CHEMISTRY OF HETEROANALOGS OF ISOFLAVONES

13*. 1,3-BENZODIOXAN ANALOGS OF FLAVONOIDS

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Some 1,3-benzodioxan analogs of chalcones and their epoxides have been obtained, and used to prepare pyrazolines and novel flavone and flavanone analogs of flavolignan (sylibin). The PMR spectra of novel compounds are shown and discussed, together with the results of preliminary biological tests.

Interest in benzodioxan analogs of flavonoids has arisen for the reason that they are related to sylibin, a naturally occurring flavolignan with high biological activity, which possess a benzodioxan moiety in its structure.

In a study of the effects of structural modifications of sylibin on its biological and chemical properties, we have obtained some 1,4-benzodioxan [1-3] and 1,5-benzodioxepan [4] analogs of flavonoids. Some of these showed hypolipidemic, hepatoprotectant, and other types of activity.

We here report the synthesis of some novel flavonoids incorporating the 1,3-benzodioxan nucleus. The starting materials for the preparation of novel flavonoids isomeric with sylibine in respect of the benzodioxan fragment of the molecule were chalcones (I-XVI). These were readily obtained by basic condensation of substituted 2-hydroxy- and 2-benzyloxy-acetophenones with 6-halo-1,3-benzodioxanaldehydes. Treatment of chalcones (XIII-XVI) with hydrogen peroxide in alkaline solution gave epoxides (XVII-XX).

These benzodioxan analogs of chalcones (I, III, VIII, X) were converted into the corresponding flavanone analogs (XXI-XXIV) by isomerization on Amberlyst A-21 ion-exchange resin [1].

Oxidation of the propenone (X) with hydrogen peroxide as described in [5] gave the 3-hydroxychromone (XXV). Oxidation of chalcones (I-IV) and (VI-XII) with selenium dioxide in pentanol as described in [6], or with dimethyl sulfoxide in the presence of catalytic amounts of iodine [7], gave satisfactory to good yields of the benzodioxane derivatives of chromones (XXVI-XXXVI). The cyclization times using the latter method were much shorter, and the yields of chromones higher, than when selenium dioxide was used. Several chromones, on treatment with phosphorus pentasulfide in pyridine, were converted into the thioxochromones (XXXVII-XLI).

The structures of (I-XLI) were established by PMR (Tables 1 and 2). The PMR spectra of chalcones (I-XVI) showed signals for the olefinic protons with chemical shifts in the range 7.0-8.0 ppm. The coupling constants ($J_{\alpha,\beta}$ 15.8-16.1 Hz) indicate the transoid configuration in all the chalcones prepared. The hydrogen atoms of the hydroxyl groups in (I-XII), which are involved in the formation of intramolecular hydrogen bonds (IMHB), absorb at 12.5-13.4 ppm.

*For Communication 12, see [1].

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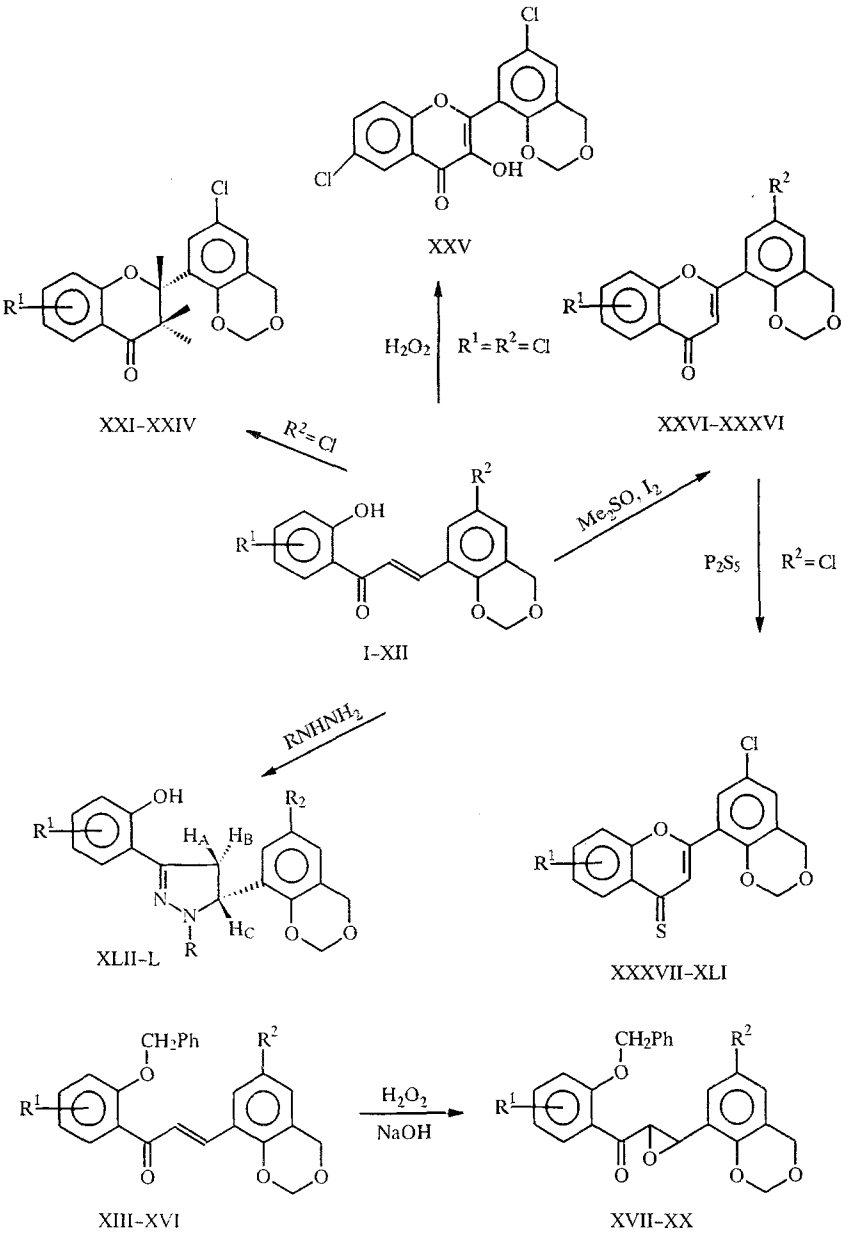

I, XV, XIX, XXI, XXVI R^1=H, R^2=Cl; II, XVI, XX, XXVII R^1=H, R^2=Br; III R^1=4-Me, R^2=Cl; IV R^1=4-Me, R^2=Br; V R^1=4,5-Me_2, R^2=Cl; VI R^1=4-OMe, R^2=Cl; VII R^1=4-OMe, R^2=Br; VIII R^1=5-F, R^2=Cl; IX R^1=5-F, R^2=Br; X, XIV, XVIII R^1=5-Cl, R^2=Cl; XI, XIII, XVII R^1=5-Cl, R^2=Br; XII R^1=5-Me, R^2=Cl; XXII, XXVIII, XXXVII R^1=7-Me, R^2=Cl; XXIII, XXXII, XXXIX R^1=6-F, R^2=Cl; XXIV, XXV, XXXIV, XL R^1=6-Cl, R^2=Cl; XXIX R^1=7-Me, R^2=Br; XXX, XXXVIII R^1=7-OMe, R^2=Cl; XXXI R^1=7-OMe, R^2=Br; XXXIII R^1=6-F, R^2=Br; XXXV R^1=6-Cl, R^2=Br; XXXVI, XLI R^1=6-Me, R^2=Cl; XLII R=Ph, R^1=H, R^2=Cl; XLIII R=H, R^1=4-Me, R^2=Cl; XLIV R=Ph, R^1=4-Me, R^2=Cl; XLV R=H, R^1=4-OMe, R^2=Cl; XLVI R=H, R^1=4-OMe, R^2=Br; XLVII R=H, R^1=5-F, R^2=Cl; XLVIII R=H, R^1=5-F, R^2=Br; XLIX R=H, R^1=5-Cl, R^2=Cl; L R=Ph, R^1=5-Cl, R^2=Cl

In the PMR spectra of epoxides (XVII-XX), the most characteristic signals are those for the methine protons of the oxirane ring, which appear as doublets with small J values (1.76-1.83 Hz, Table 2). Assignment of the signals for the oxirane protons was carried out as in [3].

TABLE 1. Physicochemical Constants of Chalcones, Flavanones, Flavones, Thioxoflavanones, and Pyrazolines

Compound	Empirical formula	mp, °C	Yield, %
I	$C_{17}H_{13}ClO_4$	149...150	68
II	$C_{17}H_{13}BrO_4$	152...153	79
III	$C_{18}H_{15}ClO_4$	175...176	67
IV	$C_{18}H_{15}BrO_4$	178...179	50
V	$C_{19}H_{17}ClO_4$	220	80
VI	$C_{18}H_{15}ClO_5$	184...185	64
VII	$C_{18}H_{15}BrO_5$	181...182	71
VIII	$C_{17}H_{12}ClFO_4$	223...224	90
IX	$C_{17}H_{12}BrFO_4$	210...211	57
X	$C_{17}H_{12}Cl_2O_4$	193...194	97
XI	$C_{17}H_{12}BrClO_4$	194...195	52
XII	$C_{18}H_{15}ClO_4$	207...208	67
XIII	$C_{24}H_{18}BrClO_4$	143...144	62
XIV	$C_{24}H_{18}Cl_2O_4$	158...159	70
XV	$C_{24}H_{19}ClO_4$	116...117	82
XVI	$C_{24}H_{19}BrO_4$	96...97	74
XVII	$C_{24}H_{18}BrClO_5$	195...196	78
XVIII	$C_{24}H_{18}Cl_2O_5$	195...196	69
XIX	$C_{24}H_{19}ClO_5$	143...144	92
XX	$C_{24}H_{19}BrO_5$	139...140	71
XXI	$C_{17}H_{13}ClO_4$	163...164	78
XXII	$C_{18}H_{15}ClO_4$	167...168	71
XXIII	$C_{17}H_{12}ClFO_4$	162...163	78
XXIV	$C_{17}H_{12}Cl_2O_4$	193...194	68
XXV	$C_{17}H_{10}Cl_2O_5$	242...243	53
XXVI	$C_{17}H_{11}ClO_4$	205...206	62
XXVII	$C_{17}H_{11}BrO_4$	216...217	36
XXVIII	$C_{18}H_{13}ClO_4$	230	90
XXIX	$C_{18}H_{13}BrO_4$	215...216	56
XXX	$C_{18}H_{13}ClO_5$	211...212	91
XXXI	$C_{18}H_{13}BrO_5$	220...221	33
XXXII	$C_{17}H_{10}ClFO_4$	225...226	96
XXXIII	$C_{17}H_{10}BrFO_4$	209...210	48
XXXIV	$C_{17}H_{10}Cl_2O_4$	223...224	79
XXXV	$C_{17}H_{10}BrClO_4$	218...219	46
XXXVI	$C_{18}H_{13}ClO_4$	184...185	90
XXXVII	$C_{18}H_{13}ClO_3S$	163...164	78
XXXVIII	$C_{18}H_{13}ClO_4S$	159...160	79
XXXIX	$C_{17}H_{10}ClFO_3S$	235...236	73
XL	$C_{17}H_{10}Cl_2O_3S$	224...225	70
XLI	$C_{18}H_{13}ClO_3S$	162...163	66
XLII	$C_{23}H_{19}ClN_2O_3$	159...161	45
XLIII	$C_{18}H_{17}ClN_2O_3$	114...115	97
XLIV	$C_{24}H_{21}ClN_2O_3$	190...192	38
XLV	$C_{18}H_{17}ClN_2O_4$	124...125	79
XLVI	$C_{18}H_{17}BrN_2O_4$	140...142	92
XLVII	$C_{17}H_{14}ClFN_2O_3$	164...165	73
XLVIII	$C_{17}H_{14}BrFN_2O_3$	167...168	89
XLIX	$C_{17}H_{14}Cl_2N_2O_3$	159...160	88
L	$C_{23}H_{18}Cl_2N_2O_3$	173...175	31

TABLE 2. PMR Spectra of Chalcones and Their Derivatives (I-XX)

Compound	Chemical shift, δ, ppm (J values, Hz)*					
	phenolic protons					—CH=CH—, —CH—CH— (O)
	2-OH, s (2-CH_2R)	3-H	4-R^1 (4-H)	5-R^1 (5-H)	6-H	
I	12,77	6,91 (dd, 7,89; 2,0)	7,50 (td, 7,89, 2,0)	7,02 (td, 7,89; 2,0)	7,91 (dd, 7,89; 2,0)	8,03, 7,72 (15,78)
II	12,77	6,92 (dd, 7,89; 2,0)	7,51 (td, 7,89; 2,0)	7,00 (td, 7,89; 2,0)	7,90 (dd, 7,89; 2,0)	8,03, 7,71 (15,78)
III	12,83	6,82, (d, 1,5)	2,37 c	6,75 (dd, 7,89; 1,5)	7,77 (d, 7,89)	8,02, 7,68 (15,78)
IV	12,83	6,81, (d, 2,0)	2,36 s	6,76 (dd, 8,00; 2,0)	7,77 (d, 8,0)	8,00, 7,67 (15,80)
V	12,64	6,82 s	2,28 s	2,28 s	7,60 s	8,04, 7,68 (15,81)
VI	13,39	6,48 (d, 2.2)	3,86 s	6,50 (dd, 9,66; 2,2)	7,81 (d, 9,66)	8,01, 7,66 (15,80)
VII	13,39	6,45 (d, 2,2)	3,86 s	6,49 (dd, 9,66; 2,63)	7,80 (d, 9,66)	8,00, 7,64 (15,81)
VIII	12,49	7,01 (d, 8,0)	7,46 (dd, 8,0; 2,5)	—	7,86 (d, 2,5)	8,08, 7,66 (15,81)
IX	12,48	7,11 (d, 8,5)	7,56 (dd, 8,5; 2,5)	—	7,61 (d, 2,5)	8,04, 7,63 (16,10)
X	12,67	7,01 (d, 9,66)	7,45 (dd, 9,66; 2,2)	—	7,84 (d, 2,2)	8,04, 7,63 (15,80)
XI	12,67	6,98 (d, 9,22)	7,44 (dd, 9,22; 2,2)	—	7,84 (d, 2,2)	8,05, 7,63 (15,81)
XII	12,60	6,94 (d, 8,3)	7,32 (dd, 8,3; 2,0)	2,36 s	7,66 (d, 2,0)	8,04, 7,67 (15,60)
XIII	5,14; 7,35	6,99 (d, 8,8)	7,39 (dd, 8,8; 2,57)	—	7,64 (d, 2,57)	7,78, 7,43 (15,76)
XIV	5,13; 7,33	7,00 (d, 8,8)	7,40 (dd, 8,8; 2,57)	—	7,66 (d, 2,57)	7,75, 7,43 (16,13)
XV	5,17; 7,31	7,0...7,4 m	7,0...7,4 m	7,0...7,4 m	7,66 (dd, 2,57; 8,0)	7,80, 7,48 (15,80)
XVI	5,16; 7,32	7,0...7,5 m	7,0...7,5 m	7,0...7,5 m	7,68 (dd, 8,06; 1,8)	7,79, 7,48 (15,80)
XVII	5,05; 7,23	6,97 (d, 9,16)	7,43 (dd, 9,16; 2,57)	—	7,81 (d, 2,57)	4,30, 4,24 (1,83)
XVIII	5,05; 7,22	6,96 (d, 9,0)	7,42 (dd, 9,0; 2,63)	—	7,80 (d, 2,63)	4,31, 4,24 (1,76)
XIX	5,07; 7,22	7,0...7,6 m	7,0...7,6 m	7,0...7,6 m	7,84 (dd, 7,5; 2,0)	4,35, 4,26 (1,83)
XX	5,07; 7,22	7,1...7,6 m	7,1...7,6 m	7,6...7,6 m	7,84 (dd, 8,06; 2,2)	4,35, 4,25 (1,83)

*The protons of the 1,3-benzodioxan fragment resonate at 5.3-5.4 (I-XII) or 5.1-5.2 (XIII-XX) (s, 2-CH_2), 4.79-4.93 (s, 4-CH_2), 6.8-7.2 (d, 2,5,5-H, 7.5-7.6 (I-XII) or 6.9-7.3 (XIII-XX) (d, 2,5,7H) ppm.

TABLE 3. PMR Spectra of Benzodioxan Analogs of Flavanones, Flavones, and 4-Thioxoflavones (XXI-XXIV, XXVI-XLI)

Compound	Chemical shift, δ ppm (coupling constant, Hz)*				
	2a-H, d.d or 3-H, s	5-H, d	6-R^1 (6-H)	7-R^1 (7-H)	8-H, d
XXI	5,73 (11,0; 4,8)	7,93 (d.d,7, 7; 1,8)	7,05 m	7,52 (d.d, 7,7; 1,8)	7,05 m
XXII	5,70 (11,0; 4,5)	7,82 (8,0)	6,9 (d.d 8,0; 2,0)	2,38 s	6,9 (2,0)
XXIII	5,69 (11,8; 4,8)	7,58 (2,5)	—	7,2 m	7,2 m
XXIV	5,71 (11,5; 4,5)	7,89 (2,0)	—	7,44 (d.d 8,0; 2,0)	7,03 (8,0)
XXVI	7,16	8,23 (d.d 8,0 2,0)	7,3...7,7 m	7,3...7,7 m	7,3...7,7 m
XXVII	7,15	8,22 (d.d 7,5; 2,0)	7,3...7,8 m	7,3...7,8 m	7,3...7,8 m
XXVIII	7,13	8,10 (8,06)	7,23 (d.d 8,06; 2,0)	2,51 s	7,36 (d 2,0)
XXIX	7,12	8,10 (8,0)	7,23 (d.d 8,0; 2,0)	2,51 s	7,36 (d, 2,0)
XXX	7,11	8,12 (9,16)	7,00 (d.d 9,16; 2,2)	3,94 s	6,95 (2,2)
XXXI	7,10	8,14 (9,5)	6,99 (d.d 9,5; 2,0)	3,95 s	6,95 (2,0)
XXXII	7,15	7,85 (d.d 8,0; 2,5)	—	7,53 m	7,53 m
XXXIII	7,14	7,85 (d.d 8,0; 2,5)	—	7,52 m	7,52 m
XXXIV	7,17	8,18 (2,57)	—	7,66 (d.d,8.8; 2,57)	7,51 (8,8)
XXXV	7,16	8,18 (2,2)	—	7,66 (d.d. 8,5; 2,2)	7,51 (8,5)
XXXVI	7,15	8,00 (2,0)	2,47 s	7,51 (d.d, 8,8; 2,0)	7,40 (8,8)
XXXVII	8,06	8,46 (8,0)	7,25 (d.d 8,0; 2,2)	2,5 s	7,37 (2,2)
XXXVIII	7,99	8,48 (8,0)	7,0 (d.d, 8,0; 2,0)	3,95 s	6,93 (2,0)
XXXIX	8,09	8,22 (2,9)	—	7,41 (d.d 9,3; 2,9)	7,58 (9,3)
XL	8,08	8,52 (2,5)	—	7,66 (d.d 8,5; 2,5)	7,50 (8,5)
XLI	8,12	8,35 (2,0)	2,48 s	7,55 (d.d 8,0; 2,0)	7,40 (8,0)

*The chemical shifts of the protons at 3-C in chromanones (XXI-XXIV) were: 2.80 (d.d, 11.0-12.0, 16.0-17.0, 3a-H), (d.d 4.5, 16.0-17.0, 3c-H) ppm. The chemical shifts for the protons of the 1,3-benzodioxan fragment were: 5.25-5.38 (s, 2-CH_2), 4.85-4.95 (s, 4-CH_2), 6.97-7.24 (d, 2,5,5-H), 7.5 (for XXI-XXIV) or 7.8-7.9 (for XXVI-XLI) (d, 2.5,7-H) ppm.

The PMR spectra of the flavanones (XXI-XXIV) showed characteristic signals at 5.70 and 2.8-3.0 ppm (Table 3). The coupling constants ($J_{2a,3a}$ = 11.0-1.8; $J_{2a,3e}$ = 4.5-4.8; $J_{3a,3e}$ = 16.0-16.9 Hz) show that the 2-H_a proton is oriented axially, while the benzodioxan residue bonded to this same carbon is oriented equatorially, so that the conformation of the pyranone ring is semi-chair.

The PMR spectra of the chromones and thioxochromones (XXVI-XLI) show signals for the chromone and benzodioxan rings. The most characteristic signals are those for 3-H and 5-H of the benzene ring. Comparing the chromones with thioxochromones, the sulfur atom in the latter gives rise to a low-field shift of the 3-H and 5-H protons of 0.8-1.0 ppm and 0.3-0.4 ppm respectively.

TABLE 4. PMR Spectra of Pyrazolines (XLII-L)

Compound	Chemical shift, δ ppm (coupling constant, J, Hz)*								
	phenolic protons					pyrazoline ring protons			
	2-OH, s	3-H, d	4-R	5-R	6-H, d	4-H_A, dd	4-H_B, dd	5-H_C, t.d	N-H or N-C_6H_5
XLII	10,35	6,8...7,4 m	6,8...7,4 m	6,8...7,4 m	6,8...7,4 m	4,03 (12,46; 17,60)	3.24 (17,6; 6,96)	5,50 (d.d, 12,46; 6,96)	6,8...7,4 m
XLIII	11,03	6,73 (2,0)	2,26 s	6,69 (d.d 2,0; 8,3)	7,15 (8,3)	3,59 (10,25; 17,09)	2,90 (10,25; 17,09)	4,85 (10,25)	7,67 s
XLIV	10,51	6,7...7,3 m	6,7...7,3 m	6,7...7,3 m	7,52 (2,5)	4,03 (12,10; 18,00)	3.27 (18,00; 6,60)	5,54 (d.d, 12,10; 6,60)	6,7...7,3 m
XLV	11,29	6,50 (2,0)	3,75 s	6,45 (d.d 2,0; 8,5)	7,21 (8,5)	3,57 (10,25; 17,09)	2,89 (10,25; 17,09)	4,89 (10,25; 3,42)	7,55 (d, 3,42)
XLVI	11,28	6,50 (2,5)	3,75 s	6,45 (d.d 2,5; 8,8)	7,20 (8,8)	3,58 (10,50; 17,33)	2,87 (10,50; 17,33)	4,90 (10,50; 3,66)	7,56 (d, 3,66)
XLVII	10,89	7,06 m	7,06 m	—	7,06 m	3,60 (11,23; 17,09)	2,96 (11,23; 17,09)	4,98 (11,23)	7,89 s
XLVIII	10,88	7,04 m	7,04 m	—	7,04 m	3,61 (10,25; 17,09)	2,94 (10,25; 17,09)	4,94 (10,25)	7,04 m
XLIX	11,14	6,92 (8,3)	7,22 (d.d, 8,3; 2,5)	—	7,34 (2,5)	3,62 (10,74; 17,58)	2,98 (10,74; 17,58)	4,98 (2,93; 10,74)	7,89 (d, 2,93)
L	10,43	6,7...7,4 m	2,28	6,7...7,4 m	6,7...7,4 m	4,02 (12,10; 17,60)	3,27 (17,60; 6,60)	5,48 (d.d, 12,60; 6,60)	6,7...7,4 m

*The protons of the 1,3-benzodioxan fragment resonate at 5.3-5.4 (s, 2-CH_2), 4.9 (s, 4-CH_2), 6.9-7.3 (d, 2,5,5-H), and 7.1-7.4 ppm (d, 2,5,7-H).

The benzodioxan analogs of chalcones (III, VI-X) react with hydrazine hydrate in alcoholic solution. After a short time, the pyrazoline ring is formed, and the structures of the products (XLIII, XLV-XLIX) were confirmed by elemental analysis and their PMR spectra. They were obtained as colorless, crystalline solids which were readily soluble in 5% sodium hydroxide solution, and gave a blue-green complex with alcoholic ferric chloride. In the PMR spectra of (XLIII, XLV-XLIX), obtained in DMSO, the signal for the 2-OH proton was seen at low field (10.9-11.3 ppm), since the hydroxyl group is involved in IMHB with the nitrogen of the pyrazoline ring. The NH proton in this ring absorbs at 7.5-7.9 ppm.

In the spectra of the 1-phenylpyrazolines (XLII, XLIV, L), the signal for the hydroxyl proton is seen at 10.4-10.5 ppm. The high-field shift of this proton by 0.4-0.7 ppm as compared with the pyrazolines (XLIII, XLV-XLIX), which do not carry a phenyl substituent at nitrogen, indicates the strength of the IMHB between the hydroxyl group and the pyrazoline nitrogen is reduced. The signals for the aromatic protons give rise to a complex system of peaks at 6.4-7.4 ppm. Using special methods, it was possible to identify a doublet for the protons of the benzodioxan fragment. Thus, by double resonance at the frequency of the signal for the 4-CH_2 group of the 1,3-dioxan, the signal for 5-H of the 1,3-benzodioxan, which interacts with the 4-CH_2 group with a small coupling constant, narrowed considerably, thereby enabling the position of this signal in the spectrum to be established. In a homonuclear Oberhauser effect (NOE) experiment, irradiation at the frequency of the 5-H_C signal of the pyrazoline ring resulted in a marked increase (by 10-20%) in the intensity of the signal for 7-H of the benzodioxane ring. This result confirmed the assignment of this signal.

The peaks for the pyrazoline ring protons were seen as an ABC system, identification of the 5-H_C signal being well established. It absorbs at 5.48-5.54 ppm. To assign the signals for H_A and H_B at 4-C of the pyrazoline ring, the NOE method was used. In a $\{5\text{-}H_C\}$ experiment, it was found that in all the compounds there was an increase in the intensity of the signal near 4.03 ppm by 5-7%. This shows that this proton is spatially adjacent to the 5-H_C proton, i.e., these protons have a cisoid orientation. It follows that in the pyrazolines (XLII, XLIV, L) the coupling constants between the 5-H_C proton and the adjacent 4-H_A proton having the cis-orientation are 12.1-12.5 Hz, and between 5-H_C and the trans-4-H_B proton, 6.6-7.0 Hz.

In pyrazolines (XLIII, XLV-XLIX), which do not have an N-phenyl substituent, the 4-H_A (CS 3.6 ppm) in a $\{5\text{-}H_C\}$ experiment also showed a significant NOE (η = 7-10%), showing that the 4-H_A proton, which has the cisoid orientation relative to 5-H_C, absorbs at lower field as in the N-phenylpyrazole derivatives (XLII, XLIV, L). This finding is of particular significance here, since the coupling constants $^3J_{5\text{-}H_C,4\text{-}H_A(cis)}$ and $^3J_{5\text{-}H_C,4\text{-}H_B(trans)}$ for pyrazolines (XLIII, XLV-XLIX) are nearly identical.

Preliminary results of biological testing have shown that some of the chalcones, flavones, and flavanones possess high antiflammatory and hepatoprotectant activity.

EXPERIMENTAL

The purities of the compounds obtained were checked by TLC on Silufol UV-254 plates in a mixture of benzene and ethanol (9:1). The PMR spectra of (I-XX) were obtained on a Bruker CXP-200 spectrometer in deuterochloroform, and those of (XXI-XLI) (in deuterochloroform) and (XLII-L) (in dimethyl sulfoxide) relative to TMS as internal standard, on a Bruker WP-100 SY instrument.

The elemental analyses for (I-L) for C, H, N, Cl, and Br were in agreement with the calculated values.

Chalcones (I-XVI) and thioxochromones (XXXVII-XLI) were obtained as yellow, orange, or red crystalline solids which were readily soluble in organic solvents. In contrast to the starting chalcones, the epoxides (XVII-XX), flavanones (XXI-XXIV), and flavones (XXVI-XXXVI) were colorless crystalline solids.

1-(2-Hydroxyphenyl)-3-(1,3-benzodioxan-8-yl)prop-1-enones (I-XII) and 1-(2-Benzyloxyphenyl)-3-(1,3-benzodioxan-8-yl)prop-1-enones (XIII-XVI). To a hot solution of 20 mmole of 2-hydroxy- or 2-benzyloxyacetophenone in alcohol was added 20 mmole of the appropriate 8-formyl-1,3-benzodioxan and 6 ml of 50% sodium hydroxide solution. The mixture was kept at ambient temperature for 20-40 h, then the solid was suspended in water and acidified with acetic acid until neutral, then filtered off and crystallized from alcohol (I-XII) or ethyl acetate (XIII-XVI).

1-(2-Benzyloxyphenyl)-3-(1,3-benzodioxan-8-yl)-2,3-epoxypropanones (XVII-XX). To a hot solution of 5 mmole of (XIII-XVI) in 50-60 ml of a mixture of acetone and methanol (15:4) was added 10 ml of 30% hydrogen peroxide solution and 5 ml of 2 N sodium hydroxide solution. When the mixture had become completely colorless, it was diluted with water, and the solid filtered off and crystallized from alcohol.

2-(6-Chloro-1,3-benzodioxan-8-yl)chromanones (XXI-XXIV). A suspension of 10 mmole of (I), (III), (VIII), or (X) and 3.5 g of Amberlyst A-21 in 60 ml of methanol was boiled with stirring for 30-60 h. The resin was then filtered off, and the solvent evaporated until crystallization of the chromanone began. The product was recrystallized from methanol.

2-(6-Chloro-1,3-benzodioxan-8-yl)-3-hydroxy-6-chlorochromone (XXV). To a hot mixture of 0.35 g (1 mmole) of (X) and 10 ml of solvent (methanol–acetone, 15:4) was added 7.5 ml of 4 N sodium hydroxide and 1 ml of 30% hydrogen peroxide. The mixture was kept at ambient temperature for 48 h, diluted with twice its volume of water, and neutralized with dilute hydrochloric acid to pH 7. The solid which separated was filtered off, and recrystallized from ethyl acetate. PMR spectrum (DMSO): chromone ring protons: 9.45 (1H, s, 3-OH), 8.07 (1H, d, J 2 Hz, 5-H), 7.83 (1H, d.d, J 2 Hz; 8 Hz, 7-H), 7.72 (1H, d, J 8 Hz, 8-H) ppm; benzodioxan protons: 5.29 (2H, s, 2-CH_2), 4.96 (2H, s, 4-CH_2), 7.39 (1H, d, J 2.2 Hz, 5-H), 7.51 (1H, d, J 2.2 Hz, 7-H) ppm.

2-(1,3-Benzodioxan-8-yl)chromones (XXVI-XXXVI). To a solution of 0.01 mole of (I-IV) or (VI-XII) in 30 ml of dimethyl sulfoxide was added a catalytic amount of iodine, and the solution boiled for 15-30 min. It was then diluted with twice its volume of water, and the solid which separated was filtered off and washed free of traces of iodine on the filter with 20% sodium thiosulfate, then recrystallized from ethyl acetate.

2-(6-Chloro-1,3-benzodioxan-8-yl)thioxochromones (XXXVII-XLI). A finely ground mixture of 5 mmole of the chromone (XXVIII, XXX, XXXII, XXXIV, or XXXVI) and 0.33 mole of phosphorus pentasulfide was dissolved in 5 ml of dry pyridine, and the mixture boiled for 1-2 h at 110-115°C. It was then cooled to ambient temperature, and diluted with 2-3 ml of acetone, then with water until a precipitate formed. The product was filtered off and recrystallized from ethyl acetate.

3-(2-Hydroxyphenyl)-5-(1,3-benzodioxan-8-yl)-2-pyrazolines (XLIII, XLV-XLIX). To a hot solution of 10 mmole of the chalcone (III or VI-X) in 100 ml of alcohol was added 1 ml of 80% hydrazine hydrate, and the mixture boiled for 20 min. It was then diluted with 100-150 ml of water, and the solid which separated was filtered off and recrystallized from alcohol.

1-Phenyl-3-(2-hydroxyphenyl)-5-(6-chloro-1,3-benzodioxan-8-yl)-2-pyrazolines (XLII, XLIV, L). A mixture of 10 mmole of the chalcone (I, III, or X) and 1.7 ml (16 mmole) of phenylhydrazine in 100 ml of alcohol was boiled for 15-20 h. It was then poured into 100 ml of water, and the product filtered off and crystallized from alcohol.

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