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SYNTHETIC ANALOGS OF NATURAL FLAVOLIGNANS. VI. SYNTHESIS OF ANALOGS OF SILYBIN AND DEHYDROSILYBIN

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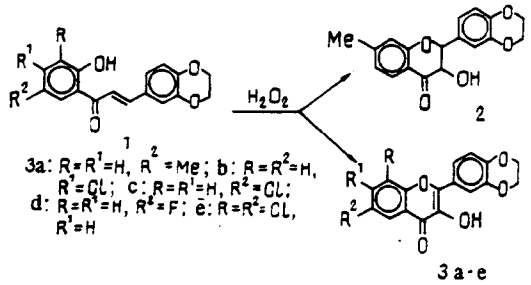
Analogs of silybin and dehydrosilybin have been obtained from 1,4-benzodioxane derivatives of chalcones, and their structures have been shown by their PMR and IR spectra.

Natural silybin has a 3′,4′-ethylenedioxy-3-hydroxyflavanone structure, and dehydrosilybin a 3′,4′-ethylenedioxy-3-hydroxyflavone structure. In view of this, it appeared of interest to synthesize and study the chemical and biological properties of silybin and dehydrosilybin analogs with similar structures.

The initial compounds for creating the silybin and dehydrosilybin analogs were the corresponding chalcone derivatives (1), which have been described in [1].



The interaction of the 2′-hydroxychalcones (1a-e) with hydrogen peroxide in an alkaline medium under the conditions of the classical variant of the Algar–Flynn–Oyamada (AFO) reaction [2] did not always lead to the desired 3-hydroxychromones (2) (method A). Under the given conditions a mixture of 3-hydroxychromanones (2) and 3-hydroxychromones (3) was obtained most frequently, although, in the majority of cases, the 3-hydroxychromones (3a-d) were the main reaction products.

On the reaction of the 2′-hydroxychalcones (1) with hydrogen peroxide in the presence of diethylamine in dioxane under the conditions given by Saxena et al. [3] (method B), various products were obtained. In the case of the chalcones (1a-d), the 3-hydroxyflavones (3a-d) were isolated as the main reaction products while the 3-hydroxyflavanones (2) were formed in insignificamt amounts as compared with the classical AFO reaction. By-products from this reaction that were isolated from the reaction mixture, in addition to the compounds mentioned above, were the chalcones (1) and benzoic acid derivatives.

The structures of the compounds obtained were confirmed by the results of analyses and by their IR and PMR spectra (Tables 1 and 2).

The IR spectra of the 3-hydroxyflavanones (2) contained characteristic absorption bands corresponding to the stretching vibrations of hydroxy groups (ν_{OH} = 3428 cm^{-1}) and carbonyl groups (ν_{CO} = 1685 cm^{-1}).

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TABLE 1. Characteristics of Compounds (2), and (3)

Compound	Yield, %	mp, °C.	Empirical formula	IR spectrum, ν, cm^{-1}		Solvent for crystalization
				νOH	νC=O	
3a	33.9[a] 40.9[b]	230—232	C18H14O5			EtOH
3b	42.3[a] 31.6[b]	245—248	C17H11ClO5	3332	1633	EtOH/EtOAc
3c	45.4[a] 74.0[b]	249—251	C17H11ClO5	3297	1631	CH3COOH
3d	67.0[b]	223—224	C17H11FO5	3292	1630	EtOH/EtOAc
3e	63.0[a]	254—256	C17H10Cl2O5			EtOAc
2	26.0[b]	167—168	C18H16O5	3428	1685	EtOH/EtOAc

[a]Yield by method A

[b]Yield by method B.

TABLE 2. PMR Spectra (DMSO-d_6, δ, ppm; J, Hz) of the Dehydrosilybin Analogs (3)

Compound	Chromone protons				
	OH-3, s	H-5	R^2-6	R^1-7	R-8
3a	9.40	7.87 d, (2.0)	2.43 s	7.75 d.d, (8.0; 2.0)	7.77 d, (8.0)
3b	9.60	8.8 d, (8.0)	7.76 d.d, (8.0; 2.3)	—	8.08 d, (2.3)
3c	9.71	8.04 d, (2.0)	—	7.64 d.d, (8.0; 2.0)	7.75 d, (8.0)
3d	9.60	7.76 m	—	7.76 m	7.76 m
3e	9.96	8.14 d,	—	7.97 d	—

Compound	Benzodioxane protons			
	H-5, d, (2.0)	H-7, d.d, (8.0; 2.0)	H-8, d, (8.0)	—OCH2CH2O—, s
3a	7.61 m	7.61 m	7.02	4.25
3b	7.81	7.49	7.03	4.31
3c	8.17	7.97	6.92	4.28
3d	7.76 m	7.76 m	7.01	4.31
3e	7.76	7.76	7.06	4.32

In the PMR spectra of the 3-hydroxyflavanones (2) taken in $CDCl_3$, the signals of the protons of the OH-3 hydroxy groups appeared in the 3.69 ppm region. A peak in a weaker field – at 4.99 ppm, corresponded to the H_{2a} proton. The H_{2a} proton interacts with two protons having different spatial positions – OH_{3a} and H_{3e} The spin–spin coupling constants are 1.9 Hz ($H_{3a}-OH_{3e}$) and 12.2 Hz ($H_{2a}-H_{3a}$), which agree in magnitude with the generally known SSCC values for axial and equatorial protons.

In the IR spectra of the 3-hydroxyflavones (3) taken in potassium bromide tablets the signals of the hydroxy groups appeared in the 3292-3332 cm^{-1} region and those of the carbonyl groups at 1630-1633 cm^{-1}.

In the PMR spectra of compounds (3), the signals of the OH-3 groups appeared in the 9.4-10 ppm region. The H-5 aromatic protons of the chromone rings gave peaks in the 7.9-8.0 region, and the H-7 and H-8 protons at 7.7-7.9 and 7.8 ppm, respectively.

Biological tests of the compounds obtained have shown that the 3-hydroxyflavones possess a considerable hepatoprotectic and cholagogic activity.

EXPERIMENTAL

2-(1,4-Benzodioxan-8-yl)-3-hydroxy-7-methylchromanone (2) and the 2-(1,4-Benzodioxan-8-yl)-3-hydroxychromones (3a-e). Method A. A solution of 3 mmole of a chalcone (1a-e) in 20 ml of methanol was treated with 5 ml of a 4 N solution of caustic soda and 1.3 ml of a 30% solution of hydrogen peroxide. The reaction mixture was held at room temperature for 48 h, and was then diluted with water and neutralized with dilute hydrochloric acid to pH 7. The precipitate

that deposited was filtered off and, by means of fractional crystallization, the 3-hydroxychromanone (2) and the 3-hydroxychromones (3a-e) were obtained. Under analogous conditions, the chalcone (1a) gave only the 3-hydroxychromone (3a).

Method B. With cooling and stirring, 5 ml of a 30% solution of hydrogen peroxide was added to a solution of 1.6 mmole of the appropriate chalcone (1b, d, e) and 0.75 ml (7.3 mmole) of diethylamine in 10 ml of dioxane. The reaction mixture was held at room temperature for 24-48 h and was then diluted with water (50 ml), and the precipitate that deposited was filtered off and washed with water, and the products were obtained in the individual state by means of fractional crystallization.

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