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SYNTHETIC ANALOGS OF NATURAL FLAVOLIGNANS. II. A NEW SYNTHESIS OF BENZODIOXEPANE ANALOGS OF SILANDRIN AND HYDNOCARPIN

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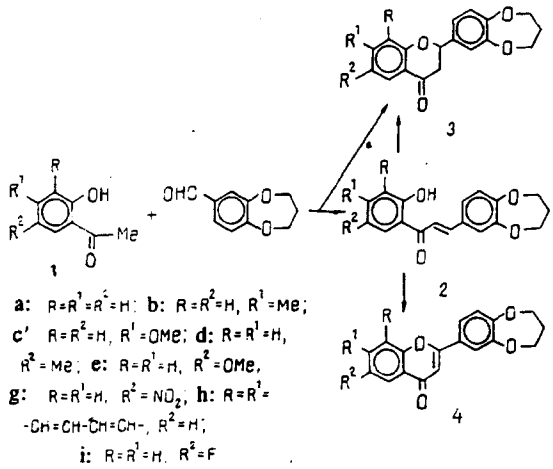
Benzodioxepane analogs of chalcones have been obtained from which analogs of natural flavolignans – silandrin and hydnocarpin – have been synthesized. The PMR spectra of the new substances are given and are discussed.

We have previously [1] given information on the synthesis of 1,4-benzodioxane analogs of silandrin and hydnocarpin and have reported [2-4] the synthesis of 1,4-benzodioxane and 1,5-benzodioxepane analogs of flavonoids of various types. In the present paper we give the results of investigations on the synthesis of new benzodioxepane analogs of silandrin and hydnocarpin and also of flavonoids synthesized previously by other methods.

As the initial compounds we took the chalcones (2), which we obtained by the Claisen–Schmidt condensation [5] of the appropriate acetophenones and 7-formyl-1,5-benzodioxepane (method A), and also by a method involving the use of DMFA as solvent and powdered caustic potash as catalyst [6] (method B).



In the first case, the condensation of ketones (1e, g) with 7-formyl-1,5-benzodioxepane gave a mixture of the chalcones (2e, g) and the flavones (3e, g). These mixtures were separated by column chromatography on silica gel. In the second case, all the chalcones (2a-h) were obtained with good yields and in a short time (about 10 min).

The benzodioxepane chalcone analogs (2) are yellow or orange crystalline substances readily soluble in organic solvents. The compounds (2) that we had obtained previously [4] were isomerized in glacial acetic acid to the corresponding benzodioxane analogs of silandrin – the flavonones (3) (method B) The mixtures of chalcones (2) and flavanones (3) were separated by column chromatography on silica gel.

The oxidation of the chalcones (2) with selenium dioxide in amyl alcohol [7] or by DMSO in the presence of catalytic amounts of iodine [8] formed the benzodioxepane flavone analogs (4c, d, g, h, i) with satisfactory or good yields (Table 1).

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TABLE 1. Characteristics of Compounds (2-4)

Compound	Yield by method A or in [7]	Yield by method B or in [8]	mp. °C	Empirical formula	Solvent for crystallization
2a		53	108—109	$C_{18}H_{16}O_4$	EtOH
2b		46.3	89—91	$C_{19}H_{18}O_4$	EtOH
2c		61.3	118—120	$C_{19}H_{18}O_5$	C_6H_6/ hexane
2e	14.7	35.1	67—68	$C_{19}H_{18}O_5$	Hexane
2g	33.7		161—162	$C_{18}H_{15}NO_6$	EtOAc
2h	30.6	48.7	140—141	$C_{22}H_{18}O_4$	MeOH
3a		52.6	94—96	$C_{18}H_{16}O_4$	MeOH
3b		71.8	93—94	$C_{19}H_{18}O_4$	EtOAc/ hexane
3c		85.4	88—89	$C_{19}H_{18}O_5$	EtOH
3e	36.3	69.3	152—153	$C_{19}H_{18}O_5$	MeOH
3g	20	72.1	165—166	$C_{18}H_{15}NO_6$	EtOAc
4a		60.5	130—132	$C_{18}H_{14}O_4$	EtOAc/ hexane
4c	37.0	61.7	162—163	$C_{19}H_{16}O_5$	EtOH/H_2O
4d	49.6	79.3	137—138	$C_{19}H_{16}O_4$	EtOH
4g		79.6	215—216	$C_{18}H_{13}NO_6$	EtOAc
4h		38	175—176	$C_{22}H_{16}O_4$	EtOH
4i		51.3	189—190	$C_{18}H_{13}FO_4$	EtOH

TABLE 2. PMR Spectra ($CDCl_3$: δ, ppm; J, Hz) of the 1,5-Benzodioxepane Flavone Analogs (4)

Compound	Protons of the chromone ring				
	H-3, s	H-5	R^2-6	R^1-7	R-8
4c	6.66	8.12 d, (J=8.59)	6.98 d.d, (J=8.59;2.9)	3.92 s	6.93 d, (J=2.9 Hz)
4d	6.69	7.98 d, (J=2.9)	2.44 s	7.48 d.d, (8.54; 2.9)	7.48 d, (J=8.54)
4g	6.97	8.70 d, (J=2.9)	—	8.53 d.d, (8.5; 2.9)	7.98 d, (J=8.5 Hz)
4h	6.86	8.17 d	7.10 d	7.5—7.8 (m, 3H, H-7, H-8, H-9), 8.59 (d.d, 1H, J=8.8; 2.9, H-10)	
4i	6.70	7.85 d, (J=2.9)	—	7.0—7.7 m	7.0—7.7 m

Compound	Benzodioxepane protons			
	H-6, d J=2.0 Hz	H-8, d.d, J=8.5; 2.0 Hz	H-9, d, J=8.5 Hz	$O(CH_2)_3O$ t.q J=5.8 Hz
4c	7.53	7.48	7.06	4.32; 2.26
4d	7.43	7.48	7.02	4.30; 2.24
4g	7.66	7.66	7.09	4.26; 2.24
4h	7.5—7.8 m	7.5—7.8 m	7.5—7.8 m	4.35; 2.28
4i	7.0—7.7 m	7.0—7.7 m	7.0—7.7 m	4.31; 2.26

The time of cyclization of the chalcones when DMSO was used as the oxidant was considerably shorter and the yields of flavanones were higher than when selenium dioxide was used.

The structures of compounds (2-4) were shown by PMR (Table 2). The PMR spectra of chalcones (2e, g, h) contained the signals of olefinic protons with chemical shifts in the 7.0-8.0 ppm region. The signals of the hydrogen atoms of the hydroxy groups in compounds (2e, g, h), which take part in the formation of intramolecular hydrogen bonds, were observed at 12.4-14.9 ppm.

The PMR spectra of the flavanones (3e, g) had characteristic signals in the 5.3-5.8 and 2.8-3.4 ppm regions.

In the PMR spectra of compounds (4) there were peaks corresponding to the chromone and benzodioxane rings. The most characteristic were the signals of the H-3 and H-5 protons of the benzene ring (6.7-8.8 ppm). The signals of the propylenedioxy group had the form of a triplet (4.3 ppm) and a quintet (2.2-2.3 ppm).

Preliminary results have shown that some representatives of the chalcones, flavanones, and flavones possess considerable hepatoprotective and cholagogic activities.

EXPERIMENTAL

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

3-(1,5-Benzodioxepan-7-yl)-1-(2-hydroxyphenyl)propen-1-ones (2e, g, h). Method A. A hot solution of 20 mmole of the appropriate acetophenone (1e, g, h) in alcohol was treatd with 3.56 g (20 mmole) of 7-formyl-1,5-benzodioxepane and 4.7 ml of a 50% solution of caustic soda. The reaction mixture was held at room temperature for 20-30 h. The precipitate was suspended and acidified with acetic acid to neutrality. The product was filtered off, and the mixture of chalcone and flavanone was separated by column chromatography on silica gel in benzene. The individual compounds were crystallized from suitable solvents.

Method B. A solution of 20 mmole of a 2-hydroxyacetophenone (1a, b, c, e, g, h) and 20 mmole of 7-formyl-1,5-benzodioxepane in 50 ml of DMFA was treated with 4.55 g of finely ground caustic potash, and the mixture was boiled with stirring for 10 min. The precipitate was suspended in water, the suspension was neutralized with hydrochloric acid, and the resulting precipitate was filtered off. If TLC showed the presence a flavanone in the products, the mixture was separated with the aid of column chromatography.

PMR spectrum ($CDCl_3$, δ, ppm): compound (2e) 12.44 (s, 1H, OH-2), 6.91 (d, 1H, J = 9 Hz, H-3), 7.13 (d.d, 1H, J = 9.0; 2.9 Hz, H-4), 3.83, (s, 3H, CH_3O-5), 7.32 (d, 1H, J = 2.9 Hz, H-6), 7.81, 7.44 (d.d, 2H, J = 15.26 Hz, COOH=CH); benzodioxepane protons: 7.29 (d, 1H, J = 2.0 Hz, H-6), 7.22 (d.d, 1H, J = 8.0; 2.0 Hz, H-8), 6.98 (d, 1H, J = 8.0 Hz, H-9), 4.29 (t, 4H, CH_2-2, CH_2-4), 2.17 (q 2H, CH_2-3).

Compound (2g) (in DMSO-d_6) 12.92 (s, 1H, OH-2), 7.16 (d, 1H, J = 9.0 Hz, H-3), 8.33 (d.d, J = 9.0; 2.9 Hz H-4), 8.80 (d, 1H, J = 2.9 Hz, H-6), 7.76 (s, 2H, COCH=CH); benzodioxepane protons: 7.58 (d, 1H, J = 2 Hz, H-6), 7.45 (d.d, 1H, J = 8.0; 2.0 Hz, H-8), 7.01 (d, 1H, J = 8.0 Hz, H-9), 4.19 (t, SSCC,* 4H, CH_2-2, CH_2-4), 2.14 (q, SSCC,* 2H, CH_2-3).

Compound (2h) (in $CDCl_3$) 14.90 (s, 1H, OH-2), 8.46 (d.d, SSCC,* 1H, H-3), 7.4-7.8 (m, 5H, H-4, H-5, H-6, H-7, H-8), 7.57, 7.90 (d.d, 2H, J = 15.26 Hz, COCH=CH); benzodioxepane protons: 7.31 (d, 1H, J = 2.0 Hz, H-6), 7.26 (d.d, 1H, J = 8.0; 2.0 Hz, H-8), 7.3 (d, 1H, J = 8.0 Hz, H-9), 4.27 (t, 4H, J = 5.87 Hz, CH_2-2, CH_2-4), 2.22 (q, 2H, SSCC,* J = 5.87 Hz, CH_2-3).

2-(1,5-Benzodioxepan-7-yl)chromanones (3a-c, e, g). Method B. A solution of 2 mmole of a 2'-hydroxychalcone (2a-c, e, g) 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 spectrum ($CDCl_3$, δ, ppm): compound (3e) 5.33 (d.d, 1H, J = 11.96; 4.39 Hz, H_a-2), 3.05 (d.d, 1H, J = 17.09; 11.96 Hz, H_a-3), 2.83 (d.d, 1H, J = 17.09; 4.39 Hz, H_e-3), 7.34 (d, J = 2.93 Hz, H-5), 3.81 (s, 3H, CH_3O-6), 6.90 (d.d, 1H, J = 8.5; 2.93 Hz, H-7), 7.20 (d, 1H, J = 8.5 Hz, H-8); benzodioxepane protons: 6.9-7.2 (m, 3H, H-6, H-8, H-9), 4.24 (t, 4H, J = 5.4 Hz, CH_2-2, CH_2-4), 2.21 (q, 2H, J = 5.4 Hz, CH_2-3).

Compound (3g) 5.77 (d.d, 1H, J = 11.96; 4.39 Hz, H_a-2), 3.43 (d.d 1H, J = 17.09; 11.96 Hz, H_a-3), 2.92 (d.d, 1H, J = 17.09; 4.39 Hz, H_e-3), 8.50 (d, 1H, J = 2.93 Hz, H-5), 8.40 (d.d, 1H, J = 8.79; 2.93 Hz, H-7), 7.33 (d, 1H, J - 8.79 Hz, H-8); benzodioxepane protons: 7.17 (d, 1H, J = 2.0 Hz, H-6), 7.15 (d.d, 1H, J - 7.81; 2.0 Hz, H-8), 7.01 (d, 1H, J = 7.81 Hz, H-9), 4.15 (t, 4H, J = 5.4 Hz, CH_2-2, CH_2-4), 2.4 (q, 2H, J = 5.4 Hz, CH_2-3).

2-(1,5-Benzodioxepan-7-yl)chromones (2a, c, d, g, h, i). Method of [7]. A solution of 20 mmole of a compound (2c, d) in the minimum amount of freshly distilled amyl alcohol was treated with 6.65 g (60 mmole) of finely ground selenium dioxide, and the mixture was boiled for 20-40 h, the course of the reaction being monitored by TLC. The metallic selenium was filtered off, and the amyl alcohol was evaporated in water-pump vacuum. The residue was crystallized from a suitable solvent.

Method of [8]. Catalytic amounts of iodine were added to a solution of 10 mmole of a compound (2a, c, d, g, h, i) in 30 ml of DMSO, and the reaction mixture was boiled for 30 min. Then it as diluted twofold with water, the precipitate that deposited was filtered off, and it was washed on the filter with a 20% solution of sodium thiosulfate to eliminate traces of iodine and crystallized from a suitable solvent.

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*The actual SSCC (J) values have been omitted –Translator.

REFERENCES

1. A. Aitmambetov and V. P. Khilya, Khim. Prir. Soedin., 669 (1993).
2. Gy. Litkei, T. Patonay, R. Bognar, V. Khilya, A. Aitmambetov, A. Turov, and F. Babichev, Pharmazie, **39,** No. 11, 741 (1984).
3. V. P. Khilya, A. Aitmambetov, A. V. Turov, M. Yu. Kornilov, D. Litkei, and T. Patonai [Patonay], Khim. Geterotsikl. Soedin., No. 2, 192 (1986).
4. V. P. Khilya, D. Litkei, T. Patonai [Patonay], L. G. Grishko, A. M. Kornilov, and A. Aitmambetov, Khim. Geterotsikl. Soedin, No. 3, 319 (1989).
5. T. Patonay, Gy. Litkei, E. Peli, V. P. Khilya, and A. Aitmambetov, Pharmazie, **42,** No. 10, 662 (1987).
6. A. G. Doshi and B. J. Ghiya, Curr. Sci., **55,** No. 10, 502 (1986).
7. H. S. Mahal and H. S. Rai, J. Chem. Soc., 866 (1935).
8. A. G. Doshi, P. A. Soni, and B. J. Ghiya, Indian J. Chem., **25B,** 759 (1986).