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SYNTHESIS AND STRUCTURE OF 4-ARYLSPIRODIHYDRO-PYRANOCHROMEN-2-ONE DERIVATIVES

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Syntheses are reported for sulfur- and nitrogen-containing derivatives of 4-arylspiro-2-benzopyranones modified at the exocyclic oxygen atom. The structure of these products was demonstrated by correlational NMR spectroscopy.

Keywords: 4-arylcoumarins, 2-benzopyranthiones, hydrazones, coumarins, oximes, spirodihydro-pyranochromen-2-ones, heteronuclear correlation.

Derivatives of 4-phenylcoumarin (neoflavones) hold interest since they are widespread throughout the plant kingdom. Thus, more than 130 compounds containing the 4-arylcoumarin system have so far been found in natural sources. Neoflavones isolated from natural sources display antibacterial [2, 3], insecticidal [2, 3], antimalarial [4], sugar-reducing [5], antitumor [6], and cytotoxic activity [7] as well as properties inhibiting HIV-1 reverse transcriptase [8]. On the other hand, neoflavones hold considerable potential for chemical transformation and extensive structural modification [9] and, thus, may display pharmacological properties. Synthetic 4-arylcoumarin derivatives have displayed cytotoxic [10], antioxidant [11], antiatherosclerotic [12], and antibacterial action [13, 14].

In the present work, we introduced the spirodihydropyran fragment into the 4-arylcoumarin molecule and also modified synthetic spiropyranocoumarins at the exocyclic oxygen atom to form sulfur and nitrogen derivatives at C-2. The structures of these products were established by correlational NMR spectroscopy.

Spiro[(7-hydroxychroman-4-one)-2,1'-cyclohexane] (**1**) required for subsequent transformations was obtained by the Kabbe condensation of 2,4-dihydroxyacetophenone with cyclohexanone in the presence of pyrrolidine [15, 16]. Spirochromanone **1** was reduced to spiro[(7-hydroxychroman-2,1'-cyclohexane] **2** under Clemmensen reaction conditions. The Pechman condensation of chromanol **2** with ethyl benzoylacetate or ethyl (4-methoxybenzoyl)acetate in the presence of concentrated sulfuric acid led to the fusion of the 2-pyranone ring to the spirochromanone system and formation of spirodihydropyranocoumarins **3** and **4**.

It is difficult to modify coumarins at the exocyclic oxygen atom starting directly from 2-benzopyranone derivatives. 2-Benzopyranthiones are convenient synthones for carrying out such chemical transformations. The much greater reactivity of 2-benzopyranthiones in comparison with 2-benzopyranones is related to the lower electronegativity of sulfur and, thus, polarizability of the C=S bond.

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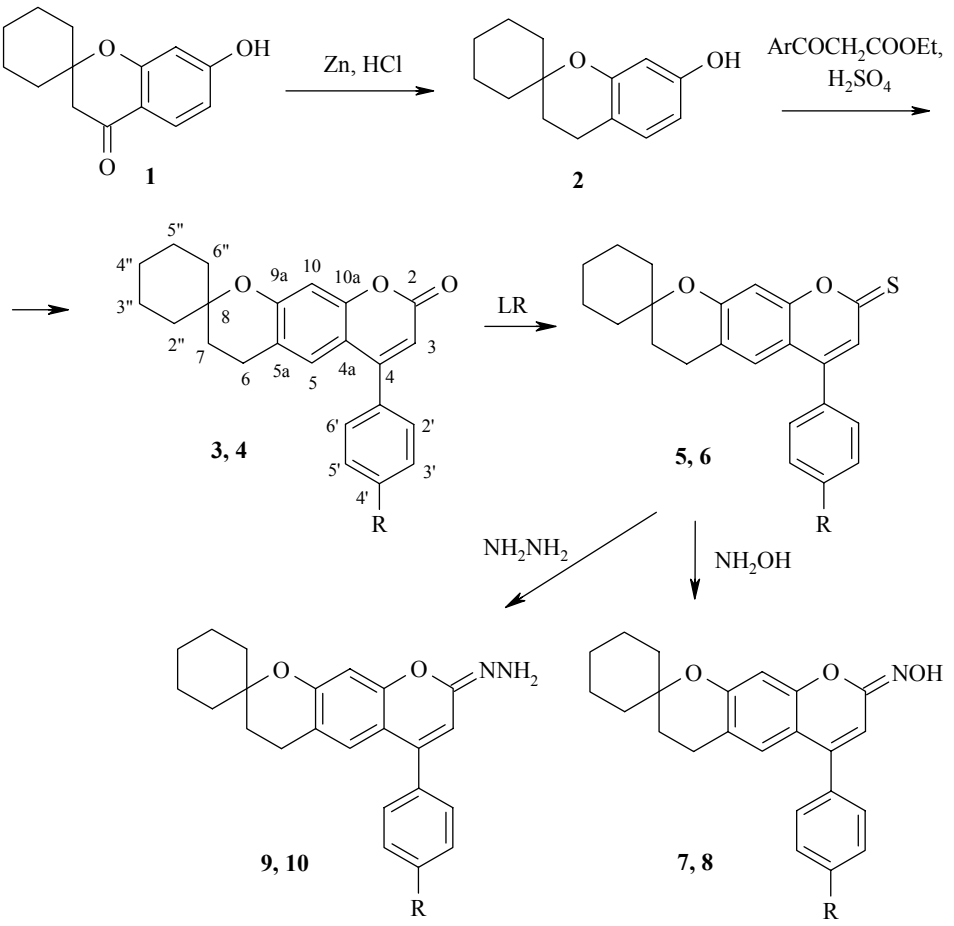
2-Benzopyranones are converted smoothly and, in most cases, with high yield to the corresponding 2-benzopyranthiones. Phosphorus pentasulfide [17-19], 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (Lawesson's reagent) [20, 21], boron sulfide [22, 23], and bis(9-borabicyclo[3.3.1]non-9-yl) sulfide [24] have served as thionylation agents in this reaction.



3,5,7,9 R = H; **4,6,8,10** R = OMe

We employed Lawesson's reagent [25] for thionylation of the exocyclic oxygen atom. 2-Benzopyranthiones **5** and **6** were synthesized smoothly and in high yield by heating spiropyrancoumarins **3** and **4** with a 10% excess of Lawesson's reagent in toluene. In contrast to colorless starting 2-benzopyranones **3** and **4**, products **5** and **6** are bright yellow compounds, whose color is due to the C=S group.

The reaction of 2-benzopyranthiones **5** and **6** with hydroxylamine hydrochloride in pyridine gave spirodihydropyranochromene oximes **7** and **8**. Treatment of solutions of thiones **5** and **6** in ethanol with hydrazine hydrate gave the corresponding spirodihydropyranochromene hydrazones **9** and **10**.

The structures of these products were supported by elemental analysis data and NMR spectroscopy. The ^{1}H NMR spectra of **3-10** given in Table 1 are in accord with the proposed structures but, since the molecular skeleton is rather complicated and lactone derivatives are unstable to the action of nucleophilic reagents, the ^{13}C NMR spectra were taken (Table 2) and experiments were carried out to determine ^{1}H-^{13}C HMQC correlation (through one chemical bond) and HMBC correlation (through two or three chemical bonds).

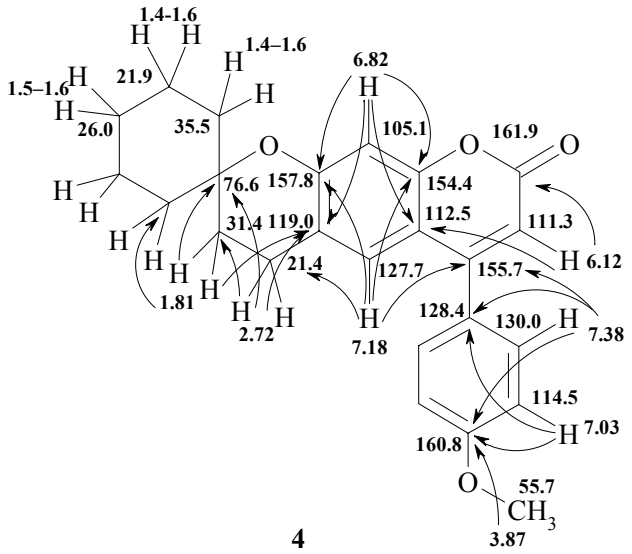
TABLE 1. ^{1}H NMR Spectra of Compounds **3-10 (***J,* Hz)

Atom No.	Chemical shifts, δ, ppm							
	3	**5**	**7**	**9**	**4**	**6**	**8**	**10**
H-3 (1H, s)	6.06	6.92	5.95	5.89	6.12	6.90	5.95	5.85
H-5(1H, s)	7.10	7.25	6.82	6.77	7.18	7.32	6.86	6.80
6-CH_2 (2H, t, J = 6.8)	2.71	2.75	2.60	2.59	2.72	2.76	2.54	2.59
7-CH_2 (2H, t, J = 6.8)	1.80	1.82	1.71	1.74	1.81	1.82	1.68	1.74
H-10 (1H, s)	6.73	6.91	6.56	6.55	6.82	6.89	6.52	6.53
H-2', H-6' (2H, m)	7.45	7.50	7.45	7.36	—	—	—	—
H-2', H-6' (2H, d, J = 8.8)	—	—	—	—	7.38	7.46	7.42	7.28
H-3', H-4', H-5' (3H, m)	7.53	7.55	7.53	7.43	—	—	—	—
H-3', H-5' (2H, d, J = 8.8)	—	—	—	—	7.03	7.07	7.01	6.96
4'-OCH_3 (3H, s)	—	—	—	—	3.87	3.87	3.79	3.82
2"-CH_2, 6"-CH_2 (4H, m)	1.4-1.6	1.6-1.7	1.6-1.7	1.6-1.7	1.4-1.6	1.6-1.7	1.6-1.7	1.6-1.7
3"-CH_2, 5"-CH_2 (4H, m)	1.4-1.6	1.4-1.5	1.4-1.5	1.4-1.5	1.4-1.6	1.4-1.5	1.4-1.5	1.4-1.5
4"-CH_2 (2H, m)	1.5-1.6	1.3-1.5	1.3-1.6	1.3-1.6	1.5-1.6	1.3-1.5	1.3-1.6	1.3-1.6
2-N=NH_2 (2H, br. s)	—	—	—	5.54	—	—	—	5.51
2-NOH (1H, s)	—	—	10.02	—	—	—	10.16	—

TABLE 2. ^{13}C NMR Spectra of Compounds **4, 6, 8,** and **10**

Atom No.	Chemical shift, δ, ppm.			
	4	**6**	**8**	**10**
C-2	161.9	196.3	149.9	143.0
C-3	111.3	125.1	113.2	115.7
C-4	155.7	147.2	140.3	137.9
C-4a	112.5	113.7	113.5	114.1
C-5	127.7	128.0	126.9	126.5
C-5a	119.0	121.0	117.6	116.5
C-6	21.4	21.5	21.0	21.2
C-7	31.4	31.2	31.2	31.8
C-8	76.6	77.1	76.2	75.1
C-9a	157.8	157.2	155.7	155.1
C-10	105.1	104.5	104.3	104.3
C-10a	154.4	158.3	152.5	153.0
C-1'	128.4	127.2	129.0	129.6
C-2', C-6'	130.0	130.6	130.2	129.9
C-3', C-5'	114.5	115.0	114.8	114.5
C-4'	160.8	161.3	160.1	159.8
4'-OCH_3	55.7	55.9	55.8	55.6
C-2", C-6"	35.5	35.4	35.1	35.2
C-3", C-5"	21.9	21.9	22.0	21.9
C-4"	26.0	25.9	25.9	26.1

All the signals in the ^{1}H NMR spectra of spirocoumarin **4** may be assigned with confidence with the exception of the signals of the exocyclic substituent, which are poorly resolved multiplets at 1.35-1.75 ppm. The correlations of the proton signals with the signals of the carbon atom signals in the HMQC spectrum permitted a reliable assignment of the signals of the carbon atoms directly bonded to protons. The existence of a correlation in the HMBC spectrum permitted assignment of the quaternary carbon atoms if these atoms were removed from the protons present by two or three chemical bonds.



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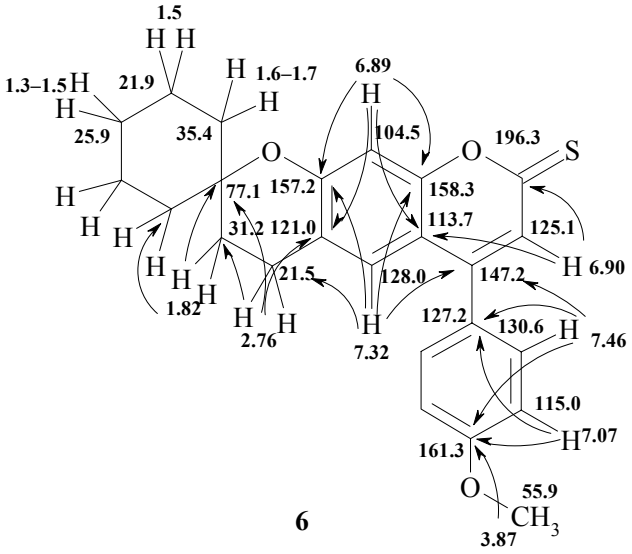

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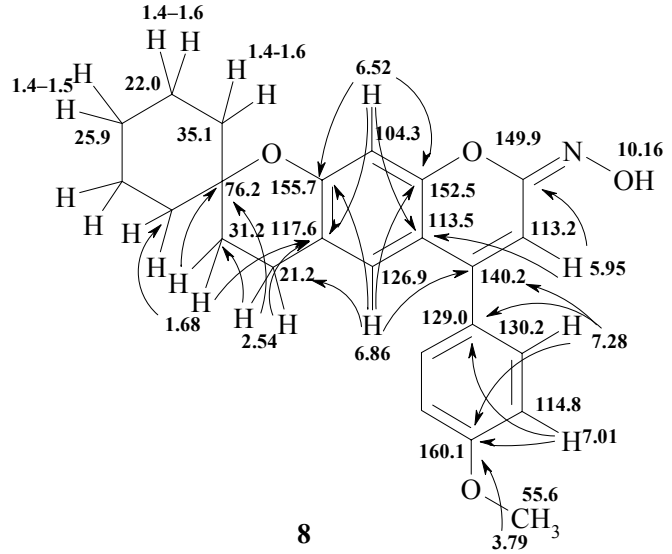
Fig. 1. Heteronuclear correlations of spiro compounds **4** and **6**.

The assignment of the signal at 160.8 ppm to C-4' follows from the correlations for this atom with the methyl group proton signal and protons H-2' and H-3' of the phenyl substituent. The signal at 128.4 ppm corresponds to C'-1 since there are correlations for this signal with protons H-2' and H-3' of the aryl substituent and also with H-3, which is removed from C'-1 by three chemical bonds. The assignment of the signal at 155.7 ppm to C-4 follows from the correlations found for this signal with H-5, H-3, and H-2. Angular

atom C-4a may be assigned on the basis of correlations with H-3, H-5, and H-10 and the ω-interaction with the protons of the methylene group H-6. The chemical shift of this atom is 112.5 ppm. The assignment of the signal at 154.4 ppm to C-10a follows from the correlations found with H-5 and H-10. A correlation is noted for angular atom C-5a with H-5, H-10, and the protons of the methylene groups 6-CH_2 and 7-CH_2. The chemical shift of this atom is 119.0 ppm. Correlations were found for C-9a, which gives rise to the signal at 157.8 ppm, with H-5 and H-10 as well as with the signal for 6-CH_2. Correlations are found for spiro atom C-8, which gives rise to the signal at 76.6 ppm, with methylene groups 6-CH_2 and 7-CH_2. Methylene group 7-CH_2 also has a correlation with the signal of atoms C-2" and C-6", which supports a spiro structure for **4** (the heteronuclear correlations found are given in Table 3). The assignments of the signals in the proton and carbon spectra and the correlations serving as a basis for the assignments are given in the figures. The short distance between H-5 and methylene group 6-CH_2 is also proven from the NOESY spectrum data. A clear cross peak is noted in the NOESY spectrum between the corresponding signals.



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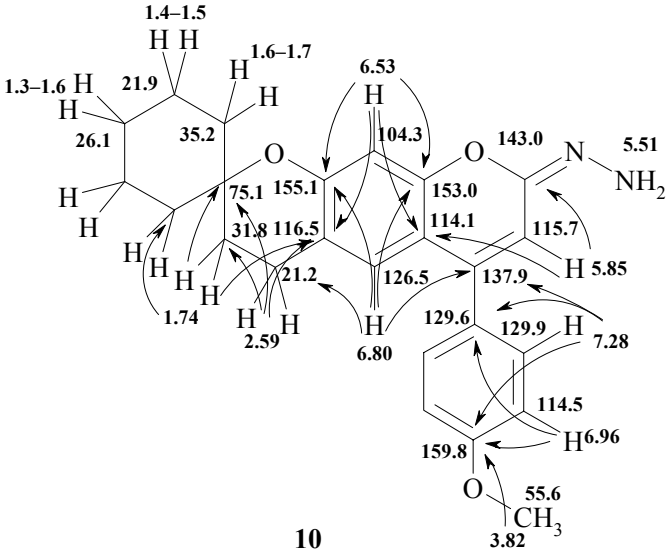

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Fig. 2. Heteronuclear correlations of spiro compounds **8** and **10**.

The structures of compounds **6, 8,** and **10** were similarly demonstrated. The observed heteronuclear correlations and assignments made for the signals in the ^{1}H and ^{13}C spectra are given in Table 3 and the figures. These findings indicate that virtually the same heteronuclear correlations in the HMBC spectra are seen for **4, 6, 8,** and **10**, which indicates lack of change in the molecular skeleton during the chemical transformations. Thus, the assignments of the signals in the ^{13}C NMR spectra of compounds **6, 8,** and **10** are virtually the same as those described for spirodihydropyranochromen-2-one **4**.

TABLE 3. Heteronuclear Correlations for Compounds **4, 6, 8,** and **10**

Compound	^{1}H NMR signals, δ, ppm	Chemical shifts of ^{13}C NMR signals, with correlation, δ, ppm	
		HMQC	HMBC
4	7.38	130.0	160.8, 155.7, 128.4
	7.18	127.7	157.8, 155.7, 154.4, 21.4
	7.03	114.5	160.8, 128.4, 114.5
	6.82	105.1	157.8, 154.4, 119.0, 112.5
	6.12	111.3	161.9, 128.4, 112.5
	3.87	55.7	160.8
	2.72	21.4	76.6, 31.4, 157.8, 112.5, 119.0
	1.81	31.4	76.6, 35.5, 21.9, 119.0
	1.4–1.6	35.5, 26.0, 21.9	–
6	7.46	130.6	161.3, 147.2, 127.2
	7.32	128.0	157.2, 147.2, 158.3, 21.5
	7.07	115.0	161.3, 127.2, 115.0
	6.90	125.1	196.3, 127.2, 113.7
	6.89	104.5	157.2, 158.3, 121.0, 113.7
	3.87	55.9	161.3
	2.76	21.5	77.1, 31.3, 157.2, 121.0, 128.0
	1.82	31.2	77.1, 35.4, 21.5, 121.0
	1.6–1.70	35.4	–
	1.35, 1.5	25.9, 21.9	–
8	10.16	–	149.9
	7.73	130.2	160.1, 140.3, 129.0, 114.8
	7.01	114.8	160.1, 129.0, 114.8
	6.86	126.9	155.7, 152.5, 140.3, 104.3
	6.52	104.3	155.7, 152.5, 140.3, 117.6, 113.5
	5.95	113.2	149.9, 140.3, 129.0, 117.6, 113.5
	3.79	55.8	160.1, 117.6
	2.54	21.0	76.2, 31.2, 155.7, 152.5, 126.9, 113.6, 117.6
	1.68	31.2	76.2, 35.1, 21.0
	1.25–1.6	35.1, 25.9, 22.0	–
10	7.28	129.9	159.8, 137.9, 129.6
	6.96	114.5	159.8, 129.6, 114.5
	6.80	126.5	155.1, 137.9, 153.0, 21.2
	6.53	104.3	155.1, 153.0, 116.5, 114.1
	5.85	115.7	143.0, 137.9, 129.6, 114.1
	5.51	–	–
	3.82	55.6	159.8
	2.59	21.2	155.1, 126.5, 116.5, 114.1, 75.1, 31.8
	1.74	31.8	75.1, 35.2, 21.2, 116.5
	1.4–1.6	35.3	–
	1.4–1.5	21.9	–
	1.4–1.5	26.1	–

Comparison of the chemical shifts found in the ^{13}C NMR spectra shows that the greatest changes, as expected, are observed in the 2-pyranone fragment. The chemical shifts are altered not only for C-2, at which the substituent changes, but also for more distant atoms. While the signal for C-4 in spirodihydropyranocoumarin **4** is observed at 155.7 ppm, the signal for C-4 is shifted upfield upon replacement of the exocyclic oxygen atom at C-2 by a nitrogen atom in oxime **10** (140.2 ppm) and hydrazone **8** (137.9 ppm). This behavior is most likely related to the bipolar structure in the conjugation system of double bonds C-3=C-4 and C-2=R. Support for this hypothesis is found in the weak effect of the substituent at C-2 on the chemical shift of C-3. The signals in the ^{1}H and ^{13}C NMR spectra of the other molecular fragments are only slightly sensitive to change in the substituent at C-2. A cross peak is noted in the NOESY spectra of **6, 8,** and **10**, as in the case of coumarin **4**, between the signals of H-5 and the protons of 6-CH_2.

Therefore, the spirodihydropyran fragment was fused to neoflavone molecules to give sulfur and nitrogen functional derivatives, which hold interest in the study of the biological activity of neoflavones.

EXPERIMENTAL

The course of the reactions and purity of the products obtained were monitored by thin-layer chromatography on Merck 60 F254 plates using 9:1 chloroform–methanol as the eluent. The melting points were determined on a Koefler block. The NMR spectra were taken on a Mercury-400 spectrometer for solutions in DMSO-d_6. The ^{1}H NMR spectra were taken at 400 MHz and the ^{13}C NMR spectra were taken at 100 MHz. The NOE experiments were carried out by the 2D NOESY technique with 200 msec mixing time. The HMQC spectra were obtained from 128 increments with 32 scans per increment. The spectral range was 4 kHz for protons and 21 kHz for carbon. The mixing time corresponded to $^{1}I_{CH} = 140$ Hz. The HMBC spectra were taken for 400 increments with 32 scans per increment. The spectral range was 4 kHz for protons and 21 kHz for carbon. The mixing time corresponded to $^{2\text{-}3}I_{CH} = 8$ kHz. The spectra were taken with proton detection and gradient selection of the signals.

Spiro[(7-hydroxy-4-chromanone)-2,1'-cyclohexane] (1). A samples of pyrrolidine (0.25 mol, 20.9 ml) and cyclohexanone (0.25 mmol, 25.9 ml) were added to a solution of 2,4-dihydroxyacetophenone (0.1 mol, 15.22 g) in acetonitrile (100 ml). The reaction mixture was maintained at 45°C for 8 h (the end-point was determined using thin-layer chromatography). At the end of the reaction, the mixture was treated with 700 ml ice water and acidified to pH 5. The precipitate formed was filtered off. The yield of **1** was 84%; mp 175-176°C (168°C [26], 170-171°C [15, 16]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15-1.95 (10H, m, 2'-CH_2, 3'-CH_2, 4'-CH_2, 5'-CH_2, 6'-CH_2); 2.57 (2H, s, 3-CH_2), 6.24 (1H, d, $J = 2.0$, H-8); 6.39 (1H, d.d, $J = 2.0$, $J = 8.8$, H-6), 7.54 (1H, d, $J = 8.8$, H-5); 10.32 (1H, s, 7-OH).

Spiro[(7-hydroxychroman)-2,1'-cyclohexane] (2). A sample of zinc dust (32 g, 0.5 mol) was added with rapid stirring to a solution of spirochromanone **1** (50 mmol, 11.61 g) in methanol (50 ml) and, then, (100 ml) concentrated hydrochloric acid was added dropwise. The reaction mixture was maintained at room temperature with rapid stirring for 2 h (the end-point was determined using thin-layer chromatography). At the end of the reaction, the residue of unreacted zinc was filtered off and (250 ml) saturated aq. sodium chloride was added to the filtrate. The product was extracted with ethyl acetate. The organic phase was dried over anhydrous magnesium sulfate. The solvent was removed in vacuum on a rotary evaporator. The yield of chromanol **2** as a light yellow oil was 95%. This product was used in subsequent transformations.

Spirodihydropyranochromen-2-ones 3 and 4. A sample of 10 ml concentrated sulfuric acid was added with rapid stirring to a solution of 10 mmols (2.18 g) **2** and 10 mmols of the corresponding ethyl benzoylacetate in (10 ml) ethanol. The reaction mixture was left overnight at room temperature and then poured into 200 ml ice water. The precipitate formed was filtered off and recrystallized from 2-propanol.

Spiro[(4-phenyl-7,8-dihydropyrano[3,2-*g*]chroman-2-one)-8,1'-cyclohexane] (3) was obtained in 68% yield; mp 154-156°C. The ^{1}H NMR spectral data are given in Table 1. Found, %: C 79.58; H 6.31. $C_{23}H_{22}O_3$. Calculated, %: C 79.74; H 6.40.

Spiro[(4-(4-methoxyphenyl)-7,8-dihydropyrano[3,2-*g*]chroman-2-one)-8,1'-cyclohexane] (4) was obtained in 76% yield; mp 199-201°C. The ^{1}H and ^{13}C NMR spectral data are given in Tables 1 and 2. Found, %: C 76.61; H 6.39. $C_{24}H_{24}O_4$. Calculated, %: C 76.57; H 6.43.

Spirodihydropyranochromene-2-thiones 5 and 6. A mixture of 10 mmol spirodihydropyranochromen-2-one **3** or **4** and Lawesson's reagent (1.23 g, 5.5 mmol) in 20 ml toluene was heated at reflux for 2 h (the end-point was determined using thin-layer chromatography). At the end of the reaction, the solvent was evaporated and the oily residue was crystallized from aqueous 2-propanol.

Spiro[(4-phenyl-7,8-dihydropyrano[3,2-*g*]chromene-2-thione)-8,1'-cyclohexane] (5) was obtained in 90% yield, mp 187-189°C. The ^{1}H NMR spectral data are given in Table 1. Found, %: C 76.33; H 5.98; S 8.81. $C_{23}H_{22}O_2S$. Calculated, %: C 76.21; H 6.12; S 8.85.

Spiro[(4-(4-methoxyphenyl)-7,8-dihydropyrano[3,2-*g*]chroman-2-thione)-8,1'-cyclohexane] (6) was obtained in 94% yield, mp 204-206°C. The ^{1}H and ^{13}C NMR spectral data are given in Tables 1 and 2. Found, %: C 73.32; H 6.19; S 8.11. $C_{24}H_{24}O_3S$. Calculated, %: C 73.44; H 6.16; S 8.17.

Oximes of Spirohydropyranochromen-2-ones 7 and 8. A sample of hydroxylamine hydrochloride (0.42 g, 6 mmol) was added to a solution of thione **5** or **6** (3 mmol) in 5 ml absolute pyridine. The mixture was maintained at 100°C (the reaction course was monitored by thin-layer chromatography). At the end of the reaction, the mixture was cooled to room temperature and poured into 100 ml 5% aq. acetic acid. The precipitate formed was filtered off and recrystallized from 2-propanol.

Oxime of Spiro[(4-phenyl-7,8-dihydropyrano[3,2-*g*]chroman-2-one)-8,1'-cyclohexane] (7) was obtained in 84% yield; mp 153-155°C. The ^{1}H NMR spectral data are given in Table 1. Found, %: C 76.31; H 6.52; N 3.82. $C_{23}H_{23}NO_3$. Calculated, %: C 76.43; H 6.41; N 3.88.

Oxime of Spiro[(4-(4-methoxyphenyl)-7,8-dihydropyrano[3,2-*g*]chroman-2-one)-8,1'-cyclohexane] (8) was obtained in 88% yield; mp 176-178°C. The ^{1}H and ^{13}C NMR spectral data are given in Tables 1 and 2. Found, %: C 73.68; H 6.39; N 3.49. $C_{24}H_{25}NO_4$. Calculated, %.: C 73.64; H 6.44; N 3.58

Hydrazones of Spirodihydropyranochromen-2-ones 9 and 10. A hydrazine hydrate (0.3 ml, 6 mmol) was added to a solution of thione **5** or **6** (3 mmol) in 10 ml ethanol. The reaction mixture was heated at reflux for 1 h with monitoring by thin-layer chromatography. At the end of the reaction, the mixture was cooled to room temperature. The precipitate formed was filtered off and recrystallized from 2-propanol.

Hydrazone of Spiro[(4-phenyl-7,8-dihydropyrano[3,2-*g*]chroman-2-one)-8,1'-cyclohexane] (9) was obtained in 85% yield; mp 98-100°C. The ^{1}H NMR spectral data are given in Table 1. Found, %: C 76.49; H 6.78; N 7.59. $C_{23}H_{24}O_2N_2$. Calculated, %: C 76.64; H 6.71; N 7.77.

Hydrazone of Spiro[(4-(4-methoxyphenyl)-7,8-dihydropyrano[3,2-*g*]chroman-2-one)-8,1'-cyclohexane] (10) was obtained in 91% yield, mp 184-186°C. The ^{1}H and ^{13}C NMR spectral data are given in Tables 1 and 2. Found, %: C 73.89; H 6.69; N 7.29. $C_{24}H_{26}N_2O_3$. Calculated, %: C 73.82; H 6.72; N 7.17.

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