CHEMISTRY OF ISOFLAVONE HETEROANALOGS.

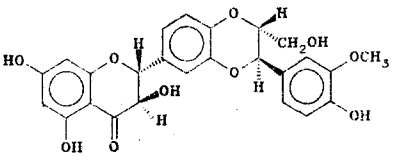
11.* BENZODIOXANE ANALOGS OF CHALCONE, FLAVONE, AND ISOFLAVONE

V. P. Khilya, A. Aitmambetov, A. V. Turov,
A. M. Kornilov, D. Litkei, and T. Patonai

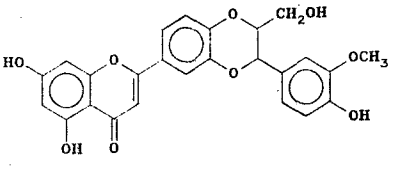
UDC 547.814.5'841.07:
543.422.25:615.272.4

Benzodioxane analogs of chalcones and their epoxides have been prepared. Different types of analogs of natural flavonolignan — silibin — have been synthesized from these compounds. The PMR spectra of the new compounds and the results of the preliminary biological testings are reported and discussed.

A complex flavanoid (sibilin [2]) and its related compounds (for example, hydrocarpine [3]), in which the chromone or chromanone nucleus is bound to 2,3-disubstituted 1,4-benzodioxane have been isolated from different types of plant material. The structure of silibin has been established and confirmed by synthesis [4-7].



Silibin



Hydrocarpine

The increased interest in this group of compounds is due to their biological activity. Thus, silibin has hepato-protective [2, 8], antiphalloidine [9], antiperoxide [10] activities and inhibits prostaglandin synthetase [11].

Natural silibin has a 3-hydroxy-3',4'-ethylenedioxyflavanoid structure. Hydrocarpine, which has been isolated later [3], is a derivative of 2-(6-benzodioxan-1,4-yl)chromone and has a similar structure. Since compounds of this type and those with other degrees of oxidation have not yet been prepared, we decided to synthesize structurally more simple benzodioxane analogs of isoflavones (VI) and flavones (VII) and to study their chemical and biological properties. The key materials for the synthesis of these compounds were substituted 3,4-ethylenedioxychalcones III and IV, obtained by an alkaline condensation of the corresponding o-hydroxyacetophenones with 6-formyl-1,4-benzodioxane by a known method [12].

The benzodioxane analogs of chalcones III and IV are fairly high-melting crystalline substances with a yellow or orange color, which are readily soluble in organic solvents (Table 1). There are intense absorption bands in the 1636-1656 cm^{-1} region in the IR spectra of these compounds, corresponding to the stretching vibrations of the chalcone carbonyl group.

In the reaction of chalcones IV with hydrogen peroxide in an alkaline medium, epoxides V are formed in good yields, which in contrast to the initial chalcones, are colorless crystalline substances, while stretching vibrations of the carbonyl in the molecules are shifted to the 1664-1687 cm^{-1} region

*For article 10, see [1].

T. G. Shevchenko Kiev State University, Kiev 252017. L. Koshut Debrecen University, Hungarian People's Republic, Debrecen N-4010. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 192-198, February, 1986. Original article submitted January 14, 1985.

0009-3122/86/2202-0149$12.50

TABLE 2. Physicochemical Constants of Benzodioxane Analogs of Isoflavones and Flavones VIa, d-k, Va-l

Compound	mp, °C	IR spectrum, $\nu_{C=O}$, cm^{-1}	Found, %			Empirical Formula	Calculated, %			Yield, %
			C	H	Hal		C	H	Hal	
VIa	196—197	1634	73,3	4,7	—	$C_{17}H_{12}O_4$	72,9	4,3	—	60
VId	189—190	1638	73,1	5,0	—	$C_{18}H_{14}O_4$	73,5	4,8	—	42
VIe	192—193	1634	69,8	4,7	—	$C_{18}H_{14}O_5$	69,7	4,5	—	63
VIf	168—169	1638			22,2	$C_{17}H_{11}BrO_4$			22,3	37
VIg	171—172	1638	65,0	4,0	11,5	$C_{17}H_{11}ClO_4$	64,8	3,5	11,3	41
VIh	209—210	1640			6,7	$C_{17}H_{11}FO_4$			6,8	43
VIi	205—206	1639	74,7	5,5	—	$C_{19}H_{16}O_4$	74,0	5,2	—	61
VIj	196—197	1637	70,2	5,0	—	$C_{18}H_{14}O_5$	69,7	4,5	—	57
VIk	189—190	1639	73,4	4,8	—	$C_{18}H_{14}O_4$	73,5	4,8	—	45
VIIa	184—185	1646	72,8	4,5	—	$C_{17}H_{12}O_4$	72,9	4,3	—	52
VIIb	205—206	1646	65,0	3,7	10,8	$C_{17}H_{11}ClO_4$	64,8	3,5	11,3	68
VIIc	213—214	1650			11,3	$C_{17}H_{11}ClO_4$			11,3	51
VIId	168—169	1644	73,4	5,0	—	$C_{18}H_{14}O_4$	73,5	4,8	—	55
VIIe	170—171	1643	70,2	5,0	—	$C_{18}H_{14}O_5$	69,7	4,5	—	31
VIIf	239—240	1633			22,1	$C_{17}H_{11}BrO_4$			22,3	43
VIIg	226—227	1641, 1633			11,5	$C_{17}H_{11}ClO_4$			11,3	50
VIIh	213—214	1634, 1630			6,8	$C_{17}H_{11}FO_4$			6,8	68
VIIi	207—208	1639	74,2	5,3	—	$C_{19}H_{16}O_4$	74,0	5,2	—	64
VIIj	194—195		69,8	4,7	—	$C_{18}H_{14}O_5$	69,7	4,5	—	28
VIIk	195—196		73,4	4,8	—	$C_{18}H_{14}O_4$	73,5	4,8	—	64
VIIl	216—217				20,3	$C_{17}H_{10}Cl_2O_4$			20,3	95

*Compounds VIa, i, j, k, and VIIe were crystallized from an ethyl acetate—petroleum ether mixture; VId and VIIa from an alcohol—octane mixture; VIf, g, and VIIc, i from alcohol; VIIf, g, h, j-l from ethyl acetate; VIId from aqueous alcohol.

isoflavones VI are preferentially high-melting colorless crystalline substances. The stretching vibrations of the carbonyl group in their molecules are present in the 1637-1650 cm^{-1} region. The physical constants, spectral and analytical characteristics of compounds VI, VII are listed in Table 2.

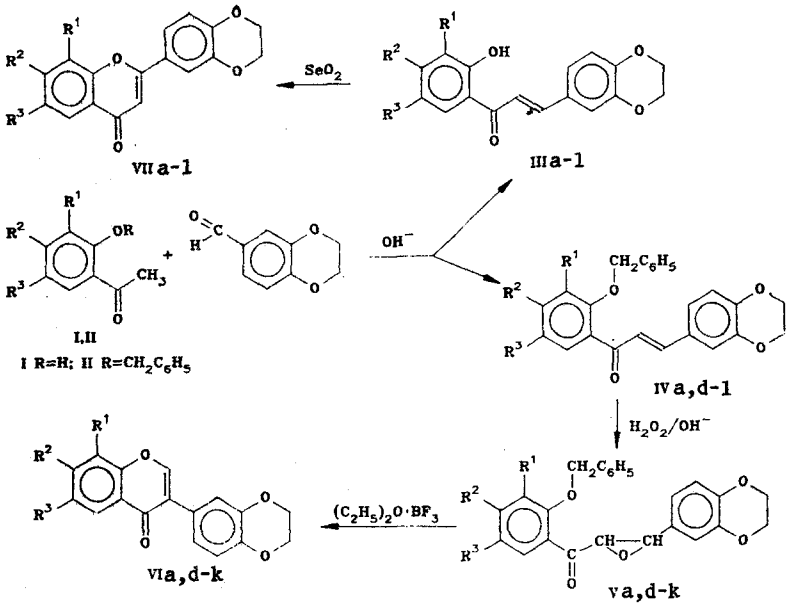
To confirm the structure and determine the configuration of chalcones III, IV, epoxides V, flavones VII and isoflavones VI we used the PMR method in the presence of a lanthanide shifting reagent (LSR), as well as the above indicated methods. In the spectra of chalcones IIIa-l, the signal of the hydroxyl proton is observed in the weakest field (13.4-14.2 ppm). The type of the functional groups located in the vicinity has only slight influence on the position of this signal. In several cases, the signals of aromatic protons of these compounds form an unresolved multiplet in the 7.0-8.3 ppm region. In all the compounds, there is a somewhat detached signal of a proton aligned with the carbonyl group (see Table 3). The chemical shift (CS) for this proton is 8-8.3 ppm. The signals of the aromatic protons of the benzodioxane ring form a multiplet with a center at 7.52-7.57 ppm, while the methylene group signals give a singlet at 4.52-4.54 ppm. Attempts to simplify the spectrum by means of LSR, europium-III tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimehtyloctane-4,6-dionate [Eu(f0d)$_3$] were unsuccessful, because of strong signal broadenings in the presence of LSR, which are clearly due to the decomposition of the LSR by the action of strongly acidic phenol proton of products IIIa-l.

The spectra of the benzyl derivatives IVa, d-l are also difficult to interpret. The aromatic and olefinic protons give an unresolved multiplet in the 7-8 ppm region (see Table 3), but they can be simplified by the action of [Eu(fod)$_3$]. When this LSR is added, considerable paramagnetic lanthanide-induced shifts (LIS) of the NMR signals are observed. Thus, the highest LIS are characteristic for the methylene proton signals of the benzyl group, signals of the olefinic protons and the signal of the aromatic proton located at the o-position with respect to the carbonyl group (see Table 3). From the shift values it follows that the coordination of LSR is brought about at two centers: at the ether oxygen atom of the O-benzyl and at the carbonyl group (cf. [15-17]). The benzodioxane ring oxygen atoms do not participate in the complexation with LSR, as follows from the absence of noticeable

TABLE 1. Physicochemical Constants of Benzodioxane Analogs of Chalcones and Epoxides IIIa-l, IVa, d-l, Va, d-k

Compound	mp, °C	IR spectrum, $\nu_{C=O}$, cm^{-1}	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	Hal		C	H	Hal	
IIIa	126—127	1638	72,3	5,0	—	$C_{17}H_{14}O_4$	72,3	5,0	—	59
IIIb	172—173	1636	64,6	4,3	11,3	$C_{17}H_{13}ClO_4$	64,5	4,1	11,2	25
IIIc	152—153	1642	64,5	4,2	11,2	$C_{17}H_{13}ClO_4$	64,5	4,1	11,2	97
IIId	127—128	1637	72,8	5,6	—	$C_{18}H_{16}O_4$	72,9	5,4	—	80
IIIe	140—141	1639	69,9	5,6	—	$C_{18}H_{16}O_5$	69,3	5,1	—	57
IIIf	140—141	1638			22,4	$C_{17}H_{13}BrO_4$			22,1	96
IIIg	135—136	1638	64,7	4,3	11,3	$C_{17}H_{13}ClO_4$	64,5	4,1	11,2	60
IIIh	173—174	1643			6,4	$C_{17}H_{13}FO_4$			6,3	78
IIIi	145—146	1640	73,6	5,6	—	$C_{19}H_{18}O_4$	73,5	5,8	—	80
IIIj	80—81		69,5	5,3	—	$C_{18}H_{16}O_5$	69,3	5,1	—	58
IIIk	138—139		72,5	5,4	—	$C_{18}H_{16}O_4$	72,9	5,4	—	90
IIIl	187—188				20,2	$C_{17}H_{12}Cl_2O_4$			20,2	85
IVa	111—112	1658	76,9	5,3	—	$C_{24}H_{20}O_4$	77,4	5,4	—	90
IVd	110—111	1659	78,1	5,9	—	$C_{25}H_{22}O_4$	77,7	5,7	—	83
IVe	113—115	1644	74,7	5,4	—	$C_{25}H_{22}O_5$	74,6	5,5	—	94
IVf	124—125	1648			18,0	$C_{24}H_{19}BrO_4$			17,8	96
IVg	119—121	1645	70,5	4,7	8,9	$C_{24}H_{19}ClO_4$	70,8	4,7	8,7	95
IVh	118—119	1643			4,8	$C_{24}H_{19}FO_4$			5,1	96
IVi	98—99	1649	77,6	6,1	—	$C_{26}H_{24}O_4$	78,0	6,0	—	95
IVj	85—86	1648	74,6	5,5	—	$C_{25}H_{22}O_5$	74,6	5,5	—	79
IVk	113—114	1645	77,9	5,7	—	$C_{25}H_{22}O_4$	77,7	5,7	—	82
IVl	125—126				16,0	$C_{24}H_{18}Cl_2O_4$			16,1	94
Va	120—121	1677	74,4	5,3	—	$C_{24}H_{20}O_5$	74,2	5,2	—	82
Vd	143—144	1672	74,5	5,5	—	$C_{25}H_{22}O_5$	74,6	5,5	—	81
Ve	101—102	1665	71,8	5,3	—	$C_{25}H_{22}O_6$	71,8	5,3	—	72
Vf	142—143	1682			16,9	$C_{24}H_{19}BrO_5$			17,1	79
Vg	147—149	1687	68,3	4,5	8,4	$C_{24}H_{19}ClO_5$	68,7	4,5	8,4	65
Vh	142—143	1678			4,7	$C_{24}H_{19}FO_5$			4,7	84
Vi	134—135	1669	75,3	5,6	—	$C_{26}H_{24}O_5$	75,0	5,8	—	87
Vj	129—130	1665	72,0	5,4	—	$C_{25}H_{22}O_6$	71,8	5,3	—	84
Vk	120—121	1667	74,4	5,7	—	$C_{25}H_{22}O_5$	74,6	5,5	—	75

*Compounds IIIa, b and Vf, g, h were crystallized from an alcohol—ethyl acetate mixture; IIIc, e, h from acetic acid; IIId, e, g, i, k, IVa-h, i, j, and Va, d, e, i-k from alcohol; IIIj from hexane; IVk from aqueous alcohol; IVl from ethyl acetate.



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

As the result of the rearrangement [13] of opoxides V under the influence of boron trifluoride etherate, benzodioxane analogs of isoflavones VI were obtained in good yields. Their isomers VII are formed from chalcones III by oxidative cyclization with selenium dioxide in amyl alcohol [14]. In contrast to the colored initial chalcones, flavones VII and

TABLE 3. PMR Spectra* of Benzodioxane Analogs of Chalcones IIIa, c-l, IVa, d-k and Their Epoxides Va, d-k

Compound	Protons of the phenol part						Protons of the benzodioxane part	
	2-OH, s, or 2-OR,† s	3-H	4-R²	5-R³	6-H	O ‖ —C—CH=CH—, d, or —C—CH—CH—, ‖ \ / O O d	5-, 7-, 8-H	—OCH_2CH_2O—, s
IIIa	13,58	7,1—7,8	7,1—7,8	7,1—7,8	8,28, dd	8,22; 7,81	7,53	4,52
IIIc	13,75	7,32	—	7,32	8,16, d	8,22; 7,71	7,55	4,54
IIId	13,60	7,14, s	2,50, s	7,14, s	8,28, d	8,20; 7,78	7,53	4,53
IIIe	14,09	6,79	4,03, s	6,76	8,11, d	8,10; 7,65	7,45	4,51
IIIf	13,47	7,25, d	7,95, dd	—	8,35, d	8,23; 7,71	7,57	4,55
IIIg	13,48	7,31, d	7,80, dd	—	8,20, d	8,24; 7,71	7,57	4,54
IIIh	12,63	6,9—7,7	6,9—7,7	—	6,9—7,7	7,84	6,9—7,7	4,38
IIIi	13,50	7,16, s	2,40, s	2,40, s	7,96, s	8,22; 7,83	7,57	4,54
IIIj	12,51	6,8—7,4	6,8—7,4	3,87, s	6,8—7,4	7,84; 7,40	6,8—7,4	4,32
IIIk	12,66	6,88, d	7,02, dd	2,38, s	7,62, d	7,80; 7,59	7,20	4,33
IIIl	13,39	—	7,49, d	—	7,70, d	7,83; 7,26	7,15; ‡ 6,86, d	4,32
IVa	5,42; 7,70 (5,6)	7,0—8,0	7,0—8,0	7,0—8,0	8,09, dd (11,5)	7,98; 7,66 (8,3; 6,6)	7,20	4,48 (0,0)
IVd	5,41; 7,76 (6,0)	7,5—8,0	2,54, s (1,1)	7,5—8,0	8,03, d (10,8)	8,04; 7,74 (9,6; 4,5)	7,19	4,48 (0,3)
IVe	5,35; 7,68 (7,9)	6,86	4,00, s (0,4)	6,86	8,18, d (7,3)	7,84, s (4,1; 3,7)	7,20	4,45 (0,2)
IVf	5,37; 7,69 (5,9)	7,5—8,1	7,5—8,1	—	8,17, d (7,3)	7,5—8,1 (6,8; 4,2)	7,24	4,50 (0,2)
IVg	5,44; 7,70 (5,3)	7,0—8,0	7,0—8,0	—	8,08, d (8,4)	7,0—8,0 (8,0; 4,4)	7,0—8,0	4,54 (0,0)
IVh	5,17; 7,22 (6,4)	6,9—7,7	6,9—7,7	—	6,9—7,7 (10,4)	6,9—7,7 (9,7; 6,0)	6,9—7,7	4,33 (0,3)
IVi	5,43; 7,77 (14,7)	7,40, s (3,8)	2,39, s (0,5)	2,46, s (2,0)	7,95, s (16,3)	7,95, s (11,8; 7,3)	7,25	4,52 (0,1)
IVj	5,37; 7,66 (7,9)	7,0—8,0	7,0—8,0	4,03, s	7,0—8,0 (7,3)	7,0—8,0 (4,1; 3,7)	7,08—8,0	4,51 (0,2)
IVk	5,35; 7,57 (8,2)	7,4—7,7	7,4—7,7	2,46, s (0,1)	7,45, d (10,5)	7,83; 7,51 (8,6; 4,5)	7,11	4,46 (0,1)
Va	5,27; 7,56	7,33, dd	7,4—7,8	7,4—7,8	8,12, dd	4,64; 4,11	7,05, s	4,43
Vd	5,28; 7,58	7,16, s	2,50, s	7,16, dd	8,10, d	4,68; 4,09	7,05	4,46
Ve	5,25; 7,60	6,81, s	4,02, s	6,88, dd	8,25, d	4,71; 4,07	7,07	4,45
Vf	5,27; 7,59	7,25, d	7,89 dd	—	8,24, d	4,64; 4,13	7,09, s.	4,49
Vg	5,26; 7,57	7,25, d	7,72, dd	—	8,07, d	4,60; 4,10	7,03, s	4,46
Vh	5,0; 7,19	6,9—7,5	6,9—7,5	—	6,9—7,0	4,42; 3,91	6,71, s	4,25
Vi	5,23; 7,56 (7,0)	7,11, s	2,28, s (1,0)	2,34, s (2,6)	7,93, s (7,0)	4,68; 4,05 (31; 28)	7,04, s	4,45
Vj	5,23; 7,57	7,5—7,7	7,5—7,7	4,00, s	7,5—7,7	4,70; 4,11	7,09, s	4,47
Vk	5,15; 7,48	7,16, d	7,54, dd	2,39, s	7,90, d	4,59; 4,04	7,07, s	4,37

*Units of measurement: δ, ppm; the values of the specific LIS are given in brackets; absence of a letter, multiplet.
†CS of 2-$OCH_2C_6H_5$ group protons.
‡CS of 8-H proton.

LIS for the methylene proton signals of the benzodioxane ring. At a 0.2-0.3 molar ratio between LSR and the substrate, doublets of the two olefinic protons can be observed separately in the PMR spectra of products IVa, d-l. The SSCC [spin—spin coupling contant] for these protons, equal to 15 Hz, indicates a trans structure of all the chalcones obtained.

In the PMR spectra of epoxides Va, d-k, the most characteristic signals are the peaks of methine protons of the oxirane ring in the form of doublets with a small SSCC (1-1.5 Hz). One of the peaks is located at 4.55-4.70, and the other at 4.0-4.1 ppm. Changes in the nature of the substituents in the molecules of the epoxides Va, d-k influence the disposition of these signals in the spectrum very slightly (see Table 3). We assigned the signals of oxirane protons on the basis of study of the interaction of LSR with compound Vi. The LIS values found are shown in Table 3. It is seen that the maximal shifts are observed for signals of the epoxide ring protons, whereby one of the signals is shifted more strongly than the other. At one side of the oxirane ring there is a carbonyl group, which, as also the epoxide oxygen atom, is capable of undergoing complexation with LSR. We therefore ascribed the signal for which a higher value of LIS is observed, to the methine proton located in the

TABLE 4. PMR Spectra* of Benzodioxane Analogs of Isoflavones VIa, d-k and Flavones VIIa, c-l

Compound	Chromone ring protons					Benzodioxane ring protons		
	2-H, s, (3-H), s	5-H	6-R^3	7-R^2	8-H	5H and 7-H	8-H, d	$-OCH_2CH_2O-$, s
VIa	8,31	8,04, dd	7,2—7,7	7,2—7,7	7,2—7,7	6,9—7,2		4,29
VIa†	7,95	8,29, dd	7,3—7,6	7,3—7,6	7,3—7,6	6,9—7,2		4,31
VId	8,34	7,94, d	6,7—7,4	2,49, s	6,7—7,4	6,7—7,4		4,25
VId†	7,83	8,09, d	6,7—7,4	2,48, s	6,7—7,4	6,7—7,4		4,27
VIe	8,25	7,94, d	6,7—7,2	3,92, s	6,7—7,2	6,7—7,2		4,30
VIf	8,42	8,13, d	—	7,88, dd	7,54, d	6,8—7,2		4,32
VIg	8,50	8,03, d	—	7,77, s	7,77, s	6,8—7,3		4,34
VIh	8,40	7,4—7,7	—	7,4—7,7	7,4—7,7	6,7—7,2		4,31
VIi†	7,91	8,04, s	2,42, s	2,42, s	6,9—7,3	6,9—7,3		4,32
VIj	8,39	7,47	3,89, s	7,47	7,47	6,7—7,2		4,30
VIJ†	7,92	7,63, d	3,93, s	6,7—7,4	6,7—7,4	6,7—7,4		4,31
VIk	8,32	7,83, d	2,09, s	7,46, s	7,46, s	6,7—7,1		4.22
VIk†	7,87	8,00, d	2,49, s	7,33, s	7,33, s	6,7—7,2		4,30
VIIa	(6,87)	8,05, dd	7,3—7,8	7,3—7,8	7,3—7,8	7,3—7,8	7,01	4,37
VIIa†	(6,71)	8,21, dd	7,3—7,7	7,3—7,7	7,3—7,7	7,3—7,7	6,97	4,36
VIIc	(6,80)	7,97, d	7,3—7,7	—	7,83, d	7,3—7,7	6,99	4,36
VIId	(6,75)	7,88, d	7,3—7,7	2,49, s	7,3—7,7	7,3—7,7	6,97	4,36
VIId†	(6,59)	7,97, d	7,0—7,4	2,51, s	7,0—7,4	7,0—7,4	6,85	4,33
VIIe	(6,79)	7,93, d	7,58	3,95, s	7,58	7,26, d	7,00	4,37
VIIe†	(6,61)	8,07, d	7,36	3,92, s	7,36	6,8—7,1	6,8—7,1	4,36
VIIf	(6,79)	8,02, d	—	7,84, dd	7,60, d	7,46	6,95	4,36
VIIf†	(6,65)	8,30, d	—	7,33, dd	7,2—7,5	7,2—7,5	6,94	4,33
VIIg	(6,83)	7,90, d	—	7,75, s	7,75, s	7,49	6,98	4,37
VIIg†	(6,66)	8,14, d	—	7,2—7,7	7,2—7,7	7,2—7,7	6,93	4,35
VIIh	(6,83)	7,4—7,9	—	7,4—7,9	7,4—7,9	7,4—7,9	6,98	4,35
VIIh†	(6,63)	7,80	—	7,2—7,6	7,2—7,6	7,2—7,6	6,94	4,33
VIIi	(6,74)	7,74, s	2,38, s	2,38, s	7,46	7,46	7,00	4,36
VIIi†	(6,66)	7,95, s	2,40, s	2,40, s	7,29, s	7,37, dd	6,95	4,34
VIIj†	(6,64)	7,51, d	3,91, s	7,32, dd	7,28, d	7,32	6,91	4,33
VIIk	(6,77)	7,79, d	2,46, s	7,53	7,53	7,53	6,98	4,33
VIIk†	(6,66)	7,96, d	2,47, s	7,40	7,40	7,40	6,93	4,31
VIIl‡	(7,82)	8,30, d	—	8,15, d	—	7,82	7,20	4,53

*Absence of a letter) multiplet.
†The spectra of the compounds were measured in $CDCl_3$, in unmarked cases, the PMR spectra of the same compounds were measured in DMSO-D_6.
‡The PMR spectrum was measured in CF_3COOH.

vicinity of the carbonyl group. The CS of signals of other protons of epoxides Va, d-k are similar to the CS of the corresponding signals of chalcones IVa, d-k.

In the PMR spectra of isoflavones VIa, d-k, the 2-H proton, located in the vicinity of the heterocyclic oxygen atom, absorbs in the weakest field (8.2-8.4 ppm, in DMSO). The nature of substituents R^1, R^2, and R^3 practically does not influence its CS. It is of interest that when the spectra are run in deuterochloroform, the CS of the 2-H proton is located 0.5 ppm in a stronger field than when the spectra are run in a DMSO solution (see Table 4). It is possible that this effect is caused by the stabilization of the bipolar form of the chromone ring due to solvation by DMSO, and as a result, by a greater pramagnetic influence of the heterocyclic oxygen atom on the position of the 2-H proton signal. The signal of the 5-H proton aligned with the carbonyl oxygen atom is present in a somewhat stronger field (7.4-8.1 ppm). The signals of the remaining aromatic protons of compounds VIa, d-k in most cases form a multiplet in the 6.7-7.4 ppm region, from which signals corresponding to individual protons cannot be isolated. The signals of the methylene groups of the benzodioxane ring appear in the form of a singlet at 4.2-4.35 ppm.

In the spectra of flavones VIIa-l, besides the signals of the chromone ring protons 3-H and 5-H located at 6.5-6.9 and 7.7-5.9 ppm, respectively, the signal of the 8-H proton of the benzodioxane ring is characteristic. It is located at 6.9-7.0 ppm and does not coincide with the multiplet of the remaining protons. As in the case of 3-(6-benzodioxan-1,4-yl)chromones, the signal of the methylene protons of the benzodioxane fragment is located at 4.3-4.4 ppm.

The results of biological tests showed that the compounds with flavone structure obtained exhibited a weakly pronounced hepato-protective action, while compounds with an isoflavone

structure have an appreciable hypolipidemic activity, and in their pharmacological effect are not inferior to the antiatherosclerotic preparation cetamiphen.

EXPERIMENTAL

The purity of the compounds was checked by TLC on Silufol UV-254 plates in a 9:1 benzene—ethanol mixture. The IR spectra were run on a UR-20 spectrophotometer in potassium bromide tablets. The PMR spectra were measured on a ZKR-60 spectrometer in $CDCl_3$ with reference to TMS (internal standard).

1-(2-Hydroxyphenyl)-3-(6-benzodioxan-1,4-yl)propenones (IIIa-l) and 1-(2-Benzyloxyphenyl)-3-(6-benzodioxan-1,4-yl)propenones (IVa, d-l). A 20 mmole portion of 6-formyl-1,4-benzodioxane and 4.7 ml of a 50% solution of sodium hydroxide are added to a solution of 20 mmoles of the corresponding 2-hydroxy-I) or 2-benzyloxyacetophenone (II) in alcohol. The reaction mixture is held at room temperature for 20-40 h. The precipitate is suspended in water and the mixture is acidified with acetic acid to a neutral reaction. The product is filtered, and crystallized from a suitable solvent.

1-(2-Benzyloxyphenyl)-3-(6-benzodioxan-1,4-yl)-2,3-epoxypropan-1-ones (Va, d-k). A 30 ml portion of 30% hydrogen peroxide and 30 ml of 2 N sodium hydroxide are added to a solution of 6 mmoles of compound IVa, d-k in a minimal amount of a 15:4 acetone—methanol mixture. After complete decoloration of the solution (12 h), the reaction mixture is diluted with water, the precipitate that separates is filtered and crystallized.

3',4'-Ethylenedioxyisoflavones (VIa, d-k). A 0.6 ml portion of boron trifluoride etherate is added to a solution of 3 mmoles of compound Va, d-k in 50 ml of absolute benzene, and the mixture is boiled for 1-3.5 h (the end of the reaction is determined from the TLC data). The solution is washed with water and benzene is evaporated under an aspirator. The precipitate is crystallized from a suitable solvent.

3',4'-Ethylenedioxyflavones (VIIa-l). A 6.65 g (60 mmole) portion of a finely divided selenium dioxide is added to a solution of 20 mmoles of IIa-l in a minimal amount of a freshly distilled amyl alcohol, and the mixture is boiled for 18-50 h, with the course of the reaction being controlled by TLC. Metallic selenium is filtered off and amyl alcohol is evaporated under an aspirator. The residue is recrystallized several times from a suitable solvent.

LITERATURE CITED

1. V. P. Khilya, M. Yu. Kornilov, N. V. Gorbulenko, G. M. Golubushina, E. N. Kovtun, N. V. Kolotusha, and G. V. Panasenko, Khim. Geterotsikl. Soedin., No. 11, 1542 (1985).
2. A. Pelter and R. Hansel, Tetrahedron Lett., No. 25, 2911 (1968).
3. K. R. Rangenathan and T. R. Seshadri, Tetrahedron Lett., No. 36, 3481 (1973).
4. R. Hansel, J. Schulz, A. Pelter, and H. Rimpler, Tetrahedron Lett., No. 51, 4417 (1969).
5. R. Hansel, J. Schulz, and A. Pelter, J. Chem. Soc. Chem. Commun., No. 3, 195 (1972).
6. L. Merlini, A. Zanarotti, A. Pelter, M. P. Rochefort, and R. Hansel, J. Chem. Soc., Perkin Trans., No. 3, 775 (1980).
7. A. Pelter and R. Hansel, Chem. Ber., 108, 790 (1975).
8. L. Cavallini and G. Lucchetti, Gazz. Med. Ital., 135, 365 (1976).
9. G. Vogel and W. Trost, Arzneim.-Forsch., 25, 392 (1975).
10. L. Cavallini, A. Bindoli, and N. Siliprandi, Pharmacol. Res. Comm., 10, 133 (1978).
11. F. Fiebrich and H. Koch, Experientia, 35, 1550 (1979).
12. R. Bognár and Gy. Litkei, Acta Chim. Acad. Sci. Hung., 67, 83 (1971).
13. Gy. Litkei, R. Bognár, and Z. Dinya, Acta Chim. Acad. Sci. Hung., 71, 403 (1972).
14. H. S. Mahal, H. S. Rai, and K. Venkataraman, J. Chem. Soc., 866 (1935).
15. I. G. Marchenko, A. V. Turov, and V. P. Khilya, Dokl. Akad. Nauk UkrSSR, Ser. B., No. 1, 43 (1979).
16. L. G. Grishko, A. V. Turov, M. G. Spasenov, and V. P. Khilya, Khim. Geterotsikl. Soedin., No. 9, 1202 (1981).
17. L. G. Grishko, A. V. Turov., I. A. Potrusaeva, and V. P. Khilya, Ukr. Khim. Zh., 49, 174 (1983).