Chemistry of Natural Compounds, Vol. 30, No. 4, 1994

SYNTHETIC ANALOGS OF NATURAL FLAVOLIGNANS. IV. SYNTHESIS OF BENZODIOXOCANE ANALOGS OF SILANDRIN AND HYDNOCARPIN

V. P. Khilya and A. Aitmambetov

UDC 547.814.5

1,6-Benzodioxocane analogs of chalcones have been synthesized. From them have been obtained benzodioxocane analogs of silandrin and hydnocarpin. The PMR spectra of the substances synthesized are given and are discussed.

The aim of the present work was to study the influence of an expansion of the benzodioxane rings of silandrin and hydnocarpin and also of a simplification of the molecular structures of these natural substances on the possibility of obtaining flavonoids and on the properties of those synthesized [1-3].

As the initial compounds for the formation of the synthetic analogs of silandrin and hydnocarpin we took the substituted 3,4-butylenedioxychalcones (2) obtained by the alkaline condensation of the corresponding *o*-hydroxyacetophenones with 8-formyl-1,6-benzodioxocane by the method of Bognar and Litkei [4].

It must be mentioned that in all cases except one, two products were formed in the course of condensation: a chalcone (2a-e, f) and a flavanone (3a-e) (a silandrin analog). The exception was the reaction of a ketone having a methoxy substituent in position 4 of the benzene ring. The mixtures obtained were separated by column chromatography on Silpearl silica gel (with benzene as the eluent).

TABLE 1. Characteristics of Compounds (2-4)

Compound	Yield, %	mp, °C	Empirical formula	Solvent for crystallization
2a	14	91—93	$C_{19}H_{18}O_4$	Hexane
2b	7.3	114—116	$C_{19}H_{17}ClO_4$	Hexane
2c	37.4	175—176	$C_{19}H_{17}NO_6$	EtOAc
2d	9.8	94—96	$C_{20}H_{20}O_4$	Hexane
2e	17.6	79—80	$C_{20}H_{20}O_5$	Hexane
2f	44.1	119—121	$C_{20}H_{20}O_5$	iso-PrOH
3a	8.1	104—106	$C_{19}H_{18}O_4$	EtOH
3b	27.6	95—97	$C_{19}H_{17}ClO_4$	EtOH
3c	7.9	161—162	$C_{19}H_{17}NO_6$	EtOH
3d	23.1	91—93	$C_{20}H_{20}O_4$	EtOH
3e	14.7	138—140	$C_{20}H_{20}O_5$	EtOH
4c	33	206—208	$C_{19}H_{15}NO_6$	EtOAc
4f	58	114—115	$C_{20}H_{18}O_5$	EtOH

Taras Shevchenko Kiev University, Ukraine. KIEN, Karakalpak Division, Academy of Sciences of the Republic of Uzbekistan, Nukus. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 490-493, July-August, 1994. Original article submitted August 27, 1993.

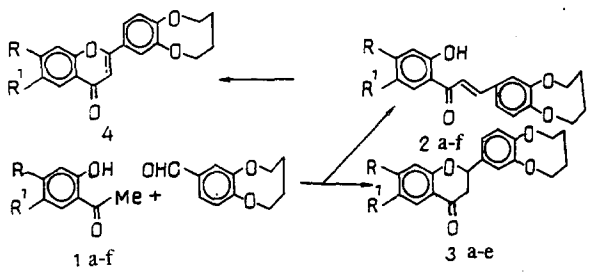
0009-3130/94/3004-0449$12.50

TABLE 2. PMR Spectra ($CDCl_3$; δ, ppm; J, Hz) of the Benzodioxocane Chalcone Analogs (2)

Compound	Protons of the phenolic moiety						Benzodioxocane protons				
	OH-2, s	H-3	R-4	R^1-5	H-6	COCH=CH, (15Hz,) d.d	H-7 d, (2.0)	H-9 d.d, (8; 2.0)	H-10, d, (J=8Hz,)	CH_2-2, CH_2-5, t.t,	CH_2-3, CH_2-4, s
2a	12.95	6.95 d.d, (8.2; 2.2)	7.45 t.d,	7.32 t.d,	7.90 d.d,	7.50; 7.86	7.02	7.02	6.92	4.51; 4.50	1.93
2b	12.82	6.98 d, (8.2)	7.44 d.d, (8.2; 2.0)	—	7.86 d, (2.0)	7.39; 7.86	7.34	7.30	6.98	4.51; 4.31	1.94
2c	13.71	7.11 d, (9.0)	8.37 d.d, (9.0; 3.0)	—	8.88 d, (3.0)	7.51; 7.96	7.40	7.40	7.02	4.53; 4.32	1.95
2d	12.72	6.91 d, (8.2)	7.30 d.d, (8.2; 2.0)	2.34 s	7.66 d, (2.0)	7.50; 7.81	7.33	7.30	6.98	4.48; 4.32	1.92
2e	12.43	6.93 d, (8.2)	7.28 d.d, (8.2; 2.0)	3.83 s	7.73 d, (2.0)	7.46; 7.85	7.31	7.24	7.05	4.48; 4.31	1.93
2f	13.48	6.45 d, (22.0)	3.85 s	6.49 d.d, (9.0; 2.0)	7.82 d, (9.0)	7.43; 7.81	7.30	7.28	6.98	4.48; 4.31	1.93

TABLE 3. PMR Spectra ($CDCl_3$; δ, ppm; J, Hz) of the Benzodioxocane Flavanone Analogs (3)

Compound	Chromanone protons							Benzodioxocane protons			
	H_a-2, d.d	H_a-3, d.d	H_e-3, d.d	H-5	R^1-6	R-7	H-8	H-7, H-9, m	H-10, d (8.0)	CH_2-2, s	CH_2-4, s
3a	5.38 (12.2; 3.9)	3.12 (12.2; 16.6)	2.87 (3.9; 16.6)	7.30 d.d, (9.0; 3.0)	7.0—7.12	7.51 t.d,	7.0—7.12 m	7.0—7.12	7.08	4.36	1.93
3b	5.37 (12.2; 4.4)	3.13 (12.2; 16.6)	2.84 (4.4; 16.6)	7.88 d, (3.0)	—	7.44 d.d, (9.0; 3)	6.9—7.1 m	6.9—7.1	6.9—7.1 m	4.36	1.92
3c	66.06 (12.7; 2.9)	3.39 (12.7; 17.1)	2.87 (2.9; 17.1)	8.52 d, (3.0)	—	8.40 d.d, (9; 3.0)	7.33 d, (9.0)	7.0—7.2	7.0—7.2 m	4.27	1.82
3d	5.34 (12.7; 4.4)	3.09 (12.7; 17.1)	2.79 (4.4; 17.1)	7.72 d, (3.0)	2.32 s	7.31 d.d, (9.0; 3.0)	7.05 d, (9.0)	7.02 m'	6.93	4.35	1.92
3e	5.33 (12.2; 3.91)	3.06 (12.2; 18.1)	2.85 (3.91; 18.1)	7.34 d, (2.0)	3.81 s	7.0—7.2 m	7.0—7.2 m	7.0—7.2 m	6.97	4.35	1.92



1-4 a: R=R¹=H; b: R=H, R¹=Cl; c: R=H, R¹=NO₂; d: R=H, R¹=Me; e: R=H, R¹=OMe; f: R=OMe, R¹=H

The benzodioxocane chalcone analogs (2a-f) were yellow or orange crystalline substances (Table 1).

The chalcones (2c, f) were converted by oxidative cyclization in DMSO in the presence of catalytic amounts of iodine into the 2-(1,6-benzodioxocan-8-yl)chromones (4c, f), which are hydnocarpin analogs (Table 1).

In contrast to the initial chalcones, the 3',4'-butylenedioxyflavanones (3) and the flavones (4) were predominantly colorless crystalline substances.

In the PMR spectra of the chalcones (Table 2) the signals of the hydroxylic protons were observed in the weakest field (12.4-13.6 ppm). The olefinic protons formed two doublets at 7.4-7.5 and 7.8-7.9 ppm with spin-spin coupling constants of 15-16 Hz, showing the transoid configuration of the chalcones under investigation

In the PMR spectra of the flavones (3) the SSCCs ($J_{2a,3a}$ = 12.7; $J_{2a,3e}$ = 3.9; $J_{3a,3e}$ = 17.1 Hz (see Table 3) show that the H_{2a} proton was oriented axially and the benzodioxocane residue on the same carbon atom equatorially. Consequently, the pyrone ring had the half-chair conformation.

In the PMR spectra of the flavones (4), in addition to the signals of the H-3 and H-5 protons of the chromone nucleus, located at 6.6-6.8 and 8.1-9.1 ppm, respectively, the signals of the H-8 proton of the benzodioxocane nucleus was characteristic. It was located at 7.0-7.5 ppm.

Thus, new types of chalcones and the corresponding flavones have been obtained for the first time by the alkaline condensation of 8-formyl-1,6-benzodioxocane with substituted 2-hydroxyacetophenones, and the transoid configuration of the olefinic fragment in the former and the half-chair conformation of the pyrone ring in the latter have been determined by the PMR method. The benzodioxocane chalcone derivatives have been converted by oxidative cyclization into the corresponding flavone hydnocarpin derivatives. A study of the biological activities of the new hydnocarpin analogs has shown that some of them possess a well-marked hepatoprotective and cholagogic activity.

EXPERIMENTAL

The conditions for recording the spectra have been described in [2].

3-(1,6-Benzodioxocan-8-yl)-1-(2-hydroxyphenyl)propen-1-ones(2a-f)and2-(1,6-Benzodioxocan-8-yl)chromanones (3a-e). A hot solution of 20 mmole of the appropriate 2-hydroxyacetophenone in the minimum amount of ethanol was treated with 3.84 g (20 mmole) of 8-formyl-1,6-benzodioxocane and 4.7 ml of a 50% solution of caustic soda. The reaction mixture was kept at room temperature for 20 h. A suspension in water of the resulting precipitate was neutralized with hydrochloric acid. The product was filtered off, and the mixture of chalcone and flavanone was separated by column chromatography on silica gel in benzene.

2-(1,6-Benzodioxocan-8-yl)chromones (4c, f). A catalytic amount of iodine was added to a solution of 10 mmole of a chalcone (2c, f) in 30 ml of DMSO, 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 and was then recrystallized from a suitable solvent.

PMR spectrum ($CDCl_3$, δ, ppm): compound (4c) 7.66 (s, 1H, H-3), 9.35 (d, 1H, J = 3.0 Hz; H-5), 8.48 (d.d, 1H, J = 9.0; 3.0 Hz, H-7), 7.05 (d, 1H, J = 9.0 Hz, H-8); benzodioxocane protons: 7.62 (d, 1H, J = 2 Hz, H-7), 7.58 (d.d, 1H, J = 8.0; 2.0 Hz, H-9), 7.65 (d, 1H, J = 8.0 Hz, H-10), 4.33; 4.57 (t.t, 4H, CH_2-2, CH_2-5), 1.94 (s, 4H, CH_2-3, CH_2-4).

Compound (4f) 6.66 (s, 1H, H-3), 8.12 (d, 1H, J = 9.0 Hz; H-5), 7.51 (d.d 1H, J = 9.0; 2.0 Hz, H-6), 3.93 (s, 3H, OMe-4), 7.56 (d, 1H, J = 2.0 Hz, H-8); benzodioxocane protons: 6.94 (d, 1H, J = 2.0 Hz, H-7), 6.97 (d.d, 1H, J = 8.5; 2.0 Hz, H-9), 7.06 (d, 1H, J = 8.5 Hz, H-10), 4.34; 4.52 (t.t, 4H, CH_2-2, CH_2-5), 1.95 (s, 4H, CH_2-3, CH_2-4).

REFERENCES

1. A. Aitmambetov, D. M. Zakharik, and V. P. Khilya, Khim. Prir. Soedin., 484 (1994) [in this issue].
2. A. Aitmambetov and V. P. Khilya, Khim. Prir. Soedin., 669 (1993).
3. A. Aitmambetov and V. P. Khilya, Khim. Prir. Soedin., 480 (1994) [in this issue].
4. R. Bognar and Gy. Litkei, Acta Chim. Acad. Sci. Hung., **67,** 83 (1971).