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SYNTHETIC AND MODIFIED ISOFLAVONOIDS. XII. SYNTHESIS OF HOMOLOGS OF 5,7-DIHYDROXY-3′,4′-METHYLENEDIOXYISOFLAVONE

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Benzodioxane and benzodioxepane analogues of 5,7-dihydroxy-3′,4′-methylenedioxyisoflavone have been synthesized from α-hetaryl-2,4,6-trihydroxyacetophenones. The structures of the compounds obtained have been shown by their PMR spectra.

5,7-Dihydroxy-3′,4′-methylenedioxyisoflavone has been isolated from the roots of the plant *Sophora japonica* L. [2]. The majority of natural flavones are 5,7-dihydroxy derivatives and their glycosides or ethers – for example, derrustone (5,7-dimethoxy-3′,4′-methylendioxyisoflavone, isolated from the plant *Derris robusta* [3]. With the aim of synthesizing and studying the properties of new analogues of 5,7-dihydroxy-3′,4′-methylenedioxyisoflavone we have developed a method for synthesizing its benzodioxane and benzodioxepane homologues.

It is known [4] that deoxybenzoins containing three hydroxy groups in positions 2, 4, and 6 and more highly hydroxylated deoxybenzoins do not form isoflavones on interaction with orthoformic ester. To synthesize dihydroxyisoflavones unsubstituted in positions 2, 5, and 7, wide use is made of the ethoxalyl chloride method with subsequent hydrolysis of the 2-ethoxycarbonyl group and decarboxylation of the 2-carboxy group [4]. In 1976 [6] a method was proposed for the synthesis of isoflavones by the formylation of 2-hydroxydeoxybenzoins with dimethylformamide/methanesulfonyl chloride in the presence of boron trifluoride etherate. It was possible to obtain isoflavones with phloroglucinol fragments in high yields by this method. We have modified this method by using phosphorus pentachoride or pentabromide in place of methanesulfonyl chloride and have used this variant for the synthesis of benzodioxane and benzoxepane homologues of 5,6-dihydroxy-3′,4′-methylenedioxyisoflavone. The initial compounds for achieving the aim set were the α-hetaryl-2,4,6-trihydroxyacetophenones (**1a**, **b**), obtained by condensing 6-cyanomethyl-1,4-benzodioxane and 7-cyanomethyl-1,5-benzodioxepane with phloroglucinol under the conditions of the Hoesch reaction.

The structures of ketones (**1a**, **b**) formed from phloroglucinol were determined unambiguously, since here only one isomer is possible. In their PMR spectra, the signals of the hydroxy groups were in the form of singlets the positions of which depended little on the structure of the hetero residue. The OH-2 and OH-6 groups gave a common signal at 11.6-12.3 ppm, and the third hydroxyl (OH-4) absorbed at 10.5-11.6 ppm. The H-3 and H-5 aromatic protons gave a two-proton singlet in the 5.9-6.9 region. The aromatic protons of the hetero residues showed up in the 6.7-6.9 region. The protons of the ethylene group gave a singlet at 4.3 ppm, and the protons of the propylenedioxy group were revealed in the form of a triplet (4.1 ppm) and a quintet (2.1 ppm).

As a result of the heating of the compounds (**1a**, **b**) with dimethyl formamide in the presence of boron trifluoride etherate and phosphorus pentachloride or pentabromide at 70°C, the 5,7-dihydroxyflavones (**2a, b**) were formed in high yields.

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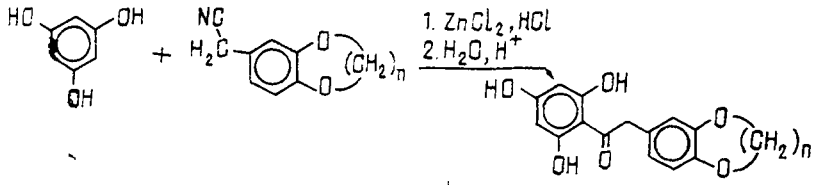
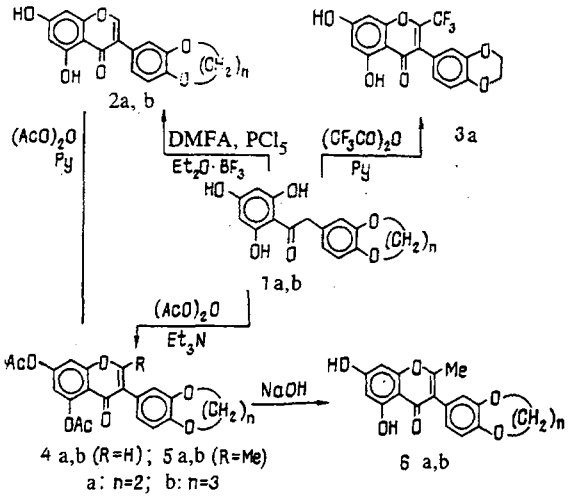


1 a,b; a:n = 2; b:n = 3

Definite interest is presented by the synthesis of isoflavones containing a methyl or trifluormethyl group in position 2. On interaction with trifluoroacetic anhydride in pyridine at 0°C followed by brief heating of the reaction mixture at 40-50°C, ketone (**1a**) gave the isoflavone (**3a**). The treatment of pyridine solutions of 5,7-dihydroxyflavones (**2a, b**) with acetic anhydride at room temperature led to the corresponding 5,7-diacetoxyisoflavones (**4a, b**). On being heated with acetic anhydride in triethylamine, compounds (**1a, b**) were converted into the corresponding 5,7-diacetoxy-2-methylisoflavones (**5a, b**), which then by brief heating with a 5% solution of alkali gave the 5,7-dihydroxy-2-methylisoflavones (**6a, b**).



4 a,b (R=H); 5 a,b (R=Me)
a: n=2; b: n=3

6 a,b

The structures of the analogues (**2-6a, b**) of the natural 5,7-dihydroxy-3',4'-methylenedioxyisoflavone were confirmed by their analytical and spectral characteristics (Tables 1 and 2).

Thus, the cyclization of benzodioxane and benzodioxepane derivatives of 2,4,6-trihydroxyacetophenone takes place readily on interaction with carboxylic acid anhydrides or the Vilsmeier reagent in a modified variant of the method. In this way, synthetic analogues of the natural 5,7-dihydroxy-3',4'-methylenedioxyisoflavone have been obtained with high yields.

EXPERIMENTAL

The conditions for chromatography and for recording the spectra have been described in [1].

α-(1,4-Benzodioxan-6-yl)-2,4,6-trihydroxyacetophenone (1a). With stirring, a rapid current of dry hydrogen chloride was passed for 10 min into a solution of 52.5 g (0.3 mole) of 6-cyanomethyl-1,4-benzodioxane in 225 ml of absolute benzene cooled to 0°C. Then a solution of 45.4 g (0.36 mole) of phloroglucinol and 20.5 g (0.15 mole) of fused zinc chloride in 171 ml of absolute ether was added. Saturation with hydrogen chloride was continued at 0°C for 3 h and then at room temperature for another 3 h. After this, the reaction mixture had thickened, and it was left overnight at room temperature. The solvent was decanted from the precipitate and the latter was triturated twice with dry benzene. After this, it was

TABLE 1. Characteristics of Compounds (2-6)

Compound	Yield, %	mp, °C	Empirical formula.
2a	99	244—245	$C_{17}H_{12}O_5$
2b	95	146—148	$C_{18}H_{14}O_6$
3a	79	228—230	$C_{18}H_{11}F_3O_6$
4a	66	193—194	$C_{22}H_{18}O_8$
4b	53	169—170	$C_{23}H_{20}O_6$
5a	76	195—196	$C_{21}H_{16}O_8$
5b	58	172—173	$C_{22}H_{18}O_8$
6a	96	224	$C_{18}H_{14}O_6$
6b	98	143—144	$C_{19}H_{16}O_6$

TABLE 2. Chemical Shifts in the PMR Spectra,* (δ, ppm) of the Homologs of 5,7-Dihydroxy-3′,4′-Methylenedioxyisoflavone (2-6a, b)

Compound	Chromone protons				
	H-2 or Me-2, s	OH-5 or OAc-5, s	H-6, d J=2.5 Hz	OH-7 or OAc-7, s	H-8, d J=2.5 Hz
2a	8.31	12.90	6.22	10.89	6.37
2b	8.37	12.87	6.23	10.93	6.39
3a	-	12.23	6.29	11.20	6.45
4a	7.85	2.42	7.23	2.34	6.85
4b	7.85	2.42	7.23	2.37	6.85
5a	2.24	2.37	7.10	2.33	6.79
5b	2.23	2.37	7.20	2.33	6.81
6a	2.23	12.93	6.18	10.81	6.32
6b	2.22	12.88	6.17	10.80	6.30

Compound	Protons of the hetero residue			
	H-5 (H-6) J=2.0 Hz	H-7 (H-8) d.d J=8.0; 2.0 Hz	H-8 (H-9) J=8.0 Hz	O(CH2)nO t,q
2a	7.08	7.03	6.88	4.26 s
2b	7.20	7.16	6.99	4.16; 2.11
3a	6.83	6.74	6.91	4.28 s
4a	7.02	6.91	6.91	4.27 s
4b	7.10	7.03	7.03	4.25; 2.21
5a	6.73	6.70	6.90	4.26 s
5b	6.84	6.77	7.00	4.24; 2.21
6a	6.77	6.72	6.90	4.27 s
6b	6.89	6.83	7.00	4.15; 2.11

*The PMR spectra of compounds (**2a, b**), (**3a**), and (**6a, b**) were measured in DMSO-d_6, and those of the other compounds in $CDCl_3$.

transferred into 900 ml of hot water and the mixture was kept at 90-100°C, pH 1, for 30 min. Then the solid matter was separated from the hot solution and was washed well on the filter with water to pH 7. Yield 50 g (55%), mp 217-218°C (from aqueous alcohol). Empirical formula $C_{16}H_{14}O_6$. PMR spectrum (DMSO-d_6, δ, ppm): 4.26 (s, 2H, $COCH_2$), 11.58 (s, 1H, OH-2), 5.87 (s, 1H, H-3), 11.58 (s, 1H, OH-4), 5.87 (s, 1H, H-5), 11.58 (m, 1H, OH-6); benzodioxane protons: 6.73 (m, 3H, H-5, H-7, H-8), 4.26 (s, 4H, OCH_2CH_2O).

α-(1,5-Benzodioxepan-7-yl)-2,4,6-trihydroxyacetophenone (1b) was obtained in a similar way to compound (**1a**). Yield 53.1 g (56%), mp 95-96°C from alcohol). Empirical formula $C_{17}H_{16}O_6$. PMR spectrum (DMSO-d_6, δ, ppm): 4.29 (s 2H, $COCH_2$), 12.29 (s, 1H, OH-2), 6.85 (s 1H, H-3), 10.49 (s, 1H, OH-4), 6.85 (s, 1H, H-5), 12.29 (s, 1H, OH-6); benzodioxane protons: (s, 3H, H-6, H-8, H-9), 4.13 (t, 4H, 2-CH_2 and CH_2-4), 2.09 (q, 2H, 3-CH_2).

3-(1,4-Benzodioxan-6-yl)-5,7-dihydroxychromone (2a). With stirring, 37 ml (0.3 mole) of boron trifluoride etherate was added dropwise to a solution of 15.1 g (0.05 mole) of the ketone (**1a**) in 75 ml (1 mole) of DMFA. Then 11 g (0.05 mole) of phosphorus pentabromide or pentachloride was added at such a rate that the temperature of the reaction mixture did not rise above 70°C. After the end of the reaction, the reaction mixture was poured into hot water and the resulting mixture was kept at 70°C for 1 h. The precipitate thas deposited was filtered off and was crystallized from aqueous alcohol.

3-(1,5-Benzodioxepan-7-yl)-5,7-dihydroxychromone (2b) was obtained in a similar way to compound (**2a**) and was crystallized from aqueous alcohol.

3-(1,4-Benzodioxan-6-yl-5,7-dihydroxy-2-trifluoromethylchromone (3a). A solution of 15.1 g (0.05 mole) of ketone (**1a**) in 40 ml of dry pyridine was cooled to 0°C, and 21.2 ml (1.5 moles) of trifluoroacetic anhydride was added dropwise. The reaction mixture was then shaken for 10-15 min, with ice cooling, and was then left at room temperature for 12 h, after which it was heated to 40-50°C and was again left at room temperature for 12 h; it was then poured into cold water and the resulting precipitate was filtered off. The desired product was crystallized from alcohol.

3-Hetaryl-5,7-acetoxychromones (4a, b). A hot solution of 40 mmole of an isoflavone (**2a, b**) in the minimum amount of pyridine was treated with 36.8 ml (400 mmoles) of acetic anhydride, and the reaction mixture was left in a refrigerator. The precipitate that had deposited was filtered off, washed on the filter with cold alcohol, and crystallized from ethyl acetate.

3-Hetaryl-5,7-diacetoxy-2-methylchromones (5a, b). A mixture of 50 mmoles of a ketone (**1a, b**), 35.2 ml (375 mmoles) of acetic anhydride, and 42 ml (345 mmoles) of triethylamine was heated at 125-130°C for 5-11 h. Then the reaction mixture was poured into cold water containing 6 ml of hydrochloric acid. The precipitate that deposited was filtered off, washed with water until the smell had disappeared, and crystallized fronm ethyl acetate.

3-Hetaryl-5,7-dihydroxy-2-methylchromones (6a, b). A boiling suspension of 20 mmoles of an isoflavone (**5a, b**) in 60 ml of alcohol was treated with 10 ml of water and 26 ml of a 5% solution of caustic soda, and the mixture was boiled for 15 min. After neutralization with dilute hydrochloric acid, the precipitate was deposited was filtered off and crystallized from aqueous alcohol.

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