychloride was added at 30–40° C to a mixture of 4.2 g of orcin, 3.5 g of malonic acid, and 10.5 g of zinc chloride. The yellow heterogeneous mass was stirred vigorously at 55–60° C for 10 hr. After this time, the mass had darkened and become viscous. It was cooled and treated with water containing ice. The resulting precipitate of impure coumarin IX was filtered off and dissolved in 100–150 ml of 10% sodium carbonate solution. Part of the insoluble residue was separated off, and the mother liquor was acidified with dil HCl (1 : 3). Yield 2 g, mp 255° C (from aqueous ethanol). Substance IX was identified in the form of the diacetate.

4, 7-Diacetoxy-5-methylcoumarin. A 0.3-g quantity of IX was dissolved in 10 ml of 20% caustic soda solution in the cold, and 5 ml of acetic anhydride was added with stirring. After 10–15 min, the clear solution deposited a precipitate. The reaction mixture was stirred at 0–6° C for 2 hr and then the precipitate was filtered off and was washed with 4% alkali solution. Mp 218–220° C (from ethanol). Found, %: C 60.53, 60.62; H 4.58, 4.50. Calculated for $C_{14}H_{12}O_6$, %: C 60.87; H 4.37.

4, 7-Dihydroxy-5-methoxycoumarin (X). At 30° C, 9.8 ml of phosphorus oxychloride was added dropwise to 6 g of 1, 3-dihydroxy-5-methoxybenzene, 4.5 g of malonic acid, and 15 g of zinc chloride. Then the reaction mixture was heated to 55° C and was kept at this temperature for 15 hr. It was then treated with water and ice, giving a resin which, after being washed several times with water, was dissolved in 10% sodium carbonate solution, and the solution was filtered and acidified. On long standing, with the removal of the first portions of resin which separated, the acid solution yielded 1 g of 4, 7-dihydroxy-5-methoxycoumarin with mp 266–267° C (from aqueous acetone). Found, %: C 57.37, 57.51; H 3.89, 3.91. Calculated for $C_{10}H_8O_5$, %: C 57.69; H 3.87.

4-Hydroxy-6-methylcoumarin [6], 4-hydroxy-8-methylcoumarin, and 4-hydroxy-6, 7-dimethylcoumarin [7] were obtained, respectively, from di-p-tolyl malonate, di-o-tolyl malonate, and bis-(3, 4-dimethylphenyl) malonate with aluminum chloride.

4-Hydroxy-7-methoxy-5-methylcoumarin (XI). Wtih cooling to 0–5° C, 1 g of 4, 7-dihydroxy-5-methylcoumarin was dissolved in 20 ml of 10% caustic potash solution, and 2 ml of dimethyl sulfate was added dropwise. The reaction mixture was stirred for 3 hr, after which it was filtered from the dimethoxy derivative that had formed and the mother liquor was acidifed. This gave 0.5 g of substance with mp 270–271° C (from aqueous ethanol). Found, %: C 64.10, 64.27; H 5.07, 5.10. Calculated for $C_{11}H_{10}O_4$, %: C 64.07; H 4.89.

The coumestans I–VI. Compounds I–VI were synthesized under identical conditions. We give one example. A mixture of 0.5 g of the appropriate 4-hydroxycoumarin derivative, 0.3 g of catechol, and 1.6 g of sodium acetate in 20 ml of aqueous acetone (1 : 1) was added dropwise to a solution of 0.4 g of KIO_3 and 0.8 g of sodium acetate in 20 ml of water. The solution became dark green. A precipitate appeared after a period of 15 min to 2 hr (for different coumestans). Table 2 gives the coumestan acetates obtained, their melting points, and their analyses.

Table 2

Coumestans	Formula	Mp, °C	Found, %		Calculated, %	
			C	H	C	H
7,11,12-Triacetoxy-5-methyl-	$C_{22}H_{16}O_8$	256–258	62,61 62,45	4,01 3,96	62,26	3,80
7,11,12-Triacetoxy-5-methoxy-	$C_{22}H_{16}O_{10}$	264–266	60,07 59,82	3,93 3,75	59,98	3,66
11,12-Diacetoxy-7-methoxy-5-methyl-	$C_{21}H_{16}O_8$	248–250	63,77 63,52	4,21 4,10	63,61	4,07
11,12-Diacetoxy-6-methyl-	$C_{20}H_{14}O_7$	237–238	65,30 65,39	3,66 3,79	65,55	3,85
11,12-Diacetoxy-8-methyl-	$C_{20}H_{14}O_7$	241–243	65,33 65,42	3,75 3,80	65,55	3,85
11,12-Diacetoxy-6,7-dimethyl-	$C_{21}H_{16}O_7$	260–262	66,68 66,52	4,50 4,38	66,30	4,24

7, 11, 12-Trimethoxy-5-methylcoumestan (VII). A solution of 1 g of 7, 11, 12-trihydroxy-5-methylcoumestan in 500 ml of dry acetone was treated with 3 g of calcined potassium carbonate and, dropwise, with 20 ml of dimethyl sulfate. The reaction mixture was boiled under reflux for 12 hr and filtered, the acetone was distilled off, and the residue was diluted with water. On cooling, a precipitate deposited. It was purified on a column of silica gel, the substance VII being eluted with benzene, mp 222–224° C (from dioxane). Found, %: C 67.26, 67.37; H 4.85, 4.69. Calculated for $C_{19}H_{16}O_6$, %: C 67.05, H 4.73.

7-Methoxy-5-Methyl-11, 12-Methylenedioxycoumestan (VIII). A mixture of 1.5 g of III, 3 g of methylene iodide, and 9 g of freshly calcined potassium carbonate in 900 ml of dry acetone was boiled under reflux for 25 hr. After filtration from the potassium carbonate and distillation of the solvent, the residue was purified on a column of silica gel, being eluted with benzene, mp 265–267° C. IR spectrum, cm^{-1}: 940, 1030 (—O—CH_2—O—), and 1735. Found, %: C 66.56, 66.43; H 3.70, 3.83. Calculated for $C_{18}H_{12}O_6$, %: C 66.66; H 3.60.

CONCLUSIONS

1. Eight new representatives of methyl- and methoxycoumestans were obtained.

2. For the synthesis of the coumestans, the following previously undescribed coumarins have been synthesized: 4, 7-dihydroxy-5-methyl-, 4, 7-dihydroxy-5-methoxy-, and 4-hydroxy-7-methoxy-5-methylcoumarins.

REFERENCES

1. E. M. Bickoff, R. R. Spencer, B. E. Knuckles, and R. E. Lundin, J. Agric. and Food Chem., **14**, 5, 444, 1966.

2. A. A. Shamshurin, M. A. Yampol'skaya, and L. L. Simonova, KhPS [Chemistry of Natural Compounds], **2**, 51, 1966.

3. L. L. Simonova and A. A. Shamshurin, KhPS [Chemistry of Natural Compounds], **3**, 367, 1967.

4. L. L. Simonova and A. A. Shamshurin, Izv. AN MSSR, ser. biol. i khim. nauk, no. 1, 90, 1970.

5. H. W. Wanzlik, Angew Chem., **76**, 8, 313, 1964.

6. D. Forrest, I. Thomas, et al., J. Am. Chem. Soc., **80**, 21, 5864, 1958.

7. E. Liegler and H. Junek, Monatschefte für Chemie, **86**, 29, 1955.

8. J. Maillard, M. Vincent, and P. Delaunay, Bull. Soc. Chem. France, no. 8, 2520, 1966.