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SYNTHETIC AND MODIFIED ISOFLAVONOIDS
IV. SYNTHESIS OF BENZODIOXEPANE ANALOGUES OF PSEUDOBAPTIGENIN

A. Aitmambetov, L. G. Grishko, and V. P. Khilya

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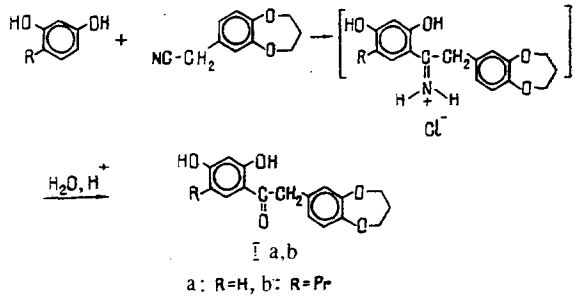
Benzodioxepane analogues of pseudobaptigenin have been synthesized and their structures have been established by chemical transformations, elementary analysis, and PMR spectroscopsy.

We have previously synthesized new derivatives of pseudobaptigenin [2, 3] and benzodioxane analogues of it [1]. The aim of the present communication was the development of methods for the synthesis of benzodioxepane analogues of pseudobaptigenin and the study of the dependence of the chemical and biological properties of the new compounds on the size and nature of the heterocycle.

The key compounds for the synthesis of the desired products were the ketones [I] obtained by the well-known Hoesch reaction and applied to the condensation of 7-cyanomethyl-1,5-benzodioxepane with the appropriate resorcinols in a mixture of dry benzene and ether in a current of hydrogen chloride in the presence of zinc chloride



I a,b

a: R=H, b: R=Pr

After the hydrolysis of the intermediately formed ketimine hydrochlorides, ketones (I) were obtained with high yields. The amount of catalyst had a substantial influence on the yield of compound (Ia). At a ratio of resorcinol and catalyst of 1:0.5, the yield did not exceed 44%, while at a ratio of 1:0.7 the yield of ketone increased to 70%.

The alkylation of ketones (I) with an equimolecular amount of dimethyl sulfate in benzene in the presence of a threefold excess of potash led to the ketones (II). The structures of the benzodioxepane ketones (I-II) were confirmed by the results of elementary analysis, qualitative reactions, and PMR spectra. Information on these compounds is given in Tables 1 and 2.

In the PMR spectrum of ketones (I) (in DMSO-d_6), the H-3 and H-6 aromatic protons of ring A appeared in the 6.3-6.4 and 7.7-7.9 ppm regions, respectively. The signal of the OH-2 group was present in the weak field at 12.4-12.6 ppm. The proton of the OH-4 group, taking part in the formation of an intermolecular hydrogen bond with the solvent, absorbed in a stronger field at 10.6-10.7 ppm. The protons of the propylenedioxy group appeared in the form of a triplet (4.1 ppm) and a quintet (2.1 ppm) with an SSCC of 5.4 Hz.

To synthesize benzodioxepane analogues of pseudobaptigenin containing no substituents in position 2 of the chromone moiety we used two approaches. According to the first of them (A), ketones (I-II) were heated with ethyl orthoformate in pyridine in the presence of piperidine at 120-130°C for 10-12 h. By method B, compounds (I-II) were treated with a Vilsmeier

Taras Shevchenko Kiev University KIEN. Karakalpak Branch, Uzbekistan Academy of Sciences. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 814-820, November-December, 1993. Original article submitted June 16, 1993.

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TABLE 1. Characteristics of Compounds (I-VII)

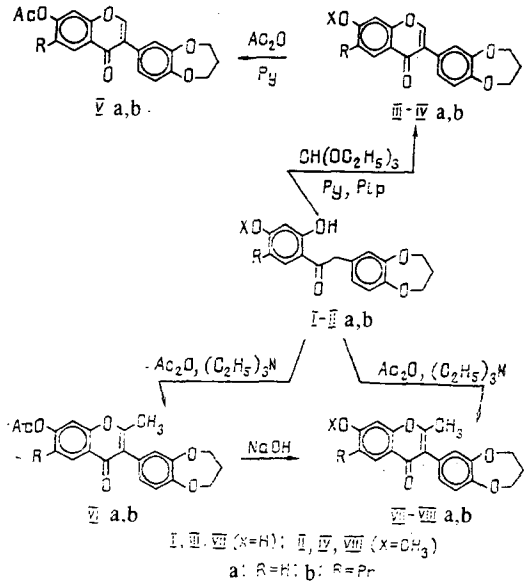
Compound	Yield, %	mp, °C	Empirical formula
Ia	70	129—130	$C_{17}H_{16}O_5$
Ib	56	120—121	$C_{20}H_{22}O_5$
IIa	73	63—64	$C_{18}H_{18}O_5$
IIIa	85**	244—245	$C_{18}H_{14}O_5$
IIIb	99**	165—167	$C_{21}H_{20}O_5$
IVa	77*, 79**	139—140	$C_{19}H_{16}O_5$
IVb	84*, 84**	141—142	$C_{22}H_{22}O_5$
Va	75	148—149	$C_{20}H_{16}O_6$
Vb	88	116—117	$C_{23}H_{22}O_6$
VIa	72	137—138	$C_{21}H_{18}O_6$
VIb	72	121—122	$C_{24}H_{24}O_6$
VIIa	99	232—233	$C_{19}H_{16}O_5$
VIIb	98	208	$C_{22}H_{22}O_5$
VIIIa	88*, 96**	154—155	$C_{20}H_{18}O_5$
VIIIb	97*	139—140	$C_{23}H_{24}O_5$

*Yield by method A.

**Yield by method B.

reagent. When phosphorus pentahalides were used as components in the preparation of the Vilsmeier reagent, the formation of the chromone system took place in 0.5 h at a temperature of about 70°C. By both variants of heterocyclization, the desired isoflavones (III-IV) were obtained in high yields.

In order to identify the isoflavones (III) we prepared their 7-acetoxy derivatives (V).



The interaction of ketones (I-II) with acetic anhydride in triethylamine led to the formation of the 2-methylchromones (VI) and (VIII). The 7-acetoxy-2-methylchromones (VI) formed initially were converted into the corresponding 7-hydroxy-2-methylchromones (VII) by brief heating with a 5% alcoholic solution of alkali. By the other method, the chromones (VIII) were obtained by the alkylation of the 7-hydroxy-2-methylchromones (VII) with dimethyl sulfate in the presence of potash in acetone. The latter method proved to be faster, and the chromones (VIII) were obtained with higher yields.

TABLE 2. Chemical Shifts in the PMR Spectra (δ, pp.; J, Hz) of the Benzodioxepane Analogues of Pseudobaptigenin (III- VIII)*

Compound	Protons of the chromone ring				Benzodioxepane protons				
	H-2 or Me-2 s	H-5 d J=8.5 Hz	R-6 H-6, dd J=8.5; 2.5 Hz	OH-7, OMe-7, OAc-7, s	H-8, d J=2,5 Hz	H-6, d J=2 Hz	H-8, dd J=8 Hz J=2 Hz	H-9, d J=8 Hz	—O(CH$_2$)$_3$O— q,t
IIIa	8.35	7.97	6.95	10.82	6.89	7.21	7.16	6.98	4.15 2.22
IIIb	8.30	7.79 s	2.59 t; 1.58 m; 0.90 t	10.88	6.92 s	7.20	7.16	6.97	4.14 2.11
IVa	7.89	8.18	6.97	3.89	6.82	7.19	7.14	7.00	4.23 2.19
IVb	7.89	8.00 s	2.65 t; 1.65 m; 0.95 t	3.91	6.78 s	7.20	7.15	7.00	4.24 2.20
Va	7.96	8.30	7.14	2.35	7.29	7.18	7.14	7.01	4.24 2.19
Vb	7.94	8.16 s	2.61 t; 1.66 m; 0.96 t	2.37	7.23 s	7.18	7.15	7.01	4.24 2.19
VIa	2.31	8.23	7.10	2.35	7.25	6.88	6.83	7.03	4.25 2.19
VIb	2.28	8.07 s	2.59 t; 1.63 m; 0.94 t	2.36	7.90 s	6.88	6.82	7.02	4.23 2.21
VIIa	2.23	7.86	6.91	10.73	6.84	6.84	6.79	6.99	4.16 2.11
VIIb	2.20	7.68 s	2.57 t; 1.55 m; 0.98 t	10.69	6.83 s	6.83	6.78	6.98	4.14 2.11
VIIIa	2.29	8.11	6.86	3.91	6.90	6.99	6.86	7.02	4.25 2.21
VIIIb	2.27	7.92 s	2.65 t; 1.62 m; 0.94 t	3.91	6.77 s	6.91	6.83	7.03	4.24 2.21

*The PMR spectra of compound (IIIa, b) and (VIIa, b) were measured in DMSO-d_6, and those of the other compounds in deuterochloroform.

The isoflavones (III)-(VIII) obtained were colorless crystalline high-melting substances readily soluble in organic solvents. In contrast to the initial ketones (I-II) they did not give a qualitative reaction with an alcoholic solution of ferric chloride, which showed the absence from their molecules of hydroxy groups capable of forming chelates. The structure of the benzodioxepane analogues of pseudobaptigenin obtained and of their derivatives
at the phenolic hydroxyl were confirmed by the results of elementary analysis and their PMR spectra. The characteristics of the new isoflavones are given in Table 1.

In the PMR spectra of the isoflavones (III-VIII), the OH-7 hydroxy protons appeared at 10.7-10.9 ppm. The acyl protons of the OAc-7 group gave singlets at 2.3-2.4 ppm. A three-proton singlet of the OMe-7 group was observed at 3.9 ppm. The H-2 and H-5 protons of the chromone ring were readily identified at 7.9 and 8.3 ppm, respectively. The methylene protons of the 1,5-benzodioxepane fragment gave a triplet and a quintet at 4.1-4.2 and 2.1-2.2 ppm, respectively.

Thus, generalizing the preceding [1-3] and present communications it is possible to draw the conclusion that the heterocyclization of α-hetaryl-2-hydroxyacetophenones taking place under the action of a Vilsmeier reagent or ethyl orthoformate or acetic anhydride with the participation of catalysts takes place readily and leads to the desired pseudobaptigenin analogues with high yields. We have found that the use of phosphorus pentachloride or pentabromide in place of the difficultly accessible methanesulfonyl chloride enables the 7-hydroxy- and 7-methoxyisoflavones to be obtained in shorter times.

It must be mentioned that the time required for the synthesis of the α-hetaryl-2-hydroxyacetophenones and their subsequent cyclization into pseudobaptigenin analogues increases on passing from benzodioxole to benzodioxane and benzodioxepane. This relationship is probably connected with the decrease in the CH-acidity of the methylene units of the ketones due to the electron-donating influence of the benzodioxole, benzodioxane, and benzodioxepane nuclei. An analogous tendency is also observed in the manifestation by the pseudobaptigenin analogues of an anabolizing action in tests on experimental animals.

EXPERIMENTAL

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

The α-(1,5-Benzodioxepan-7-yl)-2,4-dihydroxyacetophenones (Ia, b). With stirring, a rapid current of dry hydrogen chloride was passed for 10 min into a solution of 18.9 g (100 mmole) of 7-cyanomethyl-1,5-benzodioxepane in 75 ml of absolute benzene cooled to 0°C. Then a solution of 101 mmole of dry resorcinol or 4-propylresorcinol and 6.7 g (50 mmole) of fused zinc chloride in 67 ml of absolute ether was added. Saturation with hydrochloride was continued at 0°C for 3 h, and then at room temperature for another 3-4 h. After this, 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. After this, it was added to 380 ml of hot water and the mixture was kept at 90°C, pH 1, for 30 min. The solid was separated off from the hot solution and was carefully washed on the filter with water to neutrality. The compounds obtained were crystallized from benzene. PMR spectrum (in DMSO-d_6, ppm): compound (Ia): 4.21 (s, 2H, $COCH_2$), 12.58 (s, 1H, OH-2), 6.33 (d, 1H, J = 2 Hz, H-3), 10.66 (s, 1H, OH-4), 6.44 (d.d, 1H, J = 8 Hz, H-5), 7.92 (d, 1H, J = 8 Hz, H-6); 6.88 (m, 3H, H-6; H-8; H-9 of benzodioxazepane), 4.12 (t, 4H, CH_2-2, CH_2-4), 2.10 (q, 2H, J = 5.4 Hz, CH_2-3). Compound Ib: 4.19 (s, 2H, $COCH_2$), 12.43 (s, 1H, OH-2), 6.35 (s, 1H, H-3), 10.58 (s, 1H, OH-4), 2.53; 1.58; 0.88 (t, m, t, 7H, $CH_3CH_2CH_2$-5), 7.72 (s, 1H, H-6); protons of benzodioxepane: 6.86 (m, 3H, H-6, H-8, H-9), 4.09 (t, 4H, 2-CH_2 and 4-CH_2), 2.08 (q, 2H, 3-CH_2).

α-(1,5-Benzodioxepan-7-yl)-2-hydroxy-4-methoxyacetophenone (IIa). A hot solution of 3 g (10 mmole) of ketone (Ia) 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 4.5 h. Then the inorganic residue 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 ethanol. PMR spectrum (DMSO-d_6, ppm): 4.30 (s, 2H, $COCH_2$), 12.66 (s, 1H, OH-2), 6.50 (d, 1H, J = 2 Hz, H-3), 3.89 (s, 3H, CH_3O-4), 6.63 (d.d, 1H, J = 8; 2 Hz, H-5), 8.07 (d, 1H, J = 8 Hz, H-6); protons of benzodioxepane: 6.95 (m, 3H, H-8, H-9), 4.17 (t, 4H, J = 5.4 Hz, CH_2-2, CH_2-4), 2.14 (q, 2H, J = 5.4 Hz, CH_2-3).

The 3-(1,5-Benzodioxepan-7-yl)-7-hydroxychromones (IIIa, b). Method A. A mixture of 40 mmole of a ketone (Ia, b), 40 ml of methyl orthoformate, 40 ml of pyridine, and 80 drops of piperidine was heated at 120-130°C for 9-10 h. The

reaction mixture was added to 1.5 liter of cold water, and the resulting mixture was left overnight at room temperature. The precipitate that had deposited was filtered off and was crystallized from alcohol.

Method B. With stirring at room temperature, 11 ml (90 mmole) of boron trifluoride etherate was added dropwise to a solution of 15 mmole of a ketone (Ia, b) in 24 ml (300 mmole) of DMFA. Then 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 end of the reaction, it 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.

The 3-(1,5-Benzodioxepan-7-yl)-7-methoxychromones (IVa, b). Method A. A mixture of 10 mmole of a ketone (IIa, b) with 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 precipitate that 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 (IIa, b) in 7.5 ml (100 mmole) of DMFA. Then 5.5 mmole of phosphorus pentachloride or pentabromide was added at such a rate that the temperature 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 whole was kept at 70°C for 1 h. The precipitate that deposited was filtered off and crystallized from alcohol.

The 7-Acetoxy-3-(1,5-benzodioxepan-7-yl)chromones (Va, b). A hot solution of 10 mmole of a 7-hydroxyisoflavone (IVa, b) 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. Then the reaction product that had separated out was filtered off and was washed on the filter with cold alcohol and crystallized from ethyl acetate.

The 7-Acetoxy-3-(1,5-benzodioxepan-7-yl)-2-methylchromones (VIa, b). A mixture of 50 mmole of a ketone (Ia, b), 23 ml (250 mmole) of acetic anhydride, and 28 ml (200 mmole) of triethylamine was heated at 120-130°C for 10-12 h. Then the reaction mixture was poured into cold water containing 2.5 ml of hydrochloric acid. The precipitate that deposited was filtered off, washed with water until the smell had disappeared, and crystallized from ethyl acetate.

The 3-(1,5-Benzodioxepan-7-yl)-7-hydroxy-2-methylchromones (VIIa, b). A hot solution of 30 mmole of a 7-acetoxy-2-methylisoflavone (VIa, b) in the minimum amount of alcohol as treated with 24 ml (30 mmole) of water, and the mixture was boiled for 6 mn. The 20 ml of water was added, and boiling was continued for another 10 min. The reaction mkxture was neutralized with dilute hydrochloric acid to pH 7, and the precipitate was filtered off and crystallized from alcohol.

The 3-(1,5-benzodioxepan-7-yl-7-methoxy-2-methylchromones (VIIIa, b). Method A. A mixture of 40 mmole of a ketone (IIa, b), 44.8 ml (480 mmole) of acetic anhydride and 49.6 ml (320 mmole) of triethylamine was heated at 120-130°C for 12-15 h. The the reaction mixture was addd to cold water containing 8 ml ofhydrochloric acid. The precipitate that deposited was filtered off, washed with water until the smell had disappeared, and crystallized from alcohol.

Method B. A hot solution of 10 mmole of a 7-hydroxy-2-methylisoflavone (VIIa, b) 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. Then the inorganic deposit was filtered off and was washed with acetone on the filter several times. The solvent was distilled off in water-pump vacuum. The residue was crystallized from alcohol.

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