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SYNTHETIC ANALOGS OF NATURAL FLAVOLIGNANS. I. A NEW SYNTHESIS OF ANALOGUES OF SILANDRIN AND HYDNOCARPIN

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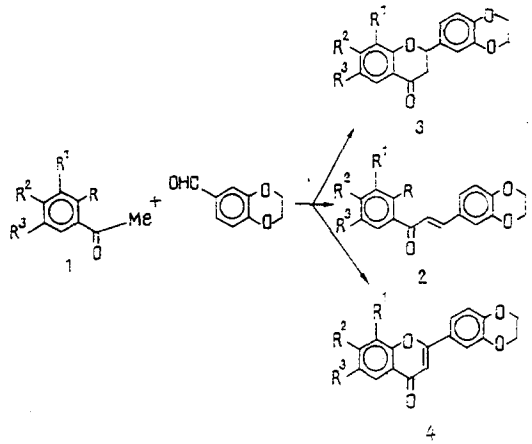
The synthesis of analogues of silandrin and hydnocarpin from 2'-hydroxy-3,4-ethylenedioxychalcones has been achieved.

Silandrin – 5,7-dihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-hydroxymethylbenzo-1,4-dioxan-6-yl]-4-chromanone [1] – and hydnocarpin – 5,7-dihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-hydroxymethylbenzo-1,4-dioxan-6-yl]-4-chromone [2] – and also some compounds related to them containing a 1,4-benzodioxane fragment in their molecule are well known complex natural flavonoids possessing considerable biological activity [3, 4]. This explains the interest in obtaining synthetic analogs of them, a whole series of which we have synthesized [5, 6]. In the search for rational methods of obtaining such analogs we have conducted investigations on their synthesis with the aim of constructing simpler compounds than silandrin and hydnocarpin.

In the present communication we give the results of the synthesis of new derivatives of them and also of previously known flavonoids, but with the use not only of methods of obtaining them that we have employed previously, but also other methods, among which are some which we have proposed for the first time.

Thus, in performing the synthesis of the chalcones (**2a-*l***) we used the conditions of the Claisen–Schmidt reaction (method A), and also another method [7] that consists in boiling the initial acetophenones with 6-formyl-1,4-benzodioxane in dimethylformamide in the presence of powdered caustic potash (method B).

The condensation of the ketones (**1k, *l***) with 6-formyl-1,4-benzodioxane under the conditions of the Claisen–Schmidt reaction led to a mixture of the chalcones (**2**) and the flavanones (**3**) (method A).



a: $R=R^1=R^2=R^3=H$; b: $R=R^1=R^3=H$, $R^2=OMe$, and for all the others, R=OH; c: $R=R^2=R^3=H$; d: $R^1=R^3=H$, $R^2=Me$; e: $R^1=R^3=H$, $R^2=OMe$; g: $R^1=R^2=H$, $R^3=Cl$; h: $R^1=R^2=H$, $R^3=F$; i: $R^1=R^2=H$, $R^3=Me$; j: $R^1=R^2=H$, $R^3=OMe$; k: $R^1=R^2=H$, $R^3=NO_2$; *l*: $R^1=R^2=$—CH=CH—CH=CH—, $R^3=H$

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TABLE 1. Characteristics of Compounds (2-4)

Compound	Yield by method A, %	Yield by method B, %	Yield by method C			mp, °C	Empirical formula	Solvent for crystallization
			10 min	1 h	2 h			
2a	65.8		64.9			125—126	$C_{17}H_{14}O_3$	EtOH
2b	54.5					81—83	$C_{18}H_{16}O_4$	EtOH
2c			51			126—127	$C_{17}H_{14}O_4$	EtOH
2e			53.5			140—141	$C_{18}H_{16}O_5$	EtOH
2g			88	53.6	8.3	135—136	$C_{17}H_{13}ClO_4$	EtOAc
2h			72.3	41.1	8.0	173—174	$C_{17}H_{13}FO_4$	EtOAc
2k	39.4					187—189	$C_{17}H_{13}NO_6$	EtOAc
2*l*	42.9		22.0	32.8	21.3	179—181	$C_{21}H_{16}O_4$	EtOAc
3c		59.7				109—110	$C_{17}H_{14}O_4$	MeOH
3d		61.2				76—77	$C_{18}H_{16}O_4$	EtOH
3e		43.6				116—117	$C_{18}H_{16}O_5$	EtOAc
3g		47.1		12.3	21(38*)	115—116	$C_{17}H_{13}ClO_4$	MeOH
3h		53.7		8.2	19(32*)	120—121	$C_{17}H_{13}FO_4$	EtOH
3k	15	61.3				198—200	$C_{17}H_{13}NO_6$	Acetone
3*l*				12.9	22	174—175	$C_{21}H_{16}O_4$	EtOH
4c	68.3					184—185	$C_{17}H_{12}O_4$	EtOAc
4d	79.9					168—169	$C_{18}H_{14}O_4$	EtOH
4e	78.4					170—171	$C_{18}H_{14}O_5$	EtOAc
4g	88.3			7.2	29.7	226—227	$C_{17}H_{11}ClO_4$	EtOH
4h	89.1			7.8	27.3	213—214	$C_{17}H_{11}FO_4$	EtOAc
4i	68.5					195—196	$C_{18}H_{14}O_4$	EtOAc
4j	81.7					194—195	$C_{18}H_{14}O_5$	EtOAc
4k	83.1					278—279	$C_{17}H_{11}NO_6$	DMFA
4*l*	63.9					207—208	$C_{21}H_{14}O_4$	EtOAc

*Yield when the reaction was performed in a current of nitrogen.

It must be mentioned that on the use of the second method (method B), the yields of the chalcones varied according to the time of holding the reaction mixture. Thus, when the reaction mixture was boiled for 10 min, the yields amounted to 50-80%. On prolonged heating (up to 1 h) the yield decreased and, in addition to the chalcone (**2**), the reaction products also contained not only the flavanones (**3**) but also the flavones (**4**) – products of the isomerization and oxidation of the chalcones. To find the reagent playing the role of oxidant of the chalcones to the flavones in this reaction, the condensation was performed over 1-4 h with or without the access of air (in the latter case, in a current of nitrogen). Analysis of the results obtained showed that when synthesis was conducted in an inert medium, mixtures of the chalcones (**2g, h**) (yield 8%) and of the flavanones (**3g, h**) (yields 32.4 and 38.7%) were obtained. In the presence of air, however, in addition to the flavone (**4**) (yield 13-30%), the flavanones (**3g, h**) were isolated with yields of 19-22%. The appearance in the reaction mixture of fairly considerable amounts of flavones not formed in the case of the inert medium unambiguously showed that oxidative processes took place during the synthesis of the chalcones. The role of oxidant in this reaction is played by atmospheric oxygen. The high temperature of the solvent and the alkaline medium promote the rapid oxidation of chalcone to flavone. In view of this, such a feature of the performance of the synthesis in the presence of atmospheric oxygen can be utilized as an independent route for obtaining flavanones and flavones without isolating the intermediate chalcones (see Table 1).

The chalcones (**2c-*l***) obtained were converted by boiling in glacial acetic acid for 20-50 h (method B) into the corresponding flavanones (**3c-*l***), which are analogues of silandrin.

The mixtures of products obtained by method A or B were separated with the aid of fractional crystallization or, in a number of cases, by column chromatography.

On the basis of the chalcones considered above, we also performed the directed synthesis of flavones, using for this reaction oxidative cyclization in dimethyl sulfoxide in the presence of catalytic amounts of iodine [8] (method B). The method is favorably distinguished from that which we employed previously with selenium dioxide as the oxidant: by a considerable

TABLE 2. PMR Spectra (δ, ppm) of the 1,4-Benzodioxane Analogues of the Chalcones (**2**) ($CDCl_3$)

Compound	Protons of the phenol moiety					
	H-2 or OH-2, s	R^1-3 d J=9.0 Hz	R^2-4	R^3-5	H-6	COCH=CH J=15.37 Hz
2a	8.00 d.d J=7.9; 2.6 Hz	7.55 m	7.55 m	8.00	8.00 J=7.9; 2.6 Hz	7.39; 7.73
2b	8.02 d, J=9.16 Hz	6.97 d.d J=9.16; 2.3Hz	3.88 s	6.97 d.d J=9.16; 2.3 Hz	8.02 d J=9.16 Hz	7.38; 7.72
2k	13.70	7.12 d J=9.0 Hz	8.36 d.d J=9; 22.4 Hz	-	8.86 d J=2.4 Hz	7.51; 7.93
2*l*	14.92	7.4—7.9 m	7.4—7.9 m (H-4, H-5), 8.49(H-6), 7.29(H-7), 7.82 (H-8)			7.57; 7.89

Compound	Benzodioxane protons			
	H-5, d, J=2 Hz	H-7, d.d, J=9; 2 Hz	H-8, d, J=9 Hz	OCH_2CH_2Oc
2a	7.20	7.16	6.89	4.30
2b	7.18	7.15	6.89	4.29
2k	7.29	7.25	6.97	4.32
2*l*	7.24	7.20	6.91	4.31

increase in the yield of the desired reaction products, by a shortening of the time of the process, and by a decrease in the amount of the by-products. The structures of the chalcones (**2**), flavanones (**3**), and flavones (**4**) synthesized were confirmed by their PMR spectra (Table 2).

In the spectra of the chalcones (**2k,*l***) the signal of the hydroxylic protons was observed in a weak field (13.7-14.9 ppm). The olefinic protons gave a doublet of doublets at 7.4-7.9 ppm. Signals of the methylene groups were in the form of singlets at 4.30 ppm.

In the PMR spectra of the flavanones (**3k,*l***) characteristic groups of signals of the chromanone ring were observed, with chemical shifts in the regions of 5.6 and 3 ppm.

In the spectra of the flavones (**4**), in addition to the signals of the H-3 and H-5 protons of the chromone nucleus, located in the 6.8-6.9 ppm and 8.1-8.7 ppm intervals, respectively, the signal of the 8-H proton of the benzodioxane nucleus was also characteristic. It was located at 7.0 ppm and did not coincide with the multiplet of the other aromatic protons. The methylene protons of the benzodioxane nucleus gave a singlet at 4.3-4.4 ppm.

Thus, we have studied the conditions for synthesizing benzodioxane analogs of flavonoids and have proposed a new one-stage method for obtaining flavone and flavanone analogs of hydnocarpin and silandrin. Trials of the biological activities of the silandrin and hydnocarpin analogs have shown that among them there are substances with a high hepatoprotective activity.

EXPERIMENTAL

The purity of the compounds obtained was checked by TLC on Silufol UV-254 plates using the benzene–ethanol (9:1) system. The PMR spectra of compounds (**2-4**) were measured on a Bruker WP-100 SU spectrometer in $CDCl_3$ relative to TMS (internal standard). The elementary analyses of compounds (**2-4**) corresponded to the calculated figures.

3-(1,4-Benzodioxan-6-yl)-1-phenylprop-1-enones (2a-*l*). Method A. A hot solution of 20 mmoles of the appropriate acetophenone (**1a-*l***) in the minimum amount of alcohol was treated with 3.28 g (20 mmoles) of 6-formyl-1,4-benzodioxane and 4.7 ml of a 50% solution of caustic soda. The reaction mixture was kept at room temperature for 20-30 h. The precipitate was suspended in water and the mixture was brought to neutrality by the addition of acetic acid. The product was filtered off and crystallized from a suitable solvent. If TLC showed the presence of a flavone in the reaction mixture, the products were separated by column chromatography on silica gel in benzene.

Method B. A solution of 20 mmole of the appropriate 2-hydroxyacetophenone (**1**) and 3.28 g (20 mmoles) of 6-formyl-1,4-benzodioxane in 50 ml of dimethylformamide was treated with 4.55 g of finely ground potash, and the mixture was boiled with stirring for from 10 min to 4 h. The precipitate was suspended in water, the mixture was neutralized with

dilute hydrochloric acid, and the solid matter that deposited was filtered off. If TLC showed the presence of a flavanone and a flavone in the products, the mixture was separated with the aid of fractional crystallization or column chromatography.

2-(1,4-Benzodioxan-6-yl)chromanones (3c-*l*). Method B. A solution of 2 mmoles of a 2-hydroxychalcone (**2c-*l***) in 30-50 ml of glacial acetic acid was boiled for 20-50 h. The solvent was distilled off and the residue was separated by fractional crystallization or column chromatography. PMR spectra ($CDCl_3$, ppm), compound (**3k**): 5.75 (d.d, 1H, J = 12.21; 3.42 Hz, Ha-2), 3.40 (d.d, 1H, J = 12.21; 3.42 Hz, H_a-3, 2.91 (d.d, 1H, J = 17.09; 3.42 Hz, H_e-3), 8.5 (d 1H, J = 2.44 Hz, H-5), 8.38 (d, 1H, J = 8.79 Hz, H-7), 7.31 (d.d, 1H, J = 8.79; 2.44 Hz, H-8). Benzodioxane protons: 7.06 (d, 1H, J = 2.0 Hz, H-5), 7.02 (d.d, 1H, J = 8.0; 2.0 Hz, H-7), 6.89 (d, 1H, J = 8.0 Hz, H-8),4.26 (s, 4H, $O(CH_2)_2O$). Compound 3*l*: 5.58 (d.d, 1H, J = 12.0; 4.00 Hz, H_a-2), 3.18 (d.d, 1H, J = 16.2; 12.00 Hz, H_a-3), 2.92 (d.d, 1H, J = 16.2; 4.0 Hz, H_e-3), 7.92 (1H, H-5), 7.44 (1H, H-6), 7.5-7.85 (4H, m, H-7, H-8, H-9, H-10); benzodioxane protons: 7.12 (d, 1H, J = 2 Hz, H-5), 7.8 (d.d, 1H, J = 8; 2 Hz, H-7), 6.94 (d, 1H, J = 8 Hz H-8), 4.30 (s, 4H, OCH_2CH_2O).

2-(1,4-Benzodioxan-6-yl)chromones (4c-*l*). Method A. A catalytic amount of iodine was added to a solution of 10 mmole of a chalcone (**2a-*l***) in 30 ml of dimethyl sulfoxide, and the mixture was boiled for 10-30 min. Then it was diluted twofold with water, and the precipitate that deposited was filtered off and was freed from traces of iodine by washing on the filter with a 20% solution of sodium thiosulfate, after which it was recrystallized from a suitable solvent. PMR spectra (DMSO-d_6, δ, ppm), compound **4k**: 6.94 (s, 1H, H-3), 8.69 (d, 1H, J = 2.43 Hz, H-5), 8.51 (d.d, 1H, J = 9.0; 2.43 Hz, H-7), 7.95 (d, 1H, J = 9 Hz, H-8); benzodioxane protons: 7.57 (m, 2H, H-5, H-7), 6.99 (d, 1H, J = 8.0 Hz, H-8), 4.32 (s 2H, OCH_2CH_2O). Compound 4*l* (in $CDCl_3$): 6.83 (s, 1H, H-3), 8.12 (d, 1H, J = 9.0 Hz, H-5), 7.6−8.0 (m, 4H, H-6, H-7, H-8, H-9), 8.55 (d.d, 1H, J = 9.0; 2.0 Hz, H-10); benzodioxane protons: 7.53 (d, 1H, J = 2 Hz, H-5), 7.49 (d.d, 1H, J = 8; 2 Hz, H-7), 7.01 (d, 1H, J = 8.0 Hz, H-8), 4.36 (s, 2H, OCH_2CH_2O).

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