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SYNTHETIC AND MODIFIED ISOFLAVONOIDS. VII. SYNTHESIS OF BENZODIOXOCANE ANALOGS OF PSEUDOBAPTIGENIN

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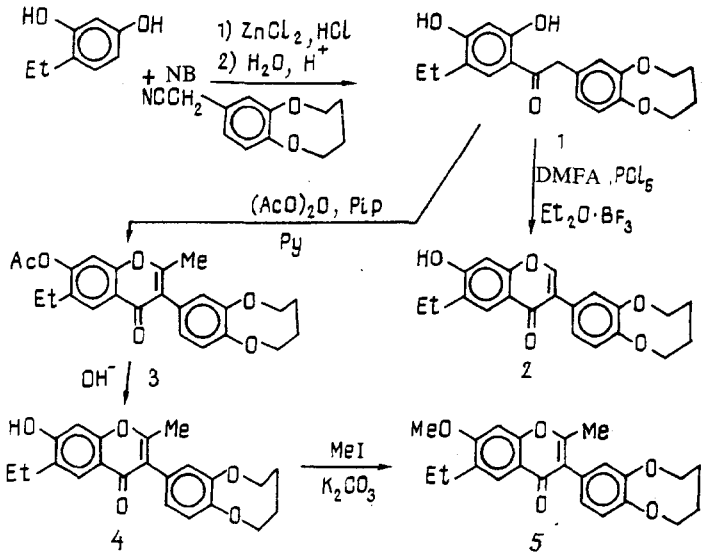
Benzodioxocane analogs of pseudobaptigenin have been synthesized, and their structures have been shown by chemical transformations and PMR spectra.

We have continued work on the synthesis of pseudobaptigenin analogs [1-6]. Our aim was the development of methods of synthesizing previously unknown benzodioxecane analogs of pseudobaptigenin and the study of the dependence of the properties of these compounds on the expansion of the lateral heterocycle.

The key substance for the synthesis of the desired isoflavones was ketone (**1**), obtained by the Hoesch reaction of 8-cyanomethyl-1,6-benzodoxecane, with 4-ethylresorcinol. This reaction takes place in a mixture of benzene and ether in a current of dry hydrogen chloride in the presence of zinc chloride.

Ketone (**1**) was an oily product. Its structure was confirmed by its PMR spectrum. In this spectrum, measured in $CDCl_3$, the protons of the hydroxy groups OH-2 and OH-4 resonated at 12.58 and 10.70 ppm, respectively The aromatic protons of the phenol ring, H-3 and H-6, gave singlets at 6.28 and 7.34 ppm. The methylene protons of the 1,6-benzodioxocane were revealed in the form of two broadened singlets at 4.23 and 1.86 ppm.



Under the action of the Vilsmeier reagent in the presence of boron trifluoride etherate at 70°C, ketone (**1**) cyclized into the isoflavone (**2**). The interaction of ketone (**1**) with acetic anhydride in the presence of triethylamine at 120-130°C yielded 7-acetoxy-2-methylisoflavone (**3**). The acetyl group in compound (**3**) was eliminated by brief boiling with one equivalent of sodium hydroxide (5% solution) in ethanol. As a result, the free 7-hydroxyisoflavone (**4**) was obtained. On alkylation with methyl iodide in the presence of potassium carbonate in boiling acetone, the latter formed compound (**5**), methylated at the 7-

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

Compound	Yield, %,	T. mp, °C	Empirical formula
1	48.2	Oil	$C_{20}H_{22}O_5$
2	8.9	219—221	$C_{21}H_{20}O_5$
3	73.3	120—121	$C_{24}H_{24}O_6$
4	93.1	>300	$C_{22}H_{22}O_5$
5	83.7	141—142	$C_{23}H_{24}O_5$

TABLE 2. Chemical Shifts in the PMR Spectra (δ, ppm) of the Benzodioxocane Analogs of Pseudobaptigenin (**2-5**)*

Compound	Chromone protons				
	H-2 or Me-2, s	H-5, s	Et-6 q.t	OH-7, OAc-7 or OMe-7, s	H-8, s
2	8.32	7.80	2.61; 1.16	10.79	6.87
3	2.28	8.10	2.64; 1.24	2.37	7.19
4	2.11	7.68	2.57; 1.14	11.10	6.94
5	2.29	7.95	2.68; 1.22	3.92	6.77

Compound	Benzodioxocane protons				
	H-7, d J=2 Hz	H-9, dd J=8 Hz; J=2 Hz	H-10, d J=8 Hz	CH_2-2 and CH_2-5, s	CH_2-3 and CH_2-4, s
2	7.20	7.15	6.95	4.26	1.80
3	6.89	6.85	7.01	4.37	1.93
4	6.8—7.0	6.8—7.0	6.8—7.0	3.99; 4.23	1.72
5	6.91	6.87	7.02	4.35	1.92

*The PMR spectra of compounds (**2**) and (**4**) were measured in DMSO-d_6, and those of the other compounds in $CDCl_3$.

OH group. Characteristics of the isoflavones obtained (**2-5**) are given in Table 1, and details of their PMR spectra in Table 2.

In the PMR spectrum of isoflavone (**2**) the H-2 proton of the pyrone ring appeared in the form of a singlet at 8.30 ppm. The signal of the hydroxy group OH-7 of the isoflavones was observed in the 10.80-11.10 ppm region. The acetyl group and the methoxy group gave singlets at 2.40 and 3.92 ppm, respectively. The protons of the butylenedioxy ring gave two broadened singlets at 3.99-4.37 and 1.70-1.90 ppm, respectively.

A comparison of the results of the synthesis of the benzodioxolane, benzodioxane, benzodioxepane, and benzodioxocane analogs of 2-hydroxydeoxybenzoin and of pseudobaptigenin showed that the tendency to an increase in the time of formation of the desired products observed on passing from the benzodioxolane to the benzodioxane and then to the benzodioxepane analogs is disturbed in the case of the benzodioxocane analogs, this probably being connected with a change in the electron-donor influence of the dioxecane ring on the CH-acidity of the methylene unit with a change in the geometry of the ring.

In a study of the biological activities of the new pseudobaptigenin analogs it was found that some of them possess a well-defined hypoglycemic activity.

EXPERIMENTAL

The course of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates. Benzene—ethanol (9:1) was used as the eluent. PMR spectra were measured on a Bruker WP-100 SU spectrometer in DMSO-d_6 or $CDCl_3$, with TMS as internal standard. The analyses of the compounds synthesized corresponded to the calculated figures.

α-(1,6-Benzodioxocan-8-yl)-5-ethyl-2,4-dihydroxyacetophenone (1). With stirring, a rapid current of dry hydrogen chloride was passed for 10 min into a solution of 20.3 g (100 mmole) of 8-cyanomethyl-1,6-benzodioxecane in 75 ml of absolute toluene cooled to 0°C. Then a solution of 13.9 g (101 mmole) of dry 4-ethylresorcinol and 6.7 g (50 mmole) of fused zinc chloride in 70 ml of absolute ether was added. Saturation with hydrogen chloride was continued for 3 h, and then at room temperature for a further 2 h. After this, the mixture thickened, and it was left overnight at room temperature. The solvent was decanted from the deposit, and the latter was triturated twice with dry toluene. It was then added to 380 ml of hot water, and the mixture was kept at 90°C and pH 1 for 30 min. The product was separated off from the hot solution and was carefully washed on the filter with water until the reaction to universal indicator paper was neutral. Oily product. PMR spectrum ($CDCl_3$, ppm): 12.58 (s, 1H, OH-2), 7.34 (s, 1H, H-3), 10.70 (s, 1H, OH-4), 2.53; 1.18 (q.t, 5H, Et-5), 6.28 (s, 1H, H-6), 4.22 (s, 2H, CH_2); Benzodiocane protons; 6.89 (s, 3H, H-7, H-9, H-10), 4.23 (s, 4H, CH_2 and CH_2-5), 1.86 (s, 4H, CH_2-3 and CH_2-4).

3-(1,6-Benzodioxocan-6-yl)-6-ethyl-7-hydroxychromone (2). With stirring, 22.2 ml (180 mmole) of boron trifluoride etherate was added dropwise to a solution of 10.3 g (30 mmole) of ketone (**1**) in 45 ml (600 mmole) of DMFA. Then 6.6 g (33 mmole) of phosphorus pentachloride was added at such a rate that the temperature of the reaction mixture did not rise above 60-70°C. After the end of the reaction, the reaction mixture was poured into 600 ml of water, and the resulting mixture was kept at 70°C for 1 h. The precipitate that deposited was filtered off and was crystallized from isopropanol.

7-Acetoxy-3-(1,6-benzodioxocan-8-yl)-6-ethyl-2-methylchromone (3). A mixture of 8.55 g (25 mmole) of ketone (**1**), 11.5 ml (125 mmole) of acetic anhydride, and 14 ml (100 mmole) of triethylamine was heated at 120-130°C for 6 h. Then the reaction mixture was added to cold water containing 1.75 ml of hydrochloric acid. The precipitate that deposited was filtered off, washed with water until free from smell, dried, and crystallized from ethyl acetate.

3-(1,6-Benzodioxocan-8-yl)-6-ethyl-7-hydroxy-3-methylchromone (4). A hot solution of 12.24 g (30 mmole) of 7-acetoxy-2-methylisoflavone (**3**) in 115 ml of ethanol was treated with 24 ml (30 mmole) of a 5% solution of caustic soda, and the mixture was boiled for 7 min. Then 20 ml of water was added and boiling was continued for another 20 min, after which the mixture was neutralized with dilute hydrochloric acid to pH 7. The precipitate that deposited was filtered off and was crystallized from ethanol.

3-(1,6-Benzodioxocan-8-yl)-6-ethyl-7-methoxy-2-methylchromone (5). A hot solution of 3.54 g (10 mmole) of 7-hydroxy-2-methylisoflavone (**4**) in 50 ml of dry acetone was treated with 4.14 g (30 mmole) of freshly fused potassium carbonate, and 0.68 ml (11 mmole) of methyl iodide, and the mixture was boiled for 45 min. The inorganic deposit was filtered off and was washed on the filter with hot acetone (2 × 10 ml). The acetone was distilled off in a water-pump vacuum, and the residue was crystallized from isopropanol.

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