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SYNTHETIC AND MODIFIED ISOFLAVONOIDS. IX. SYNTHESIS OF BENZODIOXOLANE AND BENZODIOXANE ANALOGS OF 3-ARYLCOUMARINS

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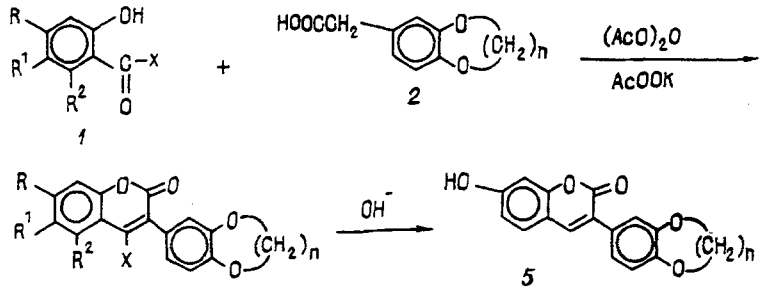
4-H(4-Me)-3-hetarylcoumarins modified by 1,3-benzodioxolane and 1,4-benzodioxane residues have been synthesized. The structures of the compounds obtained have been confirmed by PMR.

Continuing investigations of the chemical modification of synthetic analogs of natural coumarinolignans with the aim of finding new biologically active agents [1], we have synthesized new derivatives of 3-arylcoumarins.

As the starting compounds for the synthesis of modified analogs of 3-arylcoumarins unsubstituted in position 4, we used the α-(1,3-benzodioxolan-5-yl)- and α-(1,4-benzodioxan-6-yl)acetic acids (**2**) [2 and 3, respectively] and the substituted salicylaldehydes (**1**) (X = H), which, under the conditions of the Perkin reaction [4] in acetic anhydride in the presence of potassium acetate, were converted into the 3-hetarylcoumarins (**3**).



3 a-e , *4* g,h

3a: R^1–R^2–H; b: R–R^2–H, R^1–Cl; c: R–R^2–H, R^1–Br; d: R–H, R^1–R^2–HC=CH–HC=CH–; e: R^1–R^2–H, R–AcO; X–H; 3, 5: *n*=1, 2; 4g: R^1–R^2–H, R–OMe; h: R–R^2–H, R^1–Cl; X–Me; *n*=2

TABLE 1. Characteristics of Compounds (**3-5**)

Compound	Yield, %	mp, °C	Empirical formula
3a, *n*=2	12	190—191	$C_{17}H_{12}O_4$
3b, *n*=1	58	237—239	$C_{16}H_9ClO_4$
3b, *n*=2	76.3	199—201	$C_{17}H_{11}ClO_4$
3c, *n*=1	73.9	234—235	$C_{16}H_9BrO_4$
3c, *n*=2	47.4	206—207	$C_{17}H_{11}BrO_4$
3d, *n*=1	39.7	204—205	$C_{20}H_{12}O_4$
3d, *n*=2	34.8	212—214	$C_{21}H_{14}O_4$
3e, *n*=1	41	193—194	$C_{18}H_{12}O_6$
3e, *n*=2	37.5	171—173	$C_{19}H_{14}O_6$
4, *n*=1	80.4	239—241	$C_{16}H_{10}O_5$
4, *n*=2	94.7	238—240	$C_{17}H_{12}O_5$
5g	18.5	178—179	$C_{19}H_{16}O_5$
5h	27.4	246—248	$C_{18}H_{13}ClO_4$

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TABLE 2. Chemical Shifts in the PMR Spectra (δ, ppm, J, Hz) of the 3-Hetarylcoumarins (**3-5**)

Compound	Protons of the coumarin ring				
	H-4 or Me-4, s	R^2-5, d (2.4)	R^1-6	R-7 or H-9, d.d (8.3; 2.4)	H-8 or H-10, d. (8.3)
3a, *n*=2	7.74	7.49 d.d. (8.3; 2.4)	7.49 t.d (8.3; 2.4)	7.40 d.d	7.36 d.d
3b*, *n*=1	8.10	7.81	—	7.60	7.41
3b, *n*=2	7.65	7.49	—	7.44	7.35
3b*, *n*=2	8.12	7.82	—	7.60	7.42
3c, *n*=1	7.66	7.66	—	7.61	7.25
3c, *n*=2	7.64	7.64	—	7.59	7.22
3d, *n*=1	8.52	8.30 d.d (8.3; 2.4) (H-5); 7.56 t.d. (H-6); 7.71 t.d , (H-7); 7.93 d.d (8.3; 2.4), (H-8)		7.97 d (8.3)	7.49 d (8.3)
3d, *n*=2	8.47	8.27 d.d (8.3; 2.4), (H-5); 7.67 t.d (H-6); 7.52 t.d (H-7); 7.89 d. d, (8.3; 2.4), (H-8)		7.92 d (8.3)	7.45 d (8.3)
3e, *n*=1	7.73	7.53 d (8.43)	7.06 d.d (8.43; 2.2)	2.34 s	7.12 d (2.2)
3e, *n*=2	7.72	7.52 d (8.43)	7.05 d.d (8.43; 2.2)	2.34 s	7.12 d (2.2)
4*, *n*=1	8.09	7.56 d (8.4)	7.06 d.d (8.4; 2.2)	10.50 s	7.75 d (2.2)
4*, *n*=2	8.07	7.56 d (8.4)	7.05 d.d (8.4; 2.2)	10.55 s	7.74 d (2.2)
5g, *n*=2	2.28	8.08 d (8.2)	7.54 d.d (8.2; 2.2)	3.89 s	6.88 d (2.2)
5h, *n*=2	2.32	7.62	—	7.47	7.29

Compound	Protons of the hetero residue			
	H-4(5), d. (2.2)	H-6(7), d.d , (8.3; d , 2.2)	H-8(9), (8.3)	$-O(CH_2)_n$ s
3a, *n*=2	7.27	7.21	6.91	4.29
3b*, *n*=1	7.28	7.25	6.97	6.06
3b, *n*=2	7.28	7.18	6.90	4.28
3b*, *n*=2	7.26	7.22	6.92	4.28
3c, *n*=1	7.27	7.18	6.88	6.03
3c, *n*=2	7.25	7.22	6.92	4.29
3d, *n*=1	7.34	7.30	6.92	6.04
3d, *n*=2	7.35	7.32	6.95	4.30
3e, *n*=1	7.23	7.18	6.88	6.01
3e, *n*=2	7.26	7.21	6.93	4.29
4*, *n*=1	7.26	7.22	6.97	6.05
4*, *n*=2	7.24	7.18	6.89	4.27
5g, *n*=2	6.83	6.75	6.93	4.28
5h, *n*=2	6.80	6.75	6.94	4.30

*Spectra measured in DMSO-d_6; in the unmarked cases, in $CDCl_3$.

On brief heating with a 5% alcoholic caustic soda solution, the 7-acetoxycoumarin (**3e**) gave the 7-hydroxycoumarin (**5**).

Heating the substituted 2-hydroxyacetophenones (**1**) (X = Me) with α-(1,4-benzodioxan-6-yl)acetic acid (**2**) (n = 2) under the conditions of the Bargellini reaction [4] led to the 4-Me-substituted 3-hetarylcoumarins (**4**).

The 3-hetarylcoumrins (**3-5**) obtained were colorless crystalline substances readily soluble in the majority of organic solvents and insoluble in water. The structures of the compounds obtained were confirmed by the results of elementary analysis and PMR spectroscopy. The characteristics and PMR spectra of the 3-hetarylcoumarins (**3-5**) are given in Tables 1 and 2.

In the PMR spectra of the 4H-coumarins measured in $CDCl_3$, the most characteristic signals were those of the H-4 methine protons of the pyrone rings. These signals were singlets located in the weak field at 7.6-7.7 ppm. In the 6-R^1-substituted coumarins thr H-5 protons gave doublets with SSCC J = 2 Hz in the 7.5-7.6 ppm region. In the PMR spectra of the 4-Me-coumarins (**4**), the Me-4 groups were detected by the presence of a three-proton singlet at 2.3 ppm. The signals of the OH-7 groups in compounds (**5**) (DMSO-d_6) were observed at 10.5 ppm.

A comparison of the results of the synthesis of the coumarins (**3-4**) (see Table 1) shows a difference in accessibilities of the 4-Me- and 4-H-coumarins modified by 1,3-benzodioxolane and 1,4-benzodioxane nuclei.

In a study of the biological activities of the 3-arylcoumarins obtained, it was found that some of them possessed a well-marked antiatherosclerotic activity.

EXPERIMENTAL

3-Hetarylcoumrins (3a-e). A mixture of 10 mmle of an acid (**2**), 10 mmole of the appropriate aldehyde((**1a-e**), 2.95 g (30.1 mmole) of potassium acetate, and 10.3 ml of acetic anhydride was boiled for 2-6 h. Then the reaction mixture was poured into cold water, and the precipitate that deposited was filtered off and washed with water. The desired compounds (**3a-e**) were purified by crystallization from ethyl acetate.

3-Hetaryl-4-methylcoumarins (4g,h). A mixture of 20 mmole of an acid (**2**), 20 mmole of the appropriate 2-hydroxyacetophenone (**1g,h**), 5.9 g (60.2 mmole) of potassium acetate, and 20.6 ml of acetic anhydride was boiled for 6-8 h. Then the reaction mixture was poured into cold water, and the precipitate was filtered off and, after drying, it was crystallized from ethyl acetate.

3-Hetaryl-7-hydroxycoumarins (5). A hot solution of 30 mmole of the 7-acetoxycoumarin (**3e**) in 200 ml of alcohol was treated with 24 ml (30 mmole) of 5% caustic soda solution, and the mixture was boiled for 15 min. The 20 ml of water was added, and boiling was continued for another 5 min. The mixture was neutralized to pH 7 with dilute hydrochloric acid, and the precipitate was filtered off and recrystallized from alcohol.

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