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

SYNTHETIC ANALOGS OF NATURAL FLAVOLIGNANS. V. A NEW SYNTHESIS OF 6-HALOGENO-1,3-BENZODIOXANE ANALOGS OF SILANDRIN AND HYDNOCARPIN

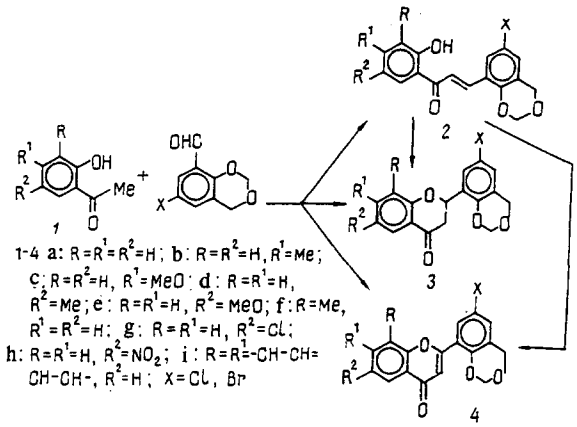
A. Aitmambetov, S. N. Shinkaruk
S. P. Bondarenko, and V. P. Khilya

UDC 547.814.5

6-Halogeno-1,3-benzodioxane analogs of chalcones have been synthesized by various methods. Flavanone and flavone analogs of silandrin and hydnocarpin have been obtained from them. The structures of the new flavonoids have been shown by their PMR spectra.

Continuing investigations begun previously [1-5], we have attempted to find a more effective method of synthesizing 6-halogeno-1,3-benzodioxane analogs of flavonoids. The results of this search are given in the present paper. The initial chalcones (2) were obtained by three methods: by the Claisen–Schmidt method (method A), by a method [6] consisting in boiling the initial ketones and 6-halogeno-8-formyl-1,3-benzodioxanes in DMFA in the presence of powdered caustic potash (method B), and by a method according to which the initial components were boiled in benzene in the presence of catalytic amounts of glacial acetic acid and piperidine with the constant elimination of water formed in the form of a binary azeotrope (benzene–water) [7] (method C).

A comparison of the results in each case has shown that the synthesis of chalcone (2) by method B is more suitable, since this excludes the formation of other compounds. An advantage of method B is the speed of obtaining the desired chalcones (10 min). However, depending on the time of holding the reaction mixture, their yields varied from 50 to 85%. The prolonged heating (up to 4 h) of a the reaction mixture led to the complete conversion of the chalcones into the flavanones (3b, g) and the flavones (4b, c, g). Performing this condensation in a current of nitrogen led to mixtures of the chalcone (2) and the flavanone (3) with yields of 9.7-12 and 38-44%, respectively (Table 1).



On being boiled in glacial acetic acid for 100-150 h, the chalcones (2a, b, d, g, h,) were converted into the corresponding flavanones (3a, b, d, g, h) (C) – silandrin analogs. The mixtures of compounds obtained by method b were separated by fractional crystallization or column chromatography.

KIEN Karakalpak Division, Academy of Sciences of the Republic of Uzbekistan, Nukus. Taras Shevchenko Kiev University, Ukraine. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 494-498, July-August, 1994. Original article submitted August 27, 1993.

0009-3130/94/3004-0453$12.50

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	4 h				
2a X=Cl				65.7	149—150	$C_{17}H_{13}ClO_4$	EtOH
2b X=Cl		54.3	9.7*	81.8	175—176	$C_{18}H_{15}ClO_4$	EtOH
2c X=Cl		79	12.3*	57.1	184—185	$C_{18}H_{15}ClO_5$	EtOH
2d X=Br	67.5	50.3		69.8	195—196	$C_{18}H_{15}BrO_4$	EtOAc
2e X=Br	53				171—173	$C_{18}H_{15}BrO_5$	EtOAc
2f X=Cl	49.8				173—174	$C_{18}H_{15}ClO_4$	EtOAc
2g X=Br		85.4		78.6	194—195	$C_{17}H_{12}BrClO_4$	EtOAc
2h X=Cl	29			78.9	228—229	$C_{17}H_{12}ClNO_5$	C_6H_6
2h X=Br	33				231—232	$C_{17}H_{12}BrNO_5$	EtOAc
2i X=Cl	38.3	51.3			195—197	$C_{21}H_{17}ClO_4$	EtOAc
3a X=Cl				68.2	169—170	$C_{17}H_{13}ClO_4$	MeOH
3b X=Cl			9.7(38*)	72.7	180—181	$C_{18}H_{15}ClO_4$	MeOH
3d X=Br			12.5	33.2	149—151	$C_{18}H_{15}BrO_4$	EtOH
3g X=Cl			12.1(44*)	50.3	193—194	$C_{17}H_{12}Cl_2O_4$	EtOH
3g X=Br				69.1	244—245	$C_{17}H_{12}BrClO_4$	EtOAc
3h X=Cl	37.7			42.3	232—233	$C_{17}H_{12}ClNO_4$	C_6H_6/EtOAc
3h X=Br	39.1				246—247	$C_{17}H_{12}BrNO_4$	EtOAc
4b X=Cl			29.4		230—231	$C_{18}H_{13}ClO_4$	EtOAc
4c X=Cl			38.3		211—212	$C_{18}H_{13}ClO_5$	EtOAc
4g X=Cl			37.1		223—224	$C_{17}H_{10}Cl_2O_4$	EtOAc
4h X=Br	83.7				286—288	$C_{17}H_{10}BrNO_6$	EtOAc
4h X=Cl	81				>255	$C_{17}H_{10}ClNO_6$	DMFA
4i X=Cl	79				261—262	$C_{21}H_{13}ClO_4$	EtOAc

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

When the chalcones (2h, i) were oxidized with dimethyl sulfoxide in the presence of catalytic amounts of iodine, the flavans (3h, i) were formed in good yield (method A).

The structures of the compounds (2-4) obtained were shown by PMR (Tables 2 and 3). In the PMR spectra of the chalcones (2) the signals of the olefinic protons were observed at 7.0-8.0 ppm. The values of the SSCC (J = 15 Hz) confirmed the transoid configurations of the chalcones obtained. The hydroxy protons absorbed at 12.3-14.8 ppm.

The PMR spectra of the flavanones (3) had characteristic signals in the 2.7-5.9 ppm (Table 3).

The PMR spectrum of the flavones (4) contained signals corresponding to the chromone and benzodioxane rings.

Thus, 6-halogeno-1,3-benzodioxane analogs of chalcone have been synthesized by various methods, and from these have been obtained flavanones and flavones – compounds related to silandrin and hydnocarpin, respectively. We have proposed a one-pot method of obtaining 1,3-benzodioxane analogs of flavanones and flavones. This feature of the performance of the reaction can be used as one of the methods for obtaining flavanoids. The study of the biological properties of the 1,3-benzodioxane flavonoid analogs has shown that some representatives of these compounds possess cholagogic activity.

EXPERIMENTAL

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

3-(6-Halogeno-1,3,benzodioxan-8-yl)-1-(2-hydroxyphenyl)propenones (2a-i). Method A. A hot solution of 20 mmole of a 2-hydroxyacetophenone (Id, e, f, h, i) in alcohol was treated with 20 mmole of the appropriate 8-formyl-1,3-benzodioxane and 4.7 ml of a 50% solution of caustic soda. The reaction mixture was held at room temperature for 20-40 h. A suspension of the resulting precipitate in water was brought to neutrality by the addition of acetic acid, and then the product was filtered off and crystalized from a suitable solvent.

Method B. A solution of 20 mmole of a 2-hydroxyacetophenone (1b, c, d, g, h) and 20 mmole of the appropriate 8-formyl-1,3-benzodioxane in 50 ml of dimethylformamide was treated with 4.55 g of finely ground caustic potash, and the mixture was boiled with stirring for from 10 min to 4 h. A suspension of the resulting precipitate in water was neutralized

TABLE 2. PMR Spectra (δ, ppm J, Hz) of 6-Halogeno-1,3- benzodioxane Analogs of Chalcones.

Compound	Protons of the phenol moiety						Benzodioxane protons			
	OH-2, s	R-3	R^1-4	R^2-5	H-6	COCH=CH d.d (15 Hz)	H-5, d (2.0)	H-7, d (2.0)	CH_2-2, s	CH_2-4, s
2d	12.58	6.92 d, (9.0)	7.31 d.d, (9.0; 3.0)	2.36 s	7.64 d (3.0)	7.67; 8.01	7.12	7.64	5.33	4.88
2e	12.33	6.96 d, (9.0)	7.15 d.d, (9.0; 3.0)	3.85 s	7.33 d, (3.0)	7.62; 8.01	7.12	7.62	5.34	4.90
2f	13.11	2.33 s	7.38 d.d, (9.0; 3.0)	6.85 t.d	7.76 d.d, (9.0; 3.0)	7.72; 8.03	7.00	7.49	5.35	4.90
2h X=Br	12.50	7.18 d, (9.0)	8.34 d.d, (9.0; 3.0)	—	8.73 d, (3.0)	7.90 s	7.27	7.90	5.39	4.91
2h X=Cl	12.60	7.18 d, (9.0)	8.34 d.d, (9.0; 3.0)	—	8.73 d, (3.0)	7.91 s	7.41	8.41	5.39	4.91
2i	14.82	8,50 d.d,	7.4—7.9 m (H-5, H-6, H-7,), 7.63 (t.d, H-4), 7.83 (d, H-8)			7.29; 8.12	7.02	7.53	5.37	4.90

*The PMR spectra of compounds (2h, X = Cl, Br) were measured in DMSO-d_6, and those of the other compounds in $CDCl_3$.

TABLE 3. PMR Spectra ($CDCl_3$; δ, ppm; J, Hz) of the 6-Halogeno-1,3-benzodioxane Flavanone Analogs

Compound	Chromanone protons							Benzodioxane protons.			
	H_a-2, d.d, (11.2; 4.5)	H_a-3, d.d, (11.2; 17.5)	H_e-3, d.d, (4.5; 17.5)	H-5	R^2-6	R^1-7	R-8	H-5, d, (2.0)	H-7, d, (2.0)	CH_2-2, s	CH_2-4, s
3b	5.69	2.93	2.79	7.80 d, (8.0)	6.90 d.d, (8.0; 2.0)	2.38 s	6.90 d (2.0)	6.90	7.51	5.25	4.88
3d	5.17	2.92	2.75	7.70 d, (2.0)	2.32 s	7.32 d.d, (8.0; 2.0)	7.00 d (8.0)	7.08	7.64	5.24	4.88
3g X=Br	5.70	2.97	2.82	7.90 d, (2.3)	—	7.47 d.d, (8.3; 2.3)	7.05 d (8.3)	7.14	7.64	5.27	4.89
3h X=Br	5.95	3.37	2.95	8.54 d, (2.5)	—	8.38 d.d, (9.0; 2.5)	7.34 d (9.0)	7.34	7.61	5.32	4.92

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

Method C. A solution of 20 mmole of a 2-hydroxyacetophenone (Ia-d, g, h) and 20 mmole of the appropriate 8-formyl-1,3-benzodioxane in 150 ml of dry benzene was boiled in the presence of 1.2 ml of piperidine and 0.4 ml of glacial acetic acid for 20-30 h with the constant elimination of the water produced in the form of a binary azeotrope (benzene–water). Then the solvent was distilled off in water-pump vacuum, and the residue was washed with water and crystallized from a suitable solvent.

2-(6-Halogeno-1,3-benzodioxan-6-yl)chromanones (3a, b, g, h). Method C. A solution of 2 mmole of a 2′-hydroxychalcone (2a, b, g, h) in 50 ml of acetic acid was boiled for 100-150 h. Then the solvent was distilled off and the residue was separated by fractional crystalization or column chromatography.

2-(6-Halogeno-1,3-benzodioxan-8-yl)chromones (4h, i). A catalytic amount of iodine was added to a solution of 10 mmole of a 2′-hydroxychalcone (2h, i) in 30 ml of DMSO, and the reaction mixture was boiled for 15-30 min. Then it was diluted twofold with water, and the precipitate that deposited was filtered off and washed on the filter with a 20% solution of sodium thiosulfate to eliminate traces of iodine and was recrystalized from a suitable solvent.

PMR spectrum (DMSO-d_6, δ, ppm): compound (4h, X = Br) 7.40 (s, 1H, H-3), 7.89 (d, 1H, J = 2.5 Hz, H-5), 7.47 (d.d, 1H, J = 8.5; 2.5 Hz, H-7), 7.35 (d, 1H, J = 8.5 Hz, H-8); benzodioxane protons: 7.47 (d, 1H, J = 2.0 Hz, H-5), 7.73 (d, 1H, J = 2.0 Hz, H-7), 5.41 (s, 2H, CH_2-2), 4.93 (s, 2H, CH_2-4).

Compound (4h, X = Cl) (in $CDCl_3$) 6.99 (s, 1H, H-3), 7.95 (d, 1H, J = 1.7 Hz, H-5), 6.99 (d.d, 1H, J = 8.0; 1.7 Hz, H-7), 7.46 (d, 1H, J = 8.0 Hz, H-8); benzodioxane protons: 7.20 (d, 1H, J = 1.4 Hz, H-5), 7.79 (d, 1H, J = 1.4 Hz, H-7), 5.32 (s, 2H, CH_2-2), 4.88 (s, 2H, CH_2-4).

Compound (4i) (in $CHCl_3$) 7.12 (s, 1H, H-3), 8.14 (d, 1H, J = 9 Hz, H-5), 7.90 (m, 4H, H-6, H-7, H-8, H-9), 8.51 (d.d, 1H, H-10); benzodioxane protons: 7.72 (d, 1H, J = 2.0 Hz, H-5), 7.85 (d, 1H, J = 2.0 Hz, H-7), 5.36 (s, 2H, CH_2-2), 4.95 (s, 2H, CH_2-4).

REFERENCES

1. V. P. Khilya and A. Aitmambetov, Khim. Prir. Soedin., 490 (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. A. Aitmambetov, D. M. Zakharik, and V. P. Khilya, 484 (1994) [in this issue].
5. V. P. Khilya, Kh. Al' Budi [H. Al Budy], A. Aitmambetov, L. G. Grishko, A. Turov, D. M. Zakharik, and D. Litkei, Khim. Geterotsikl. Soedin., No. 7, 879 (1992).
6. A. G. Doshi and B. J. Ghiya, Curr. Sci., **55**, No. 10, 502 (1986).
7. S. Kumar and S. Rastogi, Indian J. Chem., **B26,** No. 10, 968 (1987).