When the reaction was complete, the benzene was evaporated and the required product separated on a column as described above. Yields of products V-VII were 1.07, 1.1, and 1.1 g, respectively.

Compounds V-X were identified from their PMR spectra and elemental analysis data. PMR spectra were recorded at 20°C on a Tesla BS-497 spectrometer (100 MHz) in $(CD_3)_2CO$, with HMDS as internal standard.

6-(N,N-Dimethylamino)benzo-1,4-dioxane (V, $C_{10}H_{13}NO_2$): n_D^{20} 1.5685. PMR spectrum: 2.64 [6 H, m, $(CH_3)_2N$]; 4.03 (4 H, s, $2CH_2O$); 6.04-6.22, 6.46-6.68 ppm (3 H, m, C_6H_3).

6-(N,N-Diethylamino)benzo-1,4-dioxane (VI, $C_{12}H_{17}NO_2$): n_D^{20} 1.5518. PMR spectrum: 0.88 (6 H, t, $2CH_3$), 3.1 [4 H, q, $(CH_2)_2$]; 3.96 (4 H, s, $2CH_2O$); 5.95-6.16, 6.46-6.60 ppm (3 H, m, C_6H_3).

6-(N,N-Dipropylamino)benzo-1,4-dioxane (VII, $C_{14}H_{21}NO_2$): n_D^{20} 1.5430. PMR spectrum: 0.76 (6 H, t, $2CH_3$); 1.4 (4 H, m, $2CH_2$); 3.0 [4 H, t, $(CH_2)_2N$]; 4.0 (4 H, s, $2CH_2O$); 6.0-6.16, 6.48-6.62 ppm (3 H, m, C_6H_3).

6,7-Dichlorobenzo-1,4-dioxane (VIII, $C_8H_6Cl_2O_2$): mp 150°C. PMR spectrum: 4.23 (8 H, s, $2CH_2O$); 6.94 ppm (2 H, s, $C_6H_2Cl_2O_2$).

6-Chlorobenzo-1,4-dioxane (IX, $C_8H_7ClO_2$): bp 253-255°C. n_D^{20} 1.5620. PMR spectrum: 4.08 (4 H, s, $2CH_2O$); 6.62-6.78 ppm (3 H, m, C_6H_3).

6-Aminobenzo-1,4-dioxane (X, $C_8H_9NO_2$): n_D^{20} 1.5998. PMR spectrum (in CCl_4): 3.56 (2 H, s, NH_2); 3.98 (4 H, s, $2CH_2O$); 5.98 s, 6.32-6.48 ppm (3 H, m, C_6H_3).

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CHEMISTRY OF ISOFLAVONE HETEROANALOGS.

12.* BENZODIOXANE ANALOGS OF FLAVANONE AND ISOFLAVONE

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UDC 547.814.5'841.07:543.422.25:615.272.4

Benzodioxane analogs of chalcones were isomerized to the corresponding flavanones and isoflavones. The PMR and IR spectra of these compounds were discussed.

Silibine [2, 3] and some of its derivatives [4, 5] are well-known natural complex flavanoids, which possess considerable biological activity, for example, antihepatotoxic activity. Since silibine contains the benzodioxane fragment and such compounds with a different oxidation state have not been obtained, we undertook to synthesize and study the properties of benzodioxane analogs of some flavonoids, which are simpler than silibine, (2R,3R)-3,5,7-trihydroxy-2-[(2R*,3R*)-3-(4-hydroxy-3-methoxyphenyl)-2-hydroxymethyl-6-benzodioxane-1,4-yl]-4-chromanone. We have recently reported the synthesis of various analogs of silibine such as chalcones, flavones, and isoflavones containing the 1,4-benzodioxan-6-yl group [1]. The present communication gives further results in this study.

*For Communication 11, see [1].

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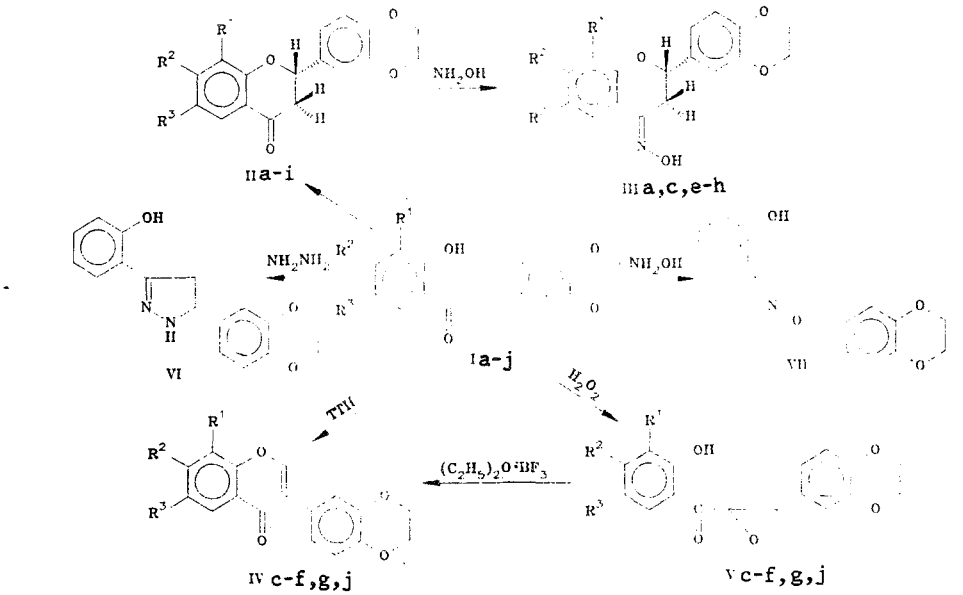
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 319-323, March, 1989. Original article submitted November 4, 1987.

Benzodioxane analogs [1] of chalcones I were obtained by isomerization and converted to the corresponding benzodioxane analogs of flavanones II. However, this conversion, which has been extensively studied for chalcones, proved difficult for their derivatives Ia-Ij. In the general case, the isomerization occurs in an acid or alkaline medium and it is impossible to predict which conditions will give greater conversion. We checked several methods for the preparation of flavanones II from 3,4-ethylenedioxy-2'-hydroxychalcones: 1) in 2 N HCl, 2) in 1.5% NaOH, and 3) in 2 N H_2SO_4. In all cases, the chromanone is formed but in quantities insufficient for its isolation from the reaction mixture by crystallization. Flavanones II were isolated after the isomerization of chalcones I on Amberlist A-21 ion-exchange resin.

It has been noted that 2'-hydroxy-5-methoxychalcone Ih is quantitatively isomerized to flavanone IIh upon recrystallization from acetic acid. The isomerizations carried out with the other chalcones showed that the flavanone derivatives II are mainly formed but we did not find a method for the rapid separation of the chalcone–flavanone mixtures, which are obtained as oils. An efficient but time-consuming method involves separation of the mixtures by chromatography on a silica gel column with benzene as the eluent.

Flavanones II are colorless, crystalline compounds with mp in the range from 76 to 181°C (Table 1). The IR spectra of flavanones II taken for the solids show the carbonyl group stretching band at 1682-1690 cm^{-1}, which indicates their chromanone structure. Additional evidence for the chromanone structure of II lies in the ready formation of oximes III in their reaction with hydroxylamine. The oxime group in the IR spectra of oximes III appears at 3260–3305 cm^{-1} (ν_{OH}) and 1618-1623 cm^{-1} ($\nu_{C=N}$) (Table 1).



I—V a-h,j R^1=H, and R^1=Cl; a,e,f,h-j R^2=H, b R^2=Cl, c,g R^2=CH_3, d R^2=OCH_3; a-d R^3=H, e,i R^3=Cl, f R^3=F, g R^3=CH_3, h R^3=OCH_3, j R^3=Br

PMR spectroscopy was used to confirm the structures of II and III. The PMR spectra of both flavanones II and their oximes show characteristic signals, whose chemical shifts lie in the vicinity of 5 and 3 ppm (Tables 2 and 3).

The coupling constants ($J_{3a,2a}$ = 13, $J_{3e,2a}$ = 3, and $J_{3a,3e}$ = 17 Hz) shows that the 2*a*-H proton is oriented axially, while the benzodioxane residue at the same carbon atom is oriented equatorially.

The reaction of chalcones I with thallium trinitrate (TTN) in methanol according to McKillop et al. [6, 7] readily gave benzodioxane analogs of isoflavanones IV in satisfactory or good yields. In previous work [1], we obtained these compounds by the rearrangement of epoxides V by the action of boron trichloride etherate, presented physical, spectral, and analytical data for IV, and discussed their PMR spectra.

Chalcone analog Ia was reacted with hydrazine hydrate in ethanol. The formation of pyrazoline ring occurred after a short period. The structure of VI was supported by its

TABLE 1. Physicochemical Indices of Flavanones II and Oximes III

Compound	Chemical formula	mp, °C*	IR spectrum, cm^{-1}**	Yield, %
IIa	$C_{17}H_{14}O_4$	108...110	1683	68
IIb	$C_{17}H_{13}ClO_4$	116...118	1689	51
IIc	$C_{18}H_{16}O_4$	76...78	1690	59
IId	$C_{18}H_{16}O_5$	116...117	—	30
IIe	$C_{17}H_{13}ClO_4$	115...116	1690	44
IIf	$C_{17}H_{13}FO_4$	119...121	1688	53
IIg	$C_{19}H_{18}O_4$	113...115	1682	44
IIh	$C_{18}H_{16}O_4$	180...181	—	35
IIi	$C_{17}H_{12}Cl_2O_4$	178...179	—	44
IIIa	$C_{17}H_{15}NO_4$	203...205	3305, 1623	93
IIIc	$C_{18}H_{17}NO_4$	205...207	3256, 1618	91
IIIe	$C_{17}H_{14}ClNO_4$	214...216	3268, 1619	91
IIIf	$C_{17}H_{14}FNO_4$	224...226	3268, 1619	93
IIIg	$C_{19}H_{19}NO_4$	226...227	3269, 1619	84
IIIh	$C_{18}H_{17}NO_5$	219...220	—	94
VI	$C_{17}H_{15}N_2O_3$	104...105	—	64
VII	$C_{17}H_{14}NO_4$	95...96,5	—	17

*IIa, IIb, and IIe-IIi were crystallized from methanol, IIc and IId were crystallized from 3:1 petroleum ether—ethyl acetate, and IIIa, IIIc-h, VI, and VII were crystallized from ethanol.

**The $\nu_{C=O}$ values are given for IIa-g, while the ν_{OH} and $\nu_{C=N}$ values are given for IIIa-g.

elemental analysis and PMR spectral data. This product is a colorless, crystalline compound which dissolves readily in 5% aq. NaOH and from a blue-green complex with ferric chloride in ethanol. The signal for the 2-OH proton in the PMR spectrum of VI is found at 11.19 ppm since the hydroxyl group forms an intramolecular hydrogen bond with the nitrogen atom of the pyrazoline ring. The N—H group proton appears at 7.77 ppm and disappears first upon the addition of heavy water. The signal for the 6-H proton of the phenolic part of the molecule is shifted upfield by 1 ppm in comparison with the starting chalcone Ia. The 4-CH_2 protons of the pyrazoline ring appear as two doublets of doublets with coupling constants of 10.83 and 17.23 ppm. The 5-H proton also is found as a doublet of doublets at 4.75 ppm with a coupling constant of 10.83 Hz (an axial-equatorial constant is not seen due to broadening of the peaks as a result of exchange of the hydrogen atom between the adjacent nitrogen atoms in the pyrazoline ring).

A mixture of products is formed in the reaction of chalcone Ia with hydroxylamine hydrochloride in dry pyridine. The major product, isoxazoline VII, was isolated by chromatography on a silica gel column with 9:1 benzene—ethanol as the eluent. The structure of isoxazoline VII was indicated by its PMR spectral data (in DMSO). The phenolic hydroxyl proton absorbs at 9.9 ppm, which indicates its participation in an intermolecular hydrogen bond with DMSO and not with the nitrogen atom of the isoxazoline ring. The 4-CH_2 and 5-H protons of the isoxaline ring, similarly to pyrazolines, also form an ABX system.

Thus, in a study of the properties of benzodioxane analogs of chalcones, we obtained 2-(6-benzodioxan-1,4-yl)chromanones and their oximes. Benzodioxane analogs of isoflavanones were synthesized by this new method and the reactions of chalcone Ia with several nucleophilic reagents were studied. Work on the synthesis of benzodioxane analogs of flavonoids and their pharmacological investigation are presently proceeding and will be published in the near future.

EXPERIMENTAL

The purity of the compounds obtained was monitored by thin-layer chromatography on Silufol UV-254 plates using 9:1 benzene—ethanol as the eluent. The IR spectra were taken on a UR-20 spectrometer for KBr pellets. The PMR spectra were taken on a Bruker CXP-200 spectrometer in deuterochloroform relative to TMS as the internal standard.

TABLE 2. PMR Spectra* of Benzodioxane Analogs of Flavanones II

Compound	Chromanone protons, δ, ppm (SSCC, J, Hz)							Benzodioxane protons, δ, ppm			
	2a-H, d.d	3a-H, d.d	3e-H, d.d	5-H	6-R^3	7-R^2	8-R^1	$-OCH_2CH_2O-$, s	5-H	7-H	8-H
IIa	5,37 (13,1; 3,0)	3,07 (16,8; 13,1)	2,85 (16,8; 3,0)	7,93 d.d	—	—	—	4,28	—	—	—
IIb	5,36 (12,8; 3,2)	3,06 (17,0; 12,8)	2,84 (17,0; 3,2)	7,83 d	7,00 d.d	—	7,03 d	4,28	6,81	6,81	6,81
IIc	5,34 (13,6; 3,9)	3,04 (16,9; 13,6)	2,81 (16,9; 3,9)	7,82 d	6,88 q	2,37 s	7,01 d	4,28	6,88	6,88	6,88
IId	5,35 (13,3; 2,9)	3,03 (16,7; 13,3)	2,77 (16,7; 3,0)	7,85 d	6,60 d.d	3,83 s	6,47 d	4,27	7,00	6,92	6,92
IIe	5,36 (13,0; 3,0)	3,06 (17,0; 13,0)	2,87 (17,0; 3,0)	7,88 d	—	7,44 d.d	7,00 d	4,29	7,01	6,93	6,93
IIf	5,38 (13,0; 3,0)	3,09 (17,0; 13,0)	2,88 (17,0; 3,0)	7,58 q	—	7,25 d.d	7,04 d	4,29	6,96	6,96	6,96
IIg	5,31 (13,0; 3,0)	3,03 (17,0; 13,0)	2,79 (17,0; 3,0)	7,63 s	2,24 s	2,28 s	6,79 s	4,28	6,93	6,93	6,93
IIh	5,30 (12,6; 3,4)	3,00 (16,6; 12,6)	2,77 (16,6; 3,4)	7,34 d	3,78 s	7,11 d.d	6,97 d	4,25	7,01	6,91	6,91

*The spectra were taken on a Bruker CXP-200 spectrometer in deuterochloroform.

TABLE 3. PMR Spectra* of Oximes of Benzodioxane Analogs of Flavanones III

Compound	Pyranone fragment protons, δ, ppm (SSCC, J, Hz)				
	2a-H, d.d	3a-H, d.d	3e-H, d.d	N—OH, s	$-OCH_2CH_2O-$, s
IIIa	5,00 (12,5; 3,0)	3,53 (17,2; 12,5)	2,74 (17,2; 3,0)	7,65	4,29
IIIc	4,98 (12,4; 3,1)	3,50 (17,4; 12,4)	2,72 (17,4; 3,1)	7,82	4,27
IIIe	5,07 (12,7; 3,2)	3,51 (17,7; 12,7)	2,72 (17,7; 3,2)	7,44	4,28
IIIf	4,96 (12,5; 3,0)	3,48 (17,3; 12,5)	2,72 (17,3; 3,0)	7,28	4,29
IIIg	4,96 (12,4; 3,0)	3,49 (17,2; 12,4)	2,72 (17,2; 3,0)	7,81	4,28
IIIh	5,03	3,07	2,96	11,35**	4,30

*The spectra were taken on a Bruker CXP-200 spectrometer in deuterochloroform.
**This spectrum was taken in DMSO.

The elemental analysis data for II, III, VI, and VII for C, H, and N corresponded to the calculated values.

2-(6-Benzodioxan-1,4-yl)chromanones (IIa)-(IIi). A suspension of 10 mmoles chalcone Ia-Ii and 3.5 g Amberlist A-21 ion-exchange resin in 60 ml methanol was heated at reflux with stirring for 7 h. The resin was then filtered off. A portion of the filtrate was evaporated until the onset of crystallization of chromanone IIa-IIi.

Oximes of 2-(6-benzodioxan-1,4-yl)chromanones (IIIa), (IIIc), and (IIIe)-(IIIh). A mixture of 2 mmoles chromanone IIa, IIc, IIe-h, and 0.43 g (6 mmoles) hydroxylamine hydrochloride in 5 ml pyridine was heated at 110-115°C for 30 min. The reaction mixture was then placed in 100 ml water and the precipitate formed was filtered off. If an oil precipitated upon the addition of water, it was triturated several times with water, which led to the formation of the solid product.

3-(6-Benzodioxan-1,4-yl)chromones (IVc-f), (IVg), and (IVj). A solution of 3 mmoles chalcone Ic-f, IIg, IIj, and 1.4 g (3.59 mmoles) thallium trinitrate in 150 ml methanol was stirred at room temperature for five days. The solvent was then evaporated. A sample of 20 ml chloroform was added to the residue and washed with 50 ml water. The aqueous phase was extracted with two 15-ml portions of chloroform. The combined chloroform extract was dried over calcium chloride and the solvent was distilled off. A sample of 25 ml 0.1 N methanolic sodium methylate was added to the residue and heated at reflux for 15 min. The precipitate formed upon cooling was recrystallized from ethyl acetate and the melting points were measured on a Koefler block. Product IVc was obtained in 42% yield, mp 203-204°C. Product IVd was obtained in 23% yield, mp 194-196°C. Product IVe was obtained in 41% yield, mp 171-173°C. Product IVf was obtained in 58% yield, mp 209-212°C. Product IVg was obtained in 51% yield, mp 229-231°C. Product IVj was obtained in 25% yield, mp 174-176°C.

3-(2-Hydroxyphenyl)-5-(6-benzodioxan-1,4-yl)pyrazoline (VI). A sample of 1 ml 80% hydrazine hydrate was added to a hot solution of 10 mmoles chalcone Ia in 100 ml ethanol and heated at reflux for 20 min. The reaction mixture was then poured into 100-150 ml water. The precipitate formed was filtered off and recrystallized from ethanol. PMR spectrum (in DMSO): phenolic fragment protons: 11.19 (2-OH), 6.92 (3-H), 7.20 (4-H), 6.94 (5-H), 7.28 (6-H) ppm; pyrazoline protons: 7.77 (N–H), 3.54, 2.96 (4-CH_2), 4.75 (5-H) ppm; benzodioxane protons: 6.96 (5-,7-,8-H), 4.21 ppm (OCH_2CH_2O).

3-(2-Hydroxyphenyl)-5-(6-benzodioxan-1,4-yl)isoxazoline (VII). A mixture of 3 mmoles chalcone Ia and 1.35 g (18 mmoles) hydroxylamine hydrochloride in 6 ml dry pyridine was heated at 110-115°C for 20 min. The hot solution was then poured into 150 ml water. The precipitate formed was filtered off. The major reaction product, VII, was isolated on a silica gel column with 9:1 benzene–ethanol as the eluent. The product obtained was crystallized from aqueous ethanol. The yield of VII was 1.5 g. PMR spectrum (in DMSO): phenolic fragment: 9.90 (2-OH), 6.98, 7.33, 7.0, 7.48 ppm (3-,4-,5-,6-H); isoxazoline ring protons: 3.90 (1 H, d. d, J = 10.83, 17.23 Hz, 4a-H), 3.37 (1 H, d. d, J = 8.37, 17.23 Hz, 4e-H), 5.60 ppm (1 H, d. d, J = 8.37, 10.83 Hz, 5a-H); benzodioxane ring protons: 6.87 (3 H, m, 5-,7-,8-H), 4.23 ppm (4 H, s, OCH_2CH_2O).

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