

SYNTHETIC AND MODIFIED ISOFLAVONOIDS.

I. SYNTHETIC ANALOGUES OF PSEUDO-BAPTIGENIN

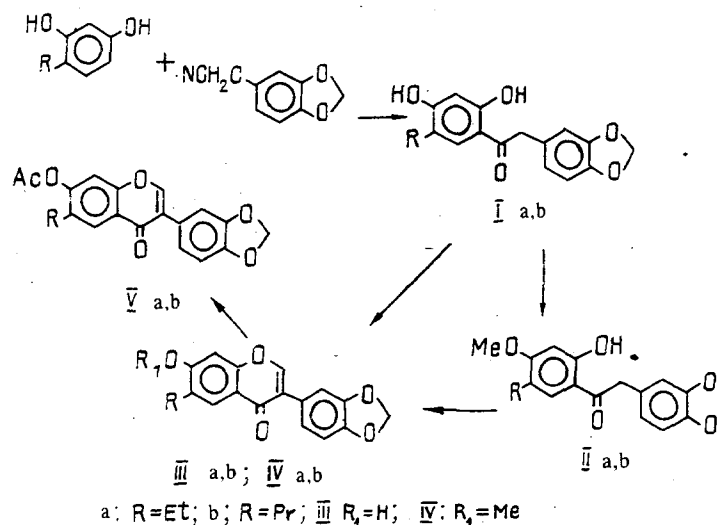
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New isoflavones derived from pseudobaptigenin containing alkyl substituents in position 6 have been synthesized. The structures of the compounds have been confirmed by PMR and IR spectroscopies.

Isoflavonoids form an extensive and peculiar group of natural compounds interest in which is constantly attracting the attention of many researchers. They exhibit a considerable physiological activity and are not toxic, and they are therefore widely used for medicinal purposes. The heterocyclic system of benzodioxole is widely distributed in nature. It is one of those heterocycles that play an important role in many processes of vital activity, mainly in the plant kingdom. The benzodioxole ring is a component of many chalcones, flavones, flavanones, 3-hydroxyflavanones, isoflavones, coumarins, and other substances. Thus, for example, flavonoids with an annelated dioxole ring possess phytotoxic, antifungal, cytotoxic, antibacterial, analgesic, and antitubercular properties.

Pseudobaptigenin (7-hydroxy-3',4'-methylenedioxyisoflavone) has been isolated from various plant species [1, 2]. In view of the useful properties of natural and synthetic flavonoids including a 1,3-benzodioxole fragment, it was of interest to synthesize new derivatives of pseudobaptigenin and to study their properties. The initial compounds for achieving the aim set were α -(1,3-benzodioxol-5-yl)-2,4-dihydroxy-5-alkylacetophenones (I). For the synthesis we used the Hoesch reaction [3], under the conditions of which we performed the condensation of 5-cyanomethyl-1,3-benzodioxole with 5-alkylresorcinols (Scheme).



The compounds (I) obtained were colorless crystalline substances readily soluble in the majority of organic solvents and in aqueous solutions of alkalis and forming with an alcoholic solution of ferric chloride colored complexes of the chelate type. To prove the structures of the ketones (I), in addition to the facts given and the results of elementary analysis we used their IR and PMR spectra.

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TABLE 1. Characteristics of Compounds (I-V)

Compound	Yield, %	T. mp, °C	Empirical formula	IR spectrum, cm ⁻¹	
				ν_{OH}	$\nu_{C=O}$
Ia	58	122—123	C ₁₇ H ₁₆ O ₅	3350	1633
Ib	72	127—128	C ₁₈ H ₁₈ O ₅	3280	1635
IIa	78	124—125	C ₁₈ H ₁₈ O ₅		
IIb	94	100—101	C ₁₉ H ₂₀ O ₅		
IIIa	96 ^c ; 97 ^d	239—240	C ₁₈ H ₁₄ O ₅	3200	1635
IIIb	87 ^c ; 89 ^d	216—217	C ₁₉ H ₁₆ O ₅	3260	1635
IVa	81 ^c ; 97 ^d	175—176	C ₁₉ H ₁₆ O ₅		1648
IVb	75 ^c ; 79 ^d	122—123	C ₂₀ H ₁₈ O ₅		1649
Va	56	147—148	C ₂₀ H ₁₆ O ₆		1650; 1743
Vb	72	123—124	C ₂₁ H ₁₈ O ₆		1650; 1742

Notes. c) Yield by method A; d) yield by method B.

The IR spectra of compounds (I) in the solid phase had intense stretching absorption bands at (cm⁻¹) 3280-3340 and 1633-1635, relating to the stretching vibrations of the phenolic hydroxyl and of a carbonyl group, respectively. The PMR spectra of the ketones (I) (in DMSO) showed that in these compounds the OH groups were in positions 2 and 4 of the benzene ring. This conclusion is in harmony with the singlet nature of the peaks of the H-3 and H-6 protons of the phenol moieties of the ketones. The protons of the methylene unit and of the hydroxy groups appeared in the form of singlets. The signal of the OH-2 proton was present in the weak field at 12.40-12.46 ppm, since this group takes part in the formation of an intramolecular hydrogen bond with the carbonyl. The proton of the OH-4 group, forming an intermolecular hydrogen bond, absorbed in a stronger field at 10.63-10.67 ppm. The aromatic protons of the benzodioxole system appeared in the 6.8-6.9 ppm region. The protons of the methylenedioxy group were detected in the form of a two-proton singlet at 5.98-6.05 ppm.

The ketones obtained were alkylated at the free phenolic hydroxyl. Thus, as a result of the interaction of compound (I) with equimolar amounts of dimethyl sulfate in the presence of potash in boiling benzene, the 4-hydroxy derivatives (II), giving a positive reaction with iron(III) chloride, were formed in high yields. In their PMR spectra, in addition to the one-proton singlet at OH-4 group at 10.6-10.7 ppm, a three-proton singlet appeared at 3.84 ppm. The characteristics of ketones (I) and (II) are given in Tables 1 and 2.

We studied the heterocyclization of ketones (I)-(II) to form new analogues (III-IV) of pseudobaptogenin by two methods. By one of them (A), consisting in heating the corresponding ketone with ethyl orthoformate in pyridine in the presence of piperidine, the formation of the chromone system requires boiling for several hours. In the second, more rapid, method (B), a Vilsmeier reagent acts on the initial ketone in the presence of boron trifluoride etherate at 70°C [4]. The isoflavones (III-IV) were obtained in practically identical yields by the two methods. By modifying method B with the use of phosphorus pentachloride or pentabromide in place of methanesulfonyl chloride, we achieved good yields of the desired products.

The action of acetic anhydride on pyridine solutions of the 7-hydroxychromones [11] at room temperature led to the formation of the 7-acetoxy derivatives (V).

The physical constants and spectral characteristics of the isoflavones obtained are given in Tables 1 and 3. The new isoflavones (III-V) are colorless crystalline high-melting substances readily soluble in organic solvents. In contrast to the initial ketones, they do not give a positive reaction with ferric chloride, which shows the absence from the molecules of a hydroxy group capable of forming a chelate.

In the IR spectra of the 7-hydroxychromones (III) there were characteristic absorption bands corresponding to the stretching vibrations of a hydroxyl (3200-3260 cm⁻¹), and to those of the carbonyl group of a pyrone ring (1635-1650 cm⁻¹), and to the skeletal vibrations of aromatic rings (1575-1615 cm⁻¹). Absorption bands of the acetyl groups of the acetoxychromone were observed at 1743-1769 cm⁻¹.

In the PMR spectra of the isoflavones (III-IV), the two-proton singlet of the methylene group and the weak-field peak of the phenolic proton had disappeared and in place of them there was a sharp single singlet of the H-2 proton in the 7.83-8.28 ppm region. A characteristic sign of the formation of a chromone ring is the presence of a peak in the 7.82-8.12 ppm region relating to the H-5 aromatic proton, which experiences the descreening effect of the neighboring carbonyl. Furthermore, this

TABLE 2. Chemical Shifts in the PMR Spectra of the α -(1,3-Benzodioxol-5-yl)-2-hydroxyacetophenones (I)-(II)

Compound	PMR spectrum, DMSO-d ₆ , δ , ppm									
	Protons of the phenolic part					Protons of the benzodioxole part				
	OH-2, s	H-3, s	OH-4 or OMe-4, s	R-5	H-6, s	CH ₂	c	H-4, d J=2 Hz	H-6, dd J=2; 7.8 Hz	H-7, H J=7.8 Hz
Ia	12.40	6.31	10.63	2.52 q; 1.13 t	7.72	4.21	6.87	6.71	6.89	5.98
Ib	12.39	6.40	10.81	2.45 t; 1.52 m; 0.87 t	7.73	4.19	6.87	6.72	6.89	5.96
IIa	12.47	6.46	3.84	2.52 q; 1.10 t	7.76	4.24	6.85	6.70	6.87	5.96
IIb	12.48	6.51	3.84	2.50 t; 1.56 m; 0.89 t	7.78	4.25	6.88	6.72	6.90	5.98

TABLE 3. Chemical Shifts in the PMR Spectra of the Pseudobaptigenin Analogues (III-V)

Compound	PMR spectrum, deuterated chloroform and dimethyl sulfoxide*, δ , ppm									
	Protons of the chromone part					Protons of the benzodioxole part				
	H-2, s	H-5, s	R-6	OH-7 or OAc-7, s	H-8, s	H-4, d J=2 Hz	H-6, dd J=2; 7.8 Hz	H-7, d J=7.8 Hz	H-7, d J=7.8 Hz	-OCH ₂ O-, s
IIIa*	8.27	7.80	2.61 q; 1.17 t	10.76	6.86	7.15	7.05	6.90	6.03	
IIIb*	8.25	7.78	2.58 t; 1.56 m; 0.89 t	10.74	6.85	7.11	7.03	6.90	6.02	
IVa	7.89	8.02	2.70 q; 1.24 t	3.92	6.78	7.10	6.98	6.84	5.98	
IVb	7.87	7.99	2.65 t; 1.63 m; 0.95 t	3.91	6.78	7.10	6.97	6.84	5.97	
Va	7.94	8.18	2.66 q; 1.26 t	2.38	7.23	7.09	6.98	6.85	5.99	
Vb	7.94	8.16	2.62 t; 1.62 m; 0.96 t	2.37	7.25	7.09	6.98	6.85	5.99	

H-5 proton undergoes a paramagnetic shift (0.18-0.40 ppm) in comparison with the corresponding proton of the initial ketone as a consequence of the formation of the coplanar benzopyran system. These facts permit the formation of the isoflavone system to be readily confirmed.

In a study of the biological activities of the new pseudobaptigenin analogues it was found that some of them possess a well-defined anabolic activity. Consequently, the further search for effective anabolics among pseudobaptin analogues is fully justified.

EXPERIMENTAL

The course of the reaction and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates. A mixture of benzene and ethanol (9:1) was used as eluent. PMR spectra were measured on a Bruker WP-100 SU instrument in dimethyl sulfoxide or deuteriochloroform with TMS as internal standard. IR spectra were measured on a PAY Unicam SP₃-300 instrument (KBr). The results of the analysis of the compounds synthesized correspond to the calculated figures.

α -(1,3-Benzodioxol-5-yl)-2,4-dihydroxy-5-alkylacetophenones (Ia, b). With stirring, a rapid current of dry hydrogen chloride was passed for 10 min into a solution of 16.1 g (100 mmole) of 5-cyanomethyl-1,3-benzodioxole in 75 ml of absolute benzene cooled to 0°C. Then a solution of 101 mmole of a dry 4-alkylresorcinol and 6.7 g (50 mmole) of fused zinc chloride in 70 ml of absolute ether were added. Saturation with hydrogen chloride was continued for 3 h, and then at room temperature for another 1.5 h, after which the reaction mixture was concentrated and was left overnight at room temperature.

The solvent was decanted from the precipitate, and the latter was triturated twice with dry benzene. The residue was added to 380 ml of hot water and the mixture was kept at 90°C, pH 1, for 30 min. The product was separated from the hot solution and was carefully washed on the filter with water until the reaction was neutral to universal indicator. Ketones (Ia, b) were purified by crystallization from aqueous alcohol or benzene.

α -(1,3-Benzodioxol-5-yl)-2-hydroxy-4-methoxy-5-alkylacetophenones (II, a, b). A hot solution of 10 mmole of a ketone (I) in 50 ml of absolute benzene was treated with 1.25 g (10 mmole) of dimethyl sulfate and 4.41 g (30 mmole) of freshly calcined potash and the mixture was boiled for 2 h. Then the inorganic matter was filtered off, and the filtrate was acidified with 2-3 drops of acetic acid. The benzene was distilled off under water-pump vacuum, and the residue was crystallized from alcohol.

3-(1,3-Benzodioxol-5-yl)-7-hydroxy-6-alkylchromones (IIIa, b). Method A. A mixture of 40 mmole of a ketone (I), 40 ml of ethyl orthoformate, 40 ml of pyridine, and 80 drops of piperidine was heated at 120-130°C for 6-7 h. The reaction mixture was poured into 0.5 liter of cold water and the mixture was left overnight at room temperature. The precipitate that had deposited was filtered off, washed on the filter with water, and crystallized from alcohol.

Method B. With stirring, 11 ml (90 mmole) of boron trifluoride etherate was added dropwise to a solution of 15 mmole of a ketone (I) in 24 ml (300 mmole) of DMFA. Then 3.3 g (16.5 mmole) of phosphorus pentachloride or pentabromide was added at such a rate that the temperature of the reaction mixture did not rise above 60-70°C. After the completion of the reaction, the reaction mixture was poured into 200-250 ml of water and the resulting mixture was kept at 70°C for 1 h. The precipitate that deposited was filtered off and crystallized from alcohol.

3-(1,3-Benzodioxol-5-yl)-7-methoxy-6-alkylchromones (IVa, b) were obtained in similar way to compound (III) from the corresponding ketone (II). Chromones (IVa, b) were crystallized from alcohol.

3-(1,3-Benzodioxol-5-yl)-7-acetoxy-6-alkylchromones (Va, b). A hot solution of 10 mmole of a 7-hydroxychromone (III) in the minimum volume of pyridine was treated with 4.6 ml (50 mmole) of acetic anhydride, and the reaction mixture was left overnight at room temperature. The reaction product that had precipitated was filtered off and was washed on the filter with cold alcohol and crystallized from ethyl acetate.

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