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MODIFIED COUMARINS. 23. SYNTHESIS AND STRUCTURE OF CYCLOHEXYLDIHYDROXANTHYLETIN DERIVATIVES

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Cyclohexyldihydroxanthyletin derivatives with S and N in place of the exocyclic O atom were synthesized. The structures of the products were proved by NMR correlation spectroscopy.

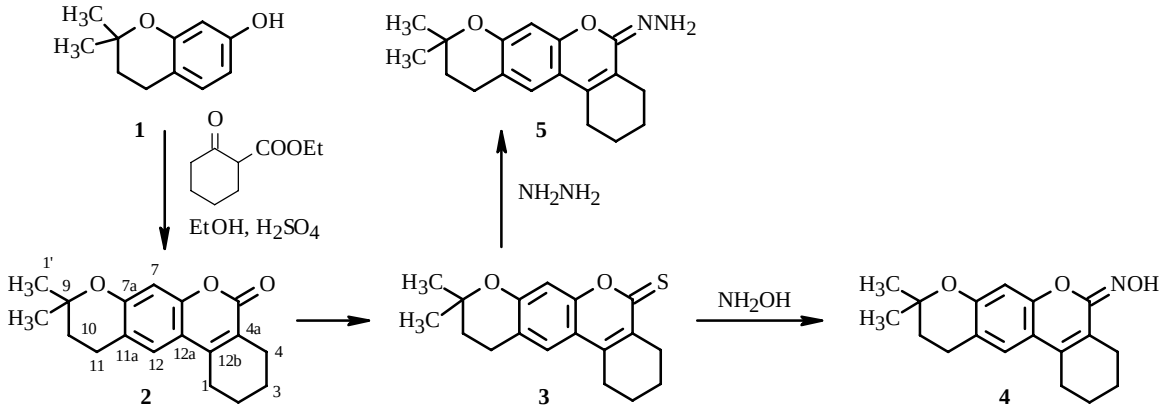
Key words: coumarins, pyranocoumarins, benzopyran-2-thiones, oximes, hydrazones, heteronuclear correlation.

Pyranocoumarins are common in nature and contain a 2,2-dimethylpyran ring annellated to a benzopyran-2-one system [1]. Most natural pyranocoumarins are derivatives of the linear pyran xanthyletin or its angular isomer seselin.

The goal of the present work was to modify the dihydropyranocoumarin system at the exocyclic O atom to form derivatives functionalized at the 2-position with S and N and to establish their structures using NMR correlation spectroscopy.

It is known that coumarins cannot be modified at the exocyclic O atom starting directly with benzopyran-2-one derivatives. Convenient synthons for synthesizing such compounds are benzopyran-2-thione derivatives. The significantly higher reactivity of benzopyran-2-thiones compared with benzopyran-2-ones is due to the lower electronegativity of S and the higher polarizability of the C=S bond.

Cyclohexyldihydroxanthyletin (**2**) that was needed for further transformations was prepared by Pechmann condensation of 2,2-dimethylchroman-7-ol (**1**) and ethyl-2-oxocyclohexanecarboxylate in the presence of conc. H_2SO_4 [2].



Lawesson reagent, the dimer of *p*-methoxyphenylphosphorus sulfide [3], was used for thiation of the exocyclic O atom. Heating **2** with a 10% excess of the reagent in toluene formed 9,9-dimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-thione (**3**). Reaction of **3** with hydroxylamine hydrochloride in pyridine gave the oxime 9,9-dimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one (**4**). Cyclohexyldihydroxanthyletin hydrazone (**5**) was prepared by reaction of **3** with hydrazine in alcohol.

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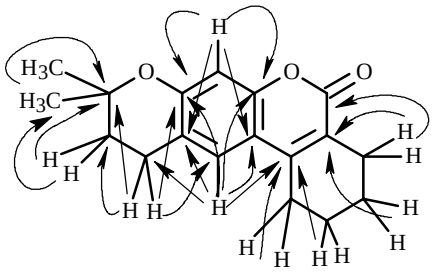
TABLE 1. PMR and ^{13}C NMR Chemical Shifts of **2-5**, ppm

C atom	**2** ($CDCl_3$)		**3** ($CDCl_3$)		**4** (DMSO-d_6)		**5** (DMSO-d_6)	
	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
1	2.71	25.5	2.75	28.4	2.50	24.2	2.41	24.3
2	1.80	22.1	1.80	22.3	1.70	22.1	1.68	21.8
3	1.80	21.7	1.80	21.2	1.65	22.1	1.61	21.8
4	2.52	24.2	2.75	25.5	2.22	23.7	2.20	25.5
4a	-	120.4	-	130.8	-	121.8	-	119.9
5	-	162.7	-	197.9	-	142.7	-	149.5
6a	-	152.0	-	154.5	-	151.0	-	150.6
7	6.68	104.5	6.83	103.7	6.41	103.0	6.44	103.0
7a	-	156.5	-	156.9	-	154.3	-	154.7
9	-	75.5	-	75.7	-	75.2	-	75.4
10	1.84	32.9	1.86	32.3	1.76	32.6	1.75	32.5
11	2.83	22.5	2.85	22.3	2.71	21.9	2.69	21.9
11a	-	118.1	-	119.5	-	116.1	-	116.5
12	7.22	124.0	7.33	123.8	7.12	123.9	7.02	124.1
12a	-	113.6	-	114.8	-	114.6	-	114.1
CH_3-9	1.35	27.2	1.37	26.8	1.28	27.0	1.27	27.0
12b	-	147.5	-	142.2	-	139.9	-	132.3



Scheme 1. Heteronuclear correlations for dihydropyranocoumarins **2**.

The compositions of the products were confirmed by elemental analyses and NMR spectroscopy (Table 1). Although the PMR spectra of **2-5** were consistent with the proposed structural formulas, ^{13}C NMR spectra were measured and heteronuclear ^1H—^{13}C HMQC and HMBC correlations were found in order to confirm the compositions because the molecular frameworks were rather complicated.

^{13}C NMR spectra of **2-5** contained the number of signals corresponding to the structural formulas. However, the signals were difficult to assign because there were several methylene signals close to each other. Furthermore, signals in the aromatic region could also be assigned differently. Signals in PMR spectra could be assigned rather reliably based on their multiplicity and chemical shifts. Those of C atoms directly bonded to protons were assigned unambiguously owing to correlations through a single chemical bond in the HMQC spectrum. Quaternary atoms could be assigned from correlations in the HMBC spectrum with protons through 2-3 chemical bonds. Because the molecules contained many protons, signals of all C atoms could be assigned based on these correlations (Scheme 1).

Thus, the signal near 75.5 ppm was assigned to C-9 in the 2,2-dimethyldihydropyran ring based on correlations through two bonds with the signal for C-9 methyl protons, which had chemical shifts of 1.25-1.35 ppm, and with signals for CH_2-10 and CH_2-11 methylene protons, which resonated near 1.85 and 2.85 ppm, respectively. The C signal at 154-157 ppm was assigned to C-7a based on its correlations with the H-7 singlet, which resonated at 6.4-6.8 ppm, H-12, which gave a singlet at 7.0-7.2 ppm, and the CH_2-11 methylene protons. Quaternary C atoms in the pyran-2-one ring were assigned analogously.

TABLE 2. Characteristic ^{1}H-^{13}C Correlations in HMBC Spectra of **2-5**

H atom	C atom
H-1	C-2; C-5 (w); C-12b; C-4a
H-2	C-12b
H-3	C-4a
H-4	C-2; C-5; C-12b; C-4a
H-7	C-7a; C-6a; C-11a; C-12a
9-CH_3	C-10; 9-CH_3; C-9
H-10	9-CH_3; C-9; C-11a; C-11
H-11	C-9; C-10; C-7a; C-12; C-11a; C-7 (w)
H-12	C-7a; C-6a; C-11; C-12b

The signal at 150.0-154.0 ppm was assigned to C-6a based on its correlations through 2-3 bonds with H-7 and H-12; the signal at 113-115 ppm, to C-12a based on correlations with H-7 and H-12; the signal at 130-147.5 ppm, to C-12b based on correlations with H-12, CH_2-1, CH_2-2, and CH_2-4. The position of the signal changed greatly from compound to compound because of conjugation of the C-4a=C-12b double bond to the C-5 substituent. The signal at 119-131 ppm was assigned to C-4a because it exhibited correlations with CH_2-4 and CH_2-3; the signal at 142-198 ppm, to C-5 because of a single correlation with the CH_2-4 protons. Table 2 gives the characteristic correlations for **2-5**.

Thus, the heteronuclear correlations of **2-5** confirmed that their C skeletons were the same. Additional confirmation that the annellated cyclohexane ring was angular was the observation of a strong Overhauser effect for CH_2-1 and CH_2-11 methylene protons with saturation of the H-12 signal. This was consistent with these protons being close to each other. This effect was observed for all studied compounds.

The ^{13}C NMR spectra of the synthesized compounds showed that the positions of most signals were largely independent of the type of C-5 substituent. Thus, the chemical shifts of the C atoms in the 2,2-dimethyldihydropyran and benzene rings changed by less than 2-3 ppm.

In contrast with this, chemical shifts of C atoms in the pyran-2-one ring changed greatly. An extremely interesting feature of the ^{13}C spectra was the strong dependence of the C-12b chemical shift on the type of C-5 substituent. Thus, whereas the C-12b chemical shift in starting **2** was 147.5 ppm, it was 132.3 and 129.9 ppm on substitution of the O atom on C-5 by N in the oxime and hydrazone, respectively. This indicated that the double bond in the pyran-2-one ring was conjugated to the exocyclic double bond of C-5 and was practically nonconjugated to the aromatic benzene ring. The location of the C-12b signal at anomalously weak field may indicate a significant contribution from a bipolar structure with localization of the positive charge on C-12b and the negative charge on the C-5 heteroatom.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Merck 60 F254 plates using $CHCl_3$:CH_3OH (9:1) eluent. Melting points were determined on a Kofler block. PMR and ^{13}C NMR spectra were recorded on a Varian Mercury-400 spectrometer at working frequency 400 MHz and 100 MHz, respectively, relative to TMS (internal standard). NOE experiments were performed using the 1D NOESY method with 500 ms mixing time. HMQC spectra were obtained for 128 increments and 32 scans per increment with a spectral range of 4 kHz for protons and 21 kHz for ^{13}C. The mixing time corresponded to $^{1}J_{CH}$ = 140 Hz. HMBC spectra were for 400 increments and 32 scans per increment with a spectral range of 4 kHz for protons and 21 kHz for ^{13}C. The mixing time corresponded to $^{2\text{-}3}J_{CH}$ = 8 Hz. Elemental analyses of all compounds agreed with those calculated.

The synthesis of 2,2-dimethylchroman (**1**) has been published [4].

9,9-Dimethyl-1,2,3,4-10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one (2). A solution of **1** (3.56 g, 20 mmol) and ethyl-2-oxocyclohexanecarboxylate (3.2 mL, 20 mmol) in ethanol (10 mL) was stirred vigorously, treated dropwise with conc. H_2SO_4 (20 mL), left overnight at room temperature, and poured into icewater (250 mL). The resulting precipitate was filtered off and crystallized from propan-2-ol. Yield 4.21 g (74%), mp 145-146°C, $C_{18}H_{20}O_3$.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.35 (6H, s, two CH_3-9), 1.80 (4H, m, CH_2-2, CH_2-3), 1.84 (2H, t, J = 7.2, CH_2-10), 2.52 (2H, m, CH_2-4), 2.71 (2H, m, CH_2-1), 2.83 (2H, t, J = 7.2, CH_2-11), 6.68 (1H, s, H-7), 7.22 (1H, s, H-12).

9,9-Dimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-thione (3). A mixture of **2** (2.84 g, 10 mmol) and Lawesson reagent (1.23 g, 5.5 mmol) in absolute toluene (20 mL) was boiled for 2 h (course of reaction monitored by TLC). After the reaction was finished the solvent was evaporated. The oily product was crystallized from aqueous propan-2-ol. Yield 2.58 g (86%), mp 149-150°C, $C_{18}H_{20}O_2S$.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.37 (6H, s, two CH_3-9), 1.80 (4H, m, CH_2-2, CH_2-3), 1.86 (2H, t, J = 7.2, CH_2-10), 2.75 (4H, m, CH_2-1, CH_2-4), 2.85 (2H, t, J = 7.2, CH_2-11), 6.83 (1H, s, H-7), 7.33 (1H, s, H-12).

9,9-Dimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one Oxime (4). A solution of **3** (0.90 g, 3 mmol) in absolute pyridine (5 mL) was treated with hydroxylamine hydrochloride (0.63 g, 9 mmol). The mixture was held at 100°C for 6 h (course of reaction monitored by TLC). After the reaction was finished the mixture was cooled to room temperature and poured into acetic acid (100 mL, 5%). The resulting precipitate was filtered and crystallized from propan-2-ol. Yield 0.60 g (67%), mp 222-223°C, $C_{18}H_{21}NO_3$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.28 (6H, s, two CH_3-9), 1.65 (2H, m, CH_2-3), 1.70 (2H, m, CH_2-2), 1.76 (2H, t, J = 7.2, CH_2-10), 2.22 (2H, m, CH_2-4), 2.50 (2H, m, CH_2-1), 2.71 (2H, t, J = 7.2, CH_2-11), 6.41 (1H, s, H-7), 7.12 (1H, s, H-12), 10.05 (1H, s, N–OH).

9,9-Dimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one Hydrazone (5). A solution of **3** (0.90 g, 3 mmol) in ethanol (10 mL) was treated with hydrazone hydrate (0.6 mL, 12 mmol). The mixture was boiled for 1 h (course of reaction monitored by TLC). After the reaction was finished the mixture was cooled to room temperature. The resulting precipitate was filtered and crystallized from propan-2-ol. Yield 0.65 g (73%), mp 156-157°C, $C_{18}H_{22}N_2O_2$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.27 (6H, s, two CH_3-9), 1.61 (2H, m, CH_2-3), 1.68 (2H, m, CH_2-2), 1.75 (2H, t, J = 7.2, CH_2-10), 2.20 (2H, m, CH_2-4), 2.41 (2H, m, CH_2-1), 2.69 (2H, t, J = 7.2, CH_2-11), 5.70 (2H, br.s, NH_2), 6.44 (1H, s, H-7), 7.02 (1H, s, H-12).

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