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SYNTHETIC AND MODIFIED ISOFLAVONOIDS. VI. SYNTHESIS OF ANALOGS OF PSEUDOBAPTIGENIN WITH ESTER GROUPS

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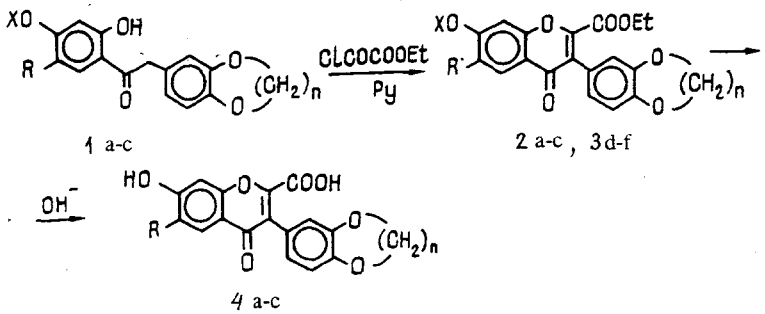
Derivatives of pseudopbaptigenin and of its benzodioxane and benzodioxepane analogs containing an ethoxycarbonyl group in position 2 have been synthesized.

We have previously [1-5] obtained new analogs of pseudobaptigenin and their methyl and trifluoromethyl derivatives. There are a number of patents devoted to drugs based on isoflavones containing an ethoxycarbonyl group in position 2 that possess anticarcinogenic and immunosuppressant activity [6, 7]. In the present paper we report the synthesis of new 2-ethoxycarbonyl-substituted analogs of pseudobaptigenin. These were obtained with the aim of elucidating the influence of this group on the chemical and biological properties of isoflavones modified by 1,3-dioxolane, 1,4-dioxane, and 1,5-dioxepane nuclei.

The initial compounds for obtaining these pseudobaptigenin analogs were the ketones (**1a-c**), which have been described in [2, 4]. Ketone (**1c**) was obtained in a similar way to ketones (**1a, b**) by condensing 7-cyanomethyl-1,5-benzodioxepane with 4-ethylresorcinol. The alkylation of ketone (**1c**) with an equimolar amount of dimethyl sulfate in the presence of potassium carbonate in boiling benzene formed the 4-methoxyketone (**1f**).

It is known [8] that the interaction of 2-hydroxydeoxybenzoins with ethoxalyl chloride in pyridine at room temperature leads to the formation of isoflavones with an ethoxy group in position 2 of the chromone system. The action of ethoxalyl chloride on ketones (**1a-c**) in pyridine led to ester derivatives of pseudobaptigenin (**2**). In contrast to the literature [8], the completion of the reaction required brief heating of the reaction mixture to 40-45°C.



a : X=H, R=Et, n=1; b : X=H, R=H, n=2; c : X=H, R=Et, n=3; d : X=Me, R=Et, n=1; e : X=Me, R=Pr, n=1; f : X=Me, R=Et, n=3.

The reaction of the 4-methoxyketones (**1d-f**) with ethoxalyl chloride took place at 50-55°C in 30 min and led to the corresponding 7-methoxyisoflavones (**3**). The 2-ethoxycarbonylisoflavones (**2**) were converted into the corresponding 2-carboxyisoflavones (**4**) by their brief heating with a 5% solution of caustic soda in ethanol.

To confirm the structures of the isoflavones (**2**)-(**4**), in addition to analytical results we used PMR spectra. The characteristics of compounds (**2**)-(**4**) are given in Table 1, and their PMR spectra in Table 2.

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TABLE 1. Characteristics of Compounds (**1-4**)

Compound	Yield, %	T. mp, °C	Empirical formula	Solvent for crystallization
1c	58.4	160—162	$C_{19}H_{20}O_5$	EtOH
1f	97.4	76—77	$C_{20}H_{22}O_5$	EtOH
2a	67.2	226—228	$C_{21}H_{18}O_7$	iso-PrOH
2b	81.2	244—246	$C_{20}H_{16}O_7$	iso-PrOH
c	75.4	189—190	$C_{23}H_{22}O_7$	EtOH
3d	70.3	163—164	$C_{22}H_{20}O_7$	iso-PrOH
3e	61.7	132—133	$C_{23}H_{22}O_7$	iso-PrOH
3f	67.9	156—157	$C_{24}H_{24}O_7$	iso-PrOH
4a	83.4	235—236	$C_{19}H_{14}O_7$	iso-PrOH
4b	85.6	279—280	$C_{18}H_{12}O_7$	iso-PrOH
4c	80	255—256	$C_{21}H_{18}O_7$	EtOH

TABLE 2. Chemical Shifts (δ, ppm) in the PMR Spectra of the 2-Ethoxycarbonyl- and 2-Carboxy-Substituted Analogs of Pseudobaptigenin (**2-4**)*

Compound	Chromone protons				
	COOEt- or COOH-2, q.t	H-5, s	R-6 q.t	OH-7 or OMe-7, s	H-8, s
2a	4.10; 0.99	7.75	2.62; 1.17	11.04	6.89
2b	4.09;. 0.98	7.78 d J=8 Hz	6.93 dd J=8; 2Hz	10.98	6.86d J=2 Hz
2c	4.10; 0.95	7.75	2.62; 1.17	11.03	6.90
3d	4.18; 1.10	7.96	2.69; 1.23	3.94	6.89
3e	4.17; 1.10	7.94	2.66; 0.95	3.93	6.89
3f	4.19; 1.05	7.96	2.69; 1.23	3.94	6.90
4a	13.66s	7.75	2.62; 1.16	10.97	6.90
4b	13.30s	7.90d J=8 Hz	6.94 dd J=8; 2Hz	11.00	6.90 J=2 Hz
4c	13.60	7.75	2.64; 1.17	10.97	6.90

Compound	Protons of the hetero residue			
	H-4 or H-5 or H-6, d, J = 2 Hz	H-6 or H-7 or H-8, d.d, J = 8 Hz; J = 2 Hz	H-7 or H-8 or H-9. d, J = 8Hz	$-O(CH_2)_nO-$, s
2a	6.82	6.64	6.92	6.05
2b	6.73	6.64	6.85	4.24
2c	6.82	6.76	6.97	4.10q; 2.12 t
3d	6.82	6.71	6.86	6.00
3e	6.81	6.70	6.85	5.99
3f	6.93	6.85	7.01	4.24q; 2.20t
4a	6.81	6.66	6.92	6.04
4b	6.75	6.70	6.85	4.25
4c	6.84	6.80	6.98	4.14q; 2.14t

*The PMR spectra of compounds (**3a-c** and **4a-c**) were measured in DMSO-d_6, and those of the other compounds in $CDCl_3$.

In the PMR spectra of the 2-ethoxycarbonylisoflavones (**2-4**), as compared with the initial ketones (**1**), the two-proton singlet of the methylene unit of the ketone and the downfield peak of the proton of the OH-2 group had disappeared and a quartet and triplet of the ethoxycarbonyl group had appeared in the 4.10-4.20 and 0.90-1.10 ppm regions. In the PMR spectrum of each 7-methoxy derivative (**3**) there was a three-proton singlet of the methoxy group at 3.90 ppm. The protons of the 6-ethyl and 6-propyl groups gave the corresponding multiplets. The protons of the carboxy groups of compounds (**4**) appeared in the form of singlets in the 13.30-13.70 region.

Thus, contrary to what is stated in the literature [8], the cyclization of α-hetaryl-2-hydroxyacetophenones under the action of ethoxalyl chloride in pyridine takes place at an elevated temperature. The results of biological trials will be given in subsequent publications.

EXPERIMENTAL

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

α-(1,5-Benzodioxepan-7-yl)-5-ethyl-2,4-dihydroxyanthraquinone (Ic). With stirring, a rapid current of hydrogen chloride was passed for 10 min into a solution of 37.8 g (0.2 mole) 7-cyanomethyl-1,5-benzodioxepane in 150 ml of absolute benzene cooled to 0°C. Then a solution of 35 g (0.2 mole) of dry 4-ethylresorcinol and 13.6 g (0.1 mole) of fused zinc chloride in 112.5 ml of absolute ether were added. Saturation with hydrogen chloride was continued for 3 h and then at room temperature for another 4 h. After this, the mixture 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 added to 760 ml of hot water, and the mixture was left at 90°C and pH 1 for 1 h.

The solid was separated off from the hot solution and was well washed on the filter with water to pH 7 and crystallized from ethanol PMR spectrum (DMSO-d_6, ppm): 12.4 (s, 1H, OH-2), 6.31 (s, 1H, H-3), 10.66 (s, 1H, OH-4), 1.12; 2.49 (t.q., 5H, CH_3CH_2–5), 7.75 (s, 1H, H-6), 4.18 (s, 2H, CH_2); protons of benzodioxepane 6.87 (m, 3H, H-6, H-8, H-9), 4.08 (t, 4H, CH_2–2 and CH_2–4), 2.05 (q, 2H, CH_2–3).

α-(1,5-Benzodioxepan-7-yl)-5-ethyl-2-hydroxy-4-methoxyacetophenone (1f). A hot solution of 9.84 g (30 mmole) of ketone (**1c**) in 150 ml of absolute benzene was treated with 12.4 g (90 mmole) of potassium carbonate and 3.45 ml (30 mmole) of dimethyl sulfate, and the mixture was boiled for 4 h. Then the inorganic residue was filtered off, and the filtrate was acidified with 6 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): 11.68 (s, 1H, OH-2), 6.49 (s, 1H, H-3), 3.83 (s, 3H, CH_3O-4), 2.50; 1.11 (t.q., 5H, CH_3CH_2–5), 7.78 (s, 1H, H-6), 4.22 (s, 2H, CH_2); protons of benzodioxepane 6.87 (m, 3H, H-6, H-8, H-9), 4.08 (t, 4H, CH_2–2 and CH_2–4), 2.05 (q, 2H, CH_2–3).

The 2-Ethoxycarbonyl-3-hetaryl-7-hydroxychromones (2a-c). A solution of 5 mmole of a ketone (**1a-c**) in 10 ml of absolute pyridine cooled to 0°C was treated dropwise with 1.2 ml (10 mmole) of ethoxalyl chloride, and the mixture was left overnight. On the following day, it was heated to 40-45°C for 10-15 min, and it was again left overnight at room temperature, after which it was poured into cold water, and the resulting precipitate was filtered off, dried, and crystallized from a suitable solvent.

The 2-Ethoxycarbonyl-3-hetaryl-7-methoxychromones (3d-f). A solution of 10 mmole of a ketone (**1d-f**) in 15 ml of absolute pyridine cooled to 0°C was treated dropwise with 1.2 ml (10 mmole) of ethoxalyl chloride, and the mixture was left overnight. On the following day it was heated to 50-55°C for 30 min and was again left overnight at room temperature. Then it was poured into cold water, and the resulting precipiate was filtered off, dried, and recrystallized from a suitable solvent.

The 2-Carboxy-3-hetaryl-7-hydroxychromones (4a—c). A hot solution of 10 mmole of a chromone (**2a-c**) in 100 ml of ethanol was treatd with 25.9 ml of a 5% solution of caustic soda, and the mixture was boiled for 10 min. After neutralization with dilute hydrochloric acid, the resulting precipitate was filtered off and crystallized from a suitable solvent.

REFERENCES

1. A. Aitmambetov and V. P. Khilya, Khim. Prir. Soedin., 820 (1993).
2. A. Aitmambetov and V. P. Khilya, Khim. Prir. Soedin., 669 (1993).
3. A. Aitmambetov and V. P. Khilya, Khim. Prir. Soedin., 674 (1993).
4. A. Aitmambetov, L. G. Grishko, and V. P. Khilya, Khim. Prir. Soedin., 808 (1993).
5. A. Aitmambetov, L. G. Grishko, and V. P. Khilya, Khim. Prir. Soedin., 814 (1993).

6. N. Ito, H. Ogawara, and S. Watanabe, US Patent No. 4,841,077 (1990).
7. N. Ito, H. Ogawara, and S. Watanabe, US Patent No. 4,960,908 (1992).
8. W. Baker, J. Chaddrton, J. B. Harborne, and W. D. Ollis, J. Chem. Soc., 1852 (1953).