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SYNTHETIC ANALOGS OF NATURAL FLAVOLIGNANS. III. SYNTHESIS OF 6-CARBOXY-1,3-BENZODIOXANE ANALOGS OF SILANDRIN AND HYDNOCARPIN

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Chalcones containing a 6-carboxy-1,3-benzodioxane fragment and, from them, flavanone and flavone analogs of silandrin and hydnocarpin have been synthesized. The structures of the compounds obtained were confirmed by their PMR spectra.

We have previously [1, 2] reported the synthesis of 1,4-benzodioxane and 1,5-benzodioxepane analogs of silandrin and hydnocarpin. In the present paper we give the results of an investigation of the synthesis of 6-carboxy-1,3-benzodioxane analogs of silandrin and hydnocarpin with simplified structures. As our investigations [3-5] have shown, a simplification of the structure of natural flavolignans (silandrin, hydnocarpin) and also the introduction of various functional groups into the molecules of their synthetic analogs, as well as a change in the mutual positions of the oxygen atoms in the benzodioxane fragment, are not infrequently accompanied by the appearance of extremely valuable biological properties and chemical characteristics. Being guided by these, we have obtained key compounds for the synthesis of silandrin and hydnocarpin analogs — substituted 2′-hydroxychalcones (1) containing a 6-carboxy-1,3-benzodioxane fragment in their molecule.

The introduction of a carboxy group into the molecule of a flavonoid makes it easily possible to convert the compounds obtained into salts, which ensures their solubility in water. However, the salt-forming reaction with the participation of the carboxy group of the aldehyde used in this work has an adverse effect on its capacity for condensing with 2-hydroxyacetophenones under the conditions of the classical Claisen–Schmidt reaction. Condensation does not take place because the alcohol-insoluble salt of 6-carboxy-8-formyl-1,3-benzodioxane is formed. We have established that in this case a suitable method of achieving condensation is that of [6], according to which the reaction is performed in dimethylformamide in the presence of powdered caustic potash. By this procedure, chalcones (2a-i) were formed with good yields.

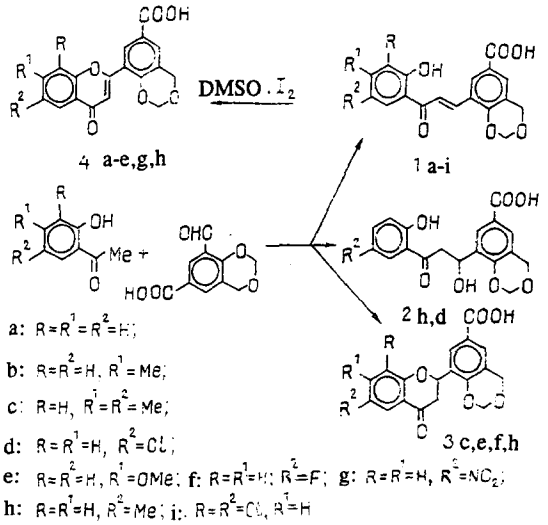

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TABLE 1. Characteristics of Compounds (1) and (2)

Compound	Yield, %	mp, °C	Empirical formula	Solvent for crystallization
1a	52	238—239	$C_{18}H_{14}O_6$	iso-PrOH
1b	50	241—242	$C_{19}H_{16}O_6$	EtOH
1c	45.7	254—255	$C_{20}H_{18}O_6$	CH_3COOH
1d	77	264—266	$C_{18}H_{13}ClO_6$	DMFA/*iso*-PrOH
1e	35.1	241—242	$C_{19}H_{16}O_7$	iso-PrOH
1f	52.1	246—247	$C_{18}H_{13}FO_6$	iso-PrOH
1g	55	>300	$C_{18}H_{13}NO_8$	CH_3COOH
1h	54.4	247—248	$C_{19}H_{16}O_6$	iso-PrOH
1i	53	240—241	$C_{18}H_{12}Cl_2O_6$	DMFA/*iso*-PrOH
2d	20.8	261—262	$C_{18}H_{15}ClO_7$	iso-PrOH
2h	18.4	240—241	$C_{19}H_{18}O_7$	iso-PrOH

TABLE 2. Characteristics of the 6-Carboxy-1,3-benzodioxane Flavanone Analogs (3)

Compound	Yield, %	mp, °C	Empirical formula	Solvent for crystallization
3c	23.7*, 43**	226—227	$C_{20}H_{18}O_6$	iso-PrOH/CH_3COCH_3
3e	12.6*, 44.5**	226—227	$C_{19}H_{16}O_7$	iso-PrOH
3f	9.8*, 51**	227—228	$C_{18}H_{13}FO_6$	EtOH
3h	6.6*, 38.9**	241—242	$C_{19}H_{16}O_6$	iso-PrOH

*Yield on heating the reaction mixture for 1 h.

**Yield on heating the reaction mixture for 2 h.

TABLE 3. Characteristics of the 6-Carboxy-1,3-benzodioxane Flavone Analogs (4)

Compound	Yield, %	mp, °C	Empirical formula	Solvent for crystallization
4a	58.8	>300	$C_{18}H_{12}O_6$	iso-PrOH
4b	71.8	>300	$C_{19}H_{14}O_6$	DMFA
4c	55.6	>300	$C_{20}H_{16}O_6$	DMFA/iso-PrOH
4d	64.3	240—241	$C_{18}H_{11}ClO_6$	CH_3COOH
4e	53.8	>300	$C_{19}H_{14}O_7$	DMFA
4f	58.5	239—240	$C_{18}H_{11}FO_6$	CH_3COOH
4g	46.5	>300	$C_{18}H_{11}NO_8$	CH_3COOH
4h	54	248—249	$C_{19}H_{14}O_6$	CH_3COOH

It must be mentioned that the use of this method leads to the formation not only of the desired chalcones (1a-i) but also of their structural isomers — the flavanones (3c, e, f, h) and also, as by-products, the β-hydroxydihydrochalcones (2h, d). We found that the yields of flavanones (3) depended on the time of heating and increased appreciably when when the reaction mixture was held for two hours or more. It is in just this way that we obtained flavanones (3c, e, f, h), which are silandrin analogs. The mixtures of chalcones (1c-h), β-hydroxydihydrochalcones (2d, h) and flavanones (3c, e, f, h) were separated by fractional crystallization from isopropanol.

The action of dimethyl sulfoxide in the presence of catalytic amounts of iodine on the chalcones (1) was accompanied by their oxidative cyclization into the corresponding hydnocarpin analogs, the flavones (4a-e, g, h).

The 6-carboxy-1,3-benzodioxane chalcone analogs (1) were yellow or light yellow crystalline substances with high melting points (Table 1) sparingly soluble in many organic solvents. In contrast to the chalcones, the flavanones (3) and the flavones (4), also possessing high melting points (Tables 2 and 3), were colorless crystalline substances readily soluble in many organic solvents.

All these compounds (1-4) were capable of forming salts through their carboxy groups. As an example, we obtained the monoethanolamine salt of 2-(6-carboxy-1,3-benzodioxan-8-yl)-6-chlorochromone (5) with a yield of 86%, which was readily soluble in water.

TABLE 4. PMR Spectra (DMSO-d_6; δ, ppm; J, Hz) of the 6-Carboxy-1,3-benzodioxane Chalcone Analogs

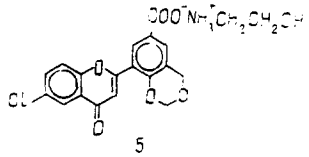
Compound	Protons of the phenolic moiety						Benzodioxane protons				
	OH-2, s	R-3	R^1-4	R^1-5	H-6	COCH=CH, s	H-5, d, J=2.0 Hz,	H-7, d, J=2.0 Hz,	COOH-6, s	CH_2-2, s	CH_2-4, s
1a	12.34	7.0 m	7.55 t.d, (9.0; 3.0)	7.0 m	8.22 d.d, (9.0; 3.0)	8.04	7.75	8.38	12.94	5.48	4.98
1b	12.60	6.80 d, (3.0)	2.33 s	6.80 d.d, (9.0; 3.0)	8.17 d, (9.0)	8.03	7.75	8.39	12.93	5.47	4.97
1c	12.44	6.82 s	2.25 s	2.25 s	8.05 s	8.05	7.78	8.39	12.98	5.49	4.99
1d	12.12	7.02 d, (8.3)	7.54 d.d, (8.3; 2.5)	—	8.18 d, (2.5)	8.00	7.76	8.32	12.92	5.47	4.98
1e	12.96	6.51 d, (2.2)	3.84 s	6.54 d.d, (8.3; 2.2)	8.29 d, (8.3)	8.04	7.76	8.32	13.34	5.49	4.99
1f	12.01	7.02 d.d, (9.0; 3.0)	7.44 t.d.	—	8.06 d.d	8.03	7.78	8.41	12.96	5.47	4.98
1g	12.88	7.16 d, (9.0)	8.33 d.d, (9.0:3.0)	—	8.69 d, (3.0)	7.94	7.77	8.30	12.98	5.47	4.98
1h	12.19	6.89 d, (9.0)	7.38 d.d, (9.0:3.0)	2.32 s	8.04 d, (3.0)	8.04	7.77	8.38	12.96	5.48	4.98
1i	13.04	—	7.91 d, (2.0)	—	8.45 d, (2.0)	8.11	7.79	8.50	13.04	5.48	4.98

TABLE 5. PMR Spectra (DMSO-d_6; δ, ppm; J, Hz) of the 6-Carboxy-1,3-benzodioxane Flavanone Analogs

Compound	Chromanone protons							Benzodioxane protons				
	Ha-2,d.d	Ha-3,d.d	He-3,d.d	H-5	R^2-6	R^1-7	R-8	H-5, d (2.0)	H-7, d (2.0)	COOH-6, s	CH_2-2, s	CH_2-4, s
3c	5.69 (12.2; 3.42)	3.12 (16.6; 12.2)	2.76 (16.6; 3.42)	7.54 s	2.22 s	2.22 s	6.96 s	7.72	8.05	12.83	5.39	4.98
3e	5.76 (12.9; 3.3)	3.12 (17.0; 12.9)	2.73 (17.0; 3.3)	7.72 d, (8.5)	6.69 d.d, (8.5:2.0)	3.82 s	6.69 d, (2.0)	7.72	8.06	12.80	5.40	4.98
3f	5.80 (13.2; 2.9)	3.26 (16.6; 13.2)	2.82 (16.6; 2.9)	7.21 d.d, (10; 4.3)	—	7.47 d.d, (10; 3.3)	7.47 d, (8.0)	7.73	8.05	12.87	5.39	4.98
3h	5.73 (12.8; 3.4)	3.06 (16.6; 12.8)	2.77 (16.6; 3.4)	7.58 d, (2.2)	2.28 s	7.41 d.d, (8.2; 2)	7.03 d, (8.2)	7.70	8.04	12.87	5.38	4.97

TABLE 6. PMR Spectra (DMSO-d_6; δ, ppm; J, Hz) of the 6-Carboxy-1,3-benzodioxane Flavone Analogs

Compound	Chromone protons					Benzodioxane protons				
	H-3, s	H-5	R^2-6	R^1-7	R-8	H-5, d	H-7, d	COOH-6, s	CH_2-2, s	CH_2-4, s
4a	6.90	8.05 d.d	7.85 m	7.53 t.d,	7.85 d.d	7.88 (2.0)	8.39 (2.0)	13.00	5.54	5.08
4b	6.91	7.91 d, (9.0)	7.30 d.d, (9.0; 2.5)	2.47 s	7.54 d, (2.5)	7.84 (2.0)	8.32 (2.0)	12.93	5.47	5.01
4c	6.86	8.28 s	2.32 s	2.36 s	7.82 s	7.74 (2.0)	8.49 (2.0)	12.98	5.47	5.01
4d	6.98	7.89 d, (9.0)	—	7.82 m	7.82 m	7.90 (2.0)	8.30 (2.0)	13.04	5.50	5.02
4e	6.85	7.96 d, (9.0)	7.06 d.d (9.0; 2.5)	3.93 s	7.19 d, (2.5)	7.84 (2.0)	8.32 (2.0)	13.00	5.49	5.03
4g	7.06	8.65 d, (2.0)	—	8.54 d.d, (9; 3.0)	7.99 d, (9.0)	7.83 (2.0)	8.32 (2.0)	12.90	5.51	5.01
4h	6.94	7.82 d, (9.0)	2.43 s	7.64 m	7.64 m	7.86 (2.0)	8.32 (2.0)	13.00	5.50	5.04



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The compositions and structures of compounds (1-4) were shown by the results of elemental analysis (Tables 1-3) and PMR spectra (Tables 4-6).

The PMR spectra (in DMSO-d_6) of the chalcones (1) (Table 4) showed the signals of the carboxy and hydroxy protons in the weakest field (12.9-13.0 ppm and 12.0-13.0 ppm, respectively). The methyl protons of the chalcones in solution in DMSO-d_6, in contrast to solution in $CDCl_3$, gave signals not in the form of doublets but as two-proton singlets. The H-5 and H-7 aromatic protons of the 1,3-benzodioxane ring were revealed in the form of doublets with a SSCC of 2.0 Hz in the 7.7-8.0 ppm region, while the signals of the CH_2-2 and CH_2-4 methylene groups had the form of two-proton singlets at 5.5 and 5.0 ppm.

In the PMR spectra of the β-hydroxydihydrochalcones (2h, d) the protons of the β-methyl groups gave quintets at 4.2 ppm and the protons of the α-methylene groups doublets at 3.50 ppm.

The PMR spectra of the flavanones (3) (Table 5) had characteristic signals of the pyran ring, with chemical shifts in the 5.8 and 3.0 ppm regions. The values of the SSCC ($J_{H\text{-}2a,3a}$ = 12.8 Hz; $J_{H\text{-}2a,3e}$ = 3.4 Hz; $J_{H\text{-}3a,3e}$ = 16.6 Hz) showed that the H-2_a proton was oriented axially and the 1,3-benzodioxane residue on the same carbon atom, equatorially.

In the PMR spectra of the flavones (4) in DMSO-d_6 (Table 6), in addition to the signals of H-3 and H-5 of the chromone nucleus located in the 6.9-7.0 and 7.9-8.3 ppm regions, respectively, the signals of the H-5 and H-7 protons of the benzodioxane nucleus (7.7 and 8.3 ppm, respectively) were characteristic.

Thus, a method has been found for obtaining 6-carboxy-1,3-benzodioxane analogs of chalcones and their structural isomers — flavanone analogs of silandrin. It has been shown that in the synthesis of these compounds it is possible to obtain and isolate intermediate compounds — β-hydroxydihydrochalcones — as by-products of the reaction. Syntheses have been performed which show the possibility of converting carboxyl-containing chalcones into flavone analogs of hydnocarpin.

The testing of the biological activities of the new compounds has shown that some of them exhibit a hepatoprotective activity.

EXPERIMENTAL

The purity of the compounds obtained was checked by the TLC method on Silufol UV-254 plates using the chloroform–methanol (9:1) system. PMR spectra were measured on a Bruker WP-100 SU instrument in DMSO-d_6 with TMS as internal standard. The results of analyses of the compounds synthesized corresponded to the calculated values.

3-(6-Carboxy-1,3-benzodioxan-8-yl)-1-(2-hydroxyphenyl)propen-1-ones (1a-i), 3-(6-Carboxy-1,3-benzodioxan-8-yl)-1-(2-hydroxyphenyl)-β-hydroxypropan-1-ones (2h, d), and 3-(6-Carboxy-1,3-benzodioxan-8-yl)-1-(2-hydroxyphenyl)-chromanones (3c, e, f, h). A solution of 20 mmole of the appropriate acetophenone and 4.16 g (20 mmole) of 6-carboxy-8-formyl-1,3-benzodioxane in 54 ml of dimethylformamide was treated with 9.1 g of finely ground caustic potash, and the mixture was boiled with stirring for 1-2 h. A suspension of the resulting precipitate in water was neutralized with hydrochloric acid, and the solid matter was then filtered off and was boiled in isopropanol. The insoluble part (chalcone) was separated off, and products (2) and (3) were obtained in the individual form from the mother liquor by fractional crystallization from isopropanol.

PMR spectrum (δ, ppm): compound (2d) 11.54 (s, 1H, OH-2), 7.51 (d 1H, J = 9 Hz, H-3), 7.51 (d.d, 1H, J = 9.0; 3.0 Hz, H-4), 7.85 (d, 1H, J = 3.0 Hz, H-6); 3.50 (d, 2H, CH_2-α), 4.16 (q, 1H, CH-β); protons of 6-carboxy-1,3-benzodioxane: 7.51 (d, 1H, J = 2.0 Hz, H-5), 12.80 (s, 1H, COOH-6), 7.77 (d, 1H, J = 2.0 Hz H-7), 5.28 (s, 2H, CH_2-2), 4.90 (s, 2H, CH_2-4).

Compound (2h) 11.57 (s, 1H, OH-2), 6.83 (d, 1H, J = 9.0 Hz, H-3), 7.31 (d.d, 1H, J = 9.0; 3.0 Hz, H-4), 2.25 (s, 3H, CH_3-5), 7.71 (d, 1H, J = 3.0 Hz, H-6); 3.51 (d, 2H, CH_2-α), 4.19 (q, 1H, CH-β); protons of 6-carboxy-1,3-benzodioxane: (s, 1H, COOH-6), 7.78 (Hz, 1H, J = 2.0 Hz, H-7), 5.27 (s, 2H, CH_2-2), 4.89 (s, 2H CH_2-4).

2-(6-Carboxy-1,3-dioxan-8-yl)chromones (4a-e, f, g, h). A catalytic amount of iodine was added to a solution of 10 mmole of the appropriate chalcone (1) in 30 ml of dimethyl sulfoxide, and the reaction mixture was boiled for 1 h. Then it

was diluted twofold with water and the precipitate that deposited was filtered off and was washed on the filter with a 20% solution of sodium thiosulfate to eliminate traces of iodine. The reaction product was crystallized from a suitable solvent.

Monoethanolamine Salt of 2-(6-Carboxy-1,3-benzodioxan-8-yl)-6-chlorochromone (5). With stirring, 0.33 g (0.32 ml) of monoethanolamine was added to a paste of 1.95 g (5.43 mmole) of chromone (4d) in 1.3 ml of water heated to 70-75°C, and heating at 70-75°C was continued until all the paste had passed into solution. Then 10.1 ml of isopropyl alcohol was added, and the mixture was left in the refrigerator; the resulting precipitate was filtered off and was washed with cold isopropyl alcohol. It was recrystallized from isopropyl alcohol. Yield 1.95 g (85.9%), mp 200-201°C. Empirical formula $C_{20}H_{18}ClNO_7$.

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