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SYNTHETIC AND MODIFIED ISOFLAVONOIDS
III. SYNTHESIS OF BENZODIOXANE ANALOGUES OF PSEUDOBAPTIGENIN

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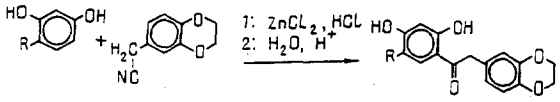
Benzodioxane analogues of pseudobaptigenin with alkyl fragments in positions 2 and 6 of the chromone ring have been synthesized from α-(1,4-benzodioxan-6-yl)-2-hydroxy-6-alkylacetophenones.

Continuing investigations into the modification of the molecules of natural isoflavonoids [1, 2], we have synthesized new benzodioxane analogues of pseudobaptigenin. Natural flavolignins - silybin, dehydrosilybin, hydnocarpin [3, 4] — contain a 1,4-benzodioxane fragment in their molecules. Many flavolignins are characterized by a considerable biological action. Thus, silybin possesses hepatoprotective, antiphalloidine, antiperoxide, and other activities. In view of this, it appeared of interest to synthesize new benzodioxane derivatives of isoflavonoids similar in structure to pseudobaptigenin and also to study the dependence of the chemical and biological properties of these compounds on the nature and dimensions of ring *B* in the isoflavone molecule.

Convenient synthons for obtaining benzodioxane analogues of pseudobaptigenin are α-(1,4-benzodioxan-6-yl)-2,4-dihydroacetophenones obtained by condensing 6-cyanomethyl-1,4-benzodioxane with the appropriate resorcinols.



I a-c

a: R=H, b: R=Et, c: R=Pr

On the interaction of 1,4-benzodioxan-6-ylacetonitrile with resorcinol or 4-alkylresorcinols, the formation of several isomeric ketones is possible. It has been found, however, that only one of them is obtained in each case from resorcinol and 4-alkylresorcinols, which is apparently due to a substantial difference in the activities of positions 2 and 4 of the dihydric phenols. To demonstrate the structures of ketones (Ia-c), in addition to the results of elementary analysis we measured their PMR spectra. The aromatic protons of ketone (Ia) formed an ABX spin system with $J_{5,6}$ = 8 Hz and $J_{3,5}$ = 2 Hz, which corresponds to the spin-spin coupling constants (SSCCs) of protons in the *ortho-* or *meta-* positions. The signal of the H-6 proton was at a distance of 1.5-1.6 ppm from those of the other two aromatic protons because of the descreening influence of the neighboring carbonyl group and the concerted negative interaction effects of the two OH groups. The signals of the latter were observed in 12.4-12.6 ppm (OH-2) and 10.6-10.9 ppm (OH-4) regions. The aromatic protons of the benzodioxane nucleus appeared at 6.6-6.8 ppm in the form of a multiplet. The protons of the ethylenedioxy group gave a singlet at 4.1-4.3 ppm.

The alkylation of compounds (Ia-c) with equimolecular amounts of dimethyl sulfate in the presence of potash in boiling benzene gave high yields of the 4-methoxyketones (IIa-c). The methylation of these substances took place at the OH-4 hydroxy, since the OH-2 hydroxyl was bound by an intramolecular bond with the carbonyl group. The structures of the methylated ketones were confirmed by chemical reactions and their PMR spectra. Ketones (I-II) dissolved in a 5% solution of caustic soda, and gave a positive reaction with an alkaline solution of ferric chloride. The characteristics and PMR spectra of ketones (I) and (II) are given in Tables 1 and 2.

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TABLE 1. Characteristics of Compounds (I-VIII)

Compound	Yield, %	mp, °C	Empirical formula
Ia	83	130—131	$C_{16}H_{14}O_5$
Ib	55	123—124	$C_{18}H_{18}O_5$
Ic	53	126—127	$C_{19}H_{20}O_5$
IIa	81	106—107	$C_{17}H_{16}O_5$
IIb	90	101—102	$C_{19}H_{20}O_5$
IIc	91	91—92	$C_{20}H_{22}O_5$
IIIa	93* 95**	265—266	$C_{17}H_{12}O_5$
IIIb	98* 97**	267—268	$C_{19}H_{16}O_5$
IIIc	92* 92**	234—236	$C_{20}H_{18}O_5$
IVa	95* 97**	192—193	$C_{18}H_{14}O_5$
IVb	80* 74**	152—153	$C_{20}H_{18}O_5$
IVc	56* 73**	155—156	$C_{21}H_{20}O_5$
Va	75	181—182	$C_{19}H_{14}O_6$
Vb	67	166—167	$C_{21}H_{18}O_6$
Vc	95	150—152	$C_{22}H_{20}O_6$
VIa	97	205—206	$C_{20}H_{16}O_6$
VIb	71	158—159	$C_{22}H_{20}O_6$
VIc	82	102—103	$C_{23}H_{22}O_6$
VIIa	97	283—285	$C_{18}H_{14}O_5$
VIIb	91	237—238	$C_{20}H_{18}O_5$
VIIc	91	204—205	$C_{21}H_{20}O_5$
VIIIa	78	187—188	$C_{19}H_{16}O_5$
VIIIb	85	210—211	$C_{21}H_{20}O_5$
VIIIc	86	148—149	$C_{22}H_{22}O_5$

*Yield by method A.

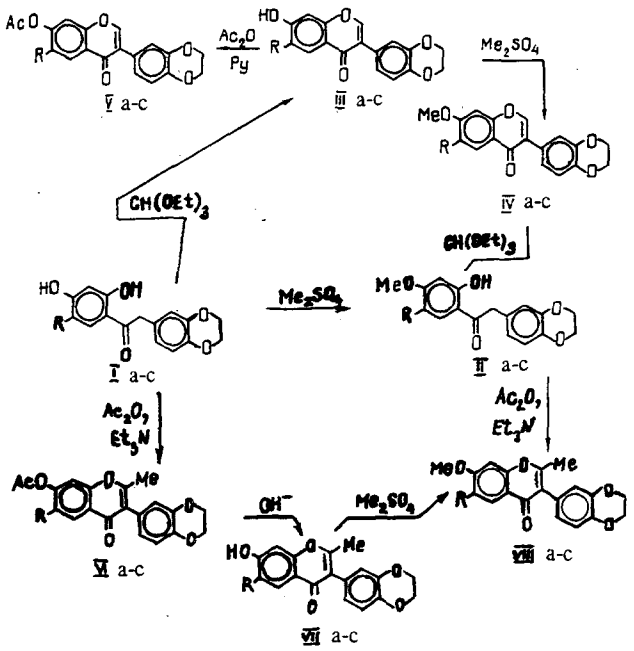
**Yield by method B.

TABLE 2. Chemical Shifts in the PMR Spectra of the α-(1,4-Benzodioxan-6-yl)-2-hydroxyacetophenones (I-II) in Deuterodimethyl Sulfoxide

Compound	δ, ppm, (J, Hz)							
	Protons of the phenol moiety					Benzodioxane protons		
	OH-2, s	H-3, s	OH-4 cr OMe-4, s	R-5	H-6, s	CH_2, s	H-5, H-7, H-8, m	$-OCH_2CH_2O-$ s
Ia	12.58	6.34 d (2.0)	10.94	6.43 dd (8.0; 2.0)	7.96 d (8.0)	4.24	6.63	4.24
Ib	12.47	6.40	10.68	2.59 q; 1.18 t	7.77	4.26	6.82	4.26
Ic	12.41	6.34	10.61	2.50 t; 1.57 m; 0.90 t	7.70	4.19	6.76	4.23
IIa	12.36	6.36 d (2.0)	3.84	6.38 dd (8.0; 2.0)	7.85 д (8.0)	4.07	6.62	4.07
IIb	12.53	6.52	3.87	2.54 q; 1.16 t	7.79	4.23	6.80	4.23
IIc	12.58	6.37	3.85	2.54 t; 1.59 m; 0.91 t	7.49	4.12	6.76	4.24

The conversion of the ketones (I-II) into benzodioxane analogues of pseudobaptigenin was effected by various methods. For the synthesis of the isoflavones (III-IVa-c) containing no substituents in position 2 of the pyrone ring we used two methods.

According to the first of them, ketones (I-II) were heated with ethyl orthoformate in pyridine in the presence of piperidine at 120-130°C for 8-10 h. By the second method, the above-mentioned compounds were treated with a Vilsmeier reagent in the presence of boron trifluoride etherate. In this case, the formation of the chromone system took place in a short time. The use of this method enabled the desired isoflavones (III-IV) to be obtained with high yields.



Under the action of acetic anhydride in pyridine, the 7-hydroxyisoflavones (IIIa-c) were converted into the corresponding 7-acetoxy derivatives (Va-c). The interaction of ketones (I-IIa-c) with acetic anhydride in the presence of triethylamine at 120-130°C formed the 2-methylisoflavones (VIa-c) and (VIIIa-c). The acetyl group in each of compounds (VIa-c) was eliminated by brief boiling by an equivalent amount of alkali. As a result of this transformation, the 7-hydroxyisoflavones were obtained in quantitative yield. The latter, (VIIa-c), on being treated with dimethyl sulfate in the presence of potash in boiling acetone formed compounds (VIIIa-c) methylated at the 7-OH group. The same compounds were obtained by cyclizing the 4-methoxyketones (IIa-c). However, this pathway for the synthesis of these compounds was less convenient because the cyclization process took a considerable time. For this reason, we obtained the 7-methoxychromones (VIIIa-c) mainly by the alkylation of the 7-hydroxyisoflavones (VIIa-c). The characteristics of the new isoflavones and their derivatives are given in Table 1, and details of their PMR spectra in Table 3.

In the PMR spectra of compounds (III-VIIIa-c), the H-2 proton of the pyrone ring appeared in the form of a narrow singlet at 7.7-8.3 ppm. The OH-7 hydroxy group was observed in the 10.7-10.8 ppm region. In the alkylated isoflavones, the 7-methoxy grouping appeared in the form of a three-proton singlet at 3.9 ppm. In compounds (V-VIa-c), the protons of the acyl group were represented by a three-proton singlet at 2.4 ppm. The H-5 proton of the chromone ring was shifted downfield (7.7-8.3 ppm) in relation to the other aromatic protons. The protons of the ethylenedioxy group appeared in the form of a singlet at 4.2-4.3 ppm. The protons of the ethyl group were represented by a quartet and a triplet, while the propyl fragment was observed in the form of a triplet, a sextet, and a triplet, respectively.

The isoflavonoids obtained were colorless crystalline substances with fairly high melting points readily soluble in the majority of organic solvents. Thus, the heterocyclization of α-(1,4-benzodioxan-6-yl)-2-hydroxyacetophenones taking place with the participation of dimethylformamide, ethyl orthoformate, and acetic anhydride proceeds readily and with good yields of the pseudobaptigenin analogues. A study of the biological activity of the isoflavonoids synthesized revealed substances possessing pronounced hypoglycemic, hypolipidemic, and anabolyzing activities among the benzodioxane analogues of pseudobaptigenin.

TABLE 3. Chemical Shifts in the PMR Spectra of the Benzodioxane Analogues of Pseudobaptogenin (III-VIII)*

Compound	δ, ppm (J, Hz)								
	Protons of the chromone ring					Benzodioxane protons			
	H-2 or Me-2 c	H-5 s	R-6	OH-7, OMe-7 or OAc-7 s	H-8, s	H-5, d J=2 Hz	H-7, dd J=8; 2 Hz	H-8, d J=8 Hz	$-CH_2CH2O-$ s
IIIa	8.30	7.94 d (8.5)	7.03 dd (8.5; 2.5)	10.78	6.86 d (2.5)	6.86	7.03	6.88	4.25
IIIb	8.29	7.81	2.62 q; 1.17 t	10.80	6.88	7.10	7.04	6.88	4.26
IIIc	8.30	7.80	2.59 t; 1.58 m; 0.91 t	10.79	6.89	7.10	7.05	6.89	4.26
IVa	7.89	8.19 d (9.0)	6.97 dd (9.0; 2.5)	3.90	6.83 d (2.5)	7.09	7.04	6.90	4.27
IVb	7.88	8.02	2.69 q; 1.23 t	3.92	6.77	7.10	7.04	6.90	4.27
IVc	7.89	8.02	2.67 t; 1.64 m; 0.96 t	3.92	6.79	7.10	7.06	6.91	4.28
Va	7.96	8.30 d (8.5)	7.15 dd (8.5; 2.0)	2.36	7.29 d (2.5)	7.10	7.05	6.91	4.28
Vb	7.94	8.19	2.65 q; 1.26 t	2.38	7.24	7.10	7.04	6.91	4.28
Vc	7.94	8.16	2.61 t; 1.65 m; 0.96 t	2.37	7.23	7.10	7.05	6.90	4.27
VIa	2.31	8.24 d (8.5)	7.10 dd (8.5; 2.5)	2.35	7.24 d (2.5)	6.77	6.74	6.92	4.28
VIb	2.32	8.10	2.64 q; 1.24 t	2.38	7.23	6.77	6.72	6.92	4.28
VIc	2.29	8.08	2.60 t; 1.65 m; 0.95 t	2.37	7.19	6.77	6.73	6.90	4.28
VIIa	2.23	7.85 d (8.5)	6.87 dd (8.5; 2.5)	10.72	6.83 d (2.5)	6.74	6.69	6.87	4.27
VIIb	2.22	7.70	2.60 q; 1.16 t	10.73	6.84	6.72	6.68	6.87	4.26
VIIc	2.22	7.69	2.58 t; 1.57 m; 0.90 t	10.70	6.84	6.73	6.67	6.88	4.27
VIIIa	2.29	8.11 d (8.5)	6.86 dd (8.5; 2.5)	3.91	6.90 d (2.5)	6.99	6.86	7.02	4.27
VIIIb	2.27	7.94	2.67 q; 1.21 t	3.91	6.77	6.78	6.72	6.91	4.27
VIIIc	2.28	7.93	2.65 t; 1.64 m; 0.94 t	3.91	6.78	6.78	6.74	6.91	4.28

*The PMR spectra of compounds (IIIa-c) and (VIIIa-C) were measured in deuterodimethyl sulfoxide, and those of the other compounds in deuterochloroform.

EXPERIMENTAL

The course of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates in benzene-ethanol (9:1). PMR spectra were measured on a Bruker WP-100 SU instrument in DMSO-d_6 or $CDCl_3$ relative to TMS (internal standard). The analyses of all the compounds corresponded to the calculated figures.

The α-(1,4-Benzodioxan-6-yl)-2,4-dihydroxyacetophenones (Ia-c). With stirring, a rapid current of dry hydrogen chloride was passed for 10 minutes through a solution of 17.5 g (100 mmole) of 6-cyanomethyl-1,4-benzodioxzane in 75 ml of absolute benzene cooled to 0°C. Then a solution of 101 mmole of the appropriate resorcinol and 6.7 g (50 mmole) of fused zinc chloride in 67 ml of absolute ether was added. The reaction mixture was saturated with hydrogen chloride at 0°C for 3 h. After being left to stand at room temperature for 2 hours in a current of hydrogen chloride, the mixture was concentrated and was left overnight at room temperature. The solution was decanted from the precipitate. The precipitate, after trituration with dry benzene, was added to 380 ml of hot water, and the resulting solution was kept at 90°C, pH 1, for 30 min. The precipitate that formed was filtered off from the hot solution and was carefully washed on the filter with water to pH 7. Compounds (Ia-c) were crystallized from benzene.

The α-1,4-Benzodioxan-6-yl)-2-hydroxy-4-methoxyacetophenones (IIa-c). A hot solution of 10 mmole of a ketone (Ia-c) in 50 ml of absolute benzene was treated with 4.14 g (30 mmole) of freshly calcined potash and 1.15 g (10 mmole) of dimethyl sulfate, and the mixture was boiled for 3-3.5 h. Then the inorganic precipitate was filtered off, and the filtrate was acidified with 2-3 drops of acetic acid. The benzene was distilled off in water-pump vacuum and the residue was crystallized from alcohol.

The 3-(1,4-Benzodioxan-6-yl)-hydroxychromones (IIIa-c). Method A. A mixture of 40 mmole of a ketone (Ia-c), 40 ml of ethyl orthoformate, 40 ml of pyridine, and 80 drops of piperidine was heated at 120-130°C for 8-9 h. The reaction mixture was poured into 0.5 liter of cold water and the resulting mixture ws left overnight at room temperature. The precipitate that had deposited was filtered off and was washed on the filter with water and was then 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 (Ia-c) in 24 ml (300 mmole) of DMFA. Then 3.3 g (16.5 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 reaction mixture had been kept at for 1 h, it was poured into 200-250 ml of water and the resulting mixture was heated to 70°C for about 1 h. The precipitate that deposited was filtered off and crystallized from alcohol.

The 3-(1,4-Benzodioxan-6-y)-7-methoxychromones (IVa-c). Method A. A mixture of 10 mmole of a ketone (IIa-b), 10 ml of ethyl orthoformate, 10 ml of pyridine, and 20 drops of piperidine was boiled at 120-130°C for 8-9 h. The reaction mixture was added to 100 ml of cold water and left overnight. The precipitate that had deposited was filtered off, washed with cold alcohol, and crystallized from alcohol.

Method B. With stirring, 3.7 ml (30 mmole) of boron trifluoride etherate was added dropwise to a solution of 5 mmole of a ketone (II-c) in 7.5 ml (100 mmole) of DMFA, and then 1.1 g (5.5 mmole) of phosphorus pentachloride was added at such a rate that that the temperature of the reaction mixture did not rise above 60-70°C. After the end of the reaction, the mixture was poured into 100-150 ml of water, and the resulting mixture was stirred at 80-90°C for 1 h. The precipitate that deposited was filtered off and crystallized from alcohol.

The 7-Acetoxy-3-(1,4-benzodioxan-6-yl)chromones (Va-c). A hot solution of 10 mmole of a chromone (IIIa-c) 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, after which the reaction product was filtered off and was washed on the filter with cold alcohol and crystallized from ethyl acetate.

The 7-Acetoxy-3-(1,4-benzodioxan-6-yl)-2-methylchromomes (VIa-c). A mixture of 50 mmole of a ketone (Ia-c), 23 ml (250 mmole) of acetic anhydride and 28 ml (200 ml) of trimethylamine was heated at 120-130°C for 8-9 h. After this, the reaction mixture was poured into water containing 2.5 ml of hydrochloric acid. The precipitate that deposited was filtered off and washed with water. The desired compounds (VIa-c) were purified by crystallization from ethyl acetate.

The 3-(1,4-Benzodioxan-6-yl)-7-hydroxy-2-methylchromonaes (VIIa-c). A hot solution of a compound (VIa-c)* in the minimum amount of alcohol was treated with 24 ml (30 mmole) of 5% solution of caustic soda, and the mixture was boiled for 6 min. Then 20 ml of water was added, and boiling was continued for another 10 min. The mixture was neutralized with dilute hydrochloric acid to pH 7, and the resulting precipitate was filtered off and crystallized from alcohol.

*No amount given — Publisher.

The 3-(1,4-Benzodioxan-6-yl)-7-methoxy-2-methylchromones (VIIIa-c). Method A. A mixture of 40 mmole of a ketone (IIa-c), 44.8 ml (480 mmole) of acetic anhydride, and 49.6 ml (320 ml) of triethylamine was heated at 120-130°C for 12 h. The subsequent procedure was similar to that for compounds (VIa-c).

Method B. A hot solution of 10 mmole of a compound (VIIa-c) in 200 ml of dry acetone was treated with 4.14 g (30 mmole) of freshly calcined potash and 1.15 ml (10 mmole) of dimethyl sulfate, and the mixture was boiled for 15-30 min. The inorganic residue was filtered off and was washed on the filter with acetone (3 × 20 ml). The solvent was evaporated off under reduced pressure, and the residue was crystallized from ethyl alcohol.

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