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Short Note

Methyl 5′-Chloro-8-formyl-5-hydroxy-1′,3′,3′-trimethyl-spiro-[chromene-2,2′-indoline]-6-carboxylate

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Abstract: Spiropyrans modified with reactive polyfunctional substituents are of great interest as building blocks for the creation of various smart systems with controllable properties for materials science and biomedicine. In this study, a new highly modified spiropyran of the indoline series, methyl 5′-chloro-8-formyl-5-hydroxy-1′,3′,3′-trimethyl-spiro[chromene-2,2′-indoline]-6-carboxylate, was obtained via the cyclocondensation reaction from 5-chloro-1,2,3,3-tetramethyl-3*H*-indolium perchlorate and methyl 3,5-diformyl-2,4-dihydroxy-benzoate. The molecular structure of the target compound was confirmed by ^{1}H, ^{13}C NMR, and IR spectroscopy, as well as LC/MS and elemental analysis. Photochemical studies revealed photochromic activity for the obtained spiropyran at room temperature. The photoinduced merocyanine form demonstrated an enhanced lifetime and fluorescent properties in the red region of the spectrum.

Keywords: spiropyran; photochromism; molecular switch; indoline; heterocycles; polyfunctional substituents

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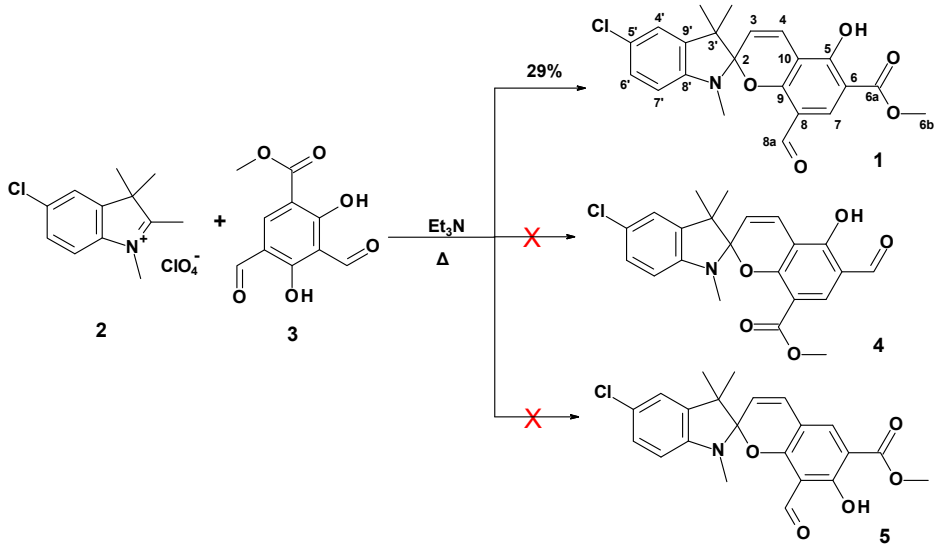
1. Introduction

Over the past several decades, organic photochromic compounds have been constantly attracting interest as components of various smart systems and dynamic materials [1,2]. Spiropyrans [3–7] represent one of the most promising classes of organic photochromes capable of reversible isomerization between the usually uncoloured cyclic (SP) and brightly coloured merocyanine (MC) forms. This process occurs with a dramatic change in the number of properties, such as dipole moment, fluorescence, acidity, etc. Another distinction of spiropyrans is their multi-sensitivity to different types of external stimuli that can induce intermolecular transformation and include the electromagnetic irradiation of various wavelengths, temperature, pH, mechanical stress, the action of metal ions and other chemical species [8–12]. Due to these features, spiropyrans are widely used in different cutting-edge fields of science, including molecular electronics [13,14], nanosensing [12,15], bio-imaging [16,17], targeted drug-delivery [18,19], and photopharmacology [20,21].

The synthesis of novel spiropyrans with different sets of reactive polyfunctional substituents represents one of the most promising directions in the field of organic photochromes. It facilitates the further modification of molecules in order to impart them with desired properties or link them to target substrates. Recently, we obtained photochromic spirocyclic compounds of the 1,3-benzoxazine [22] and indoline [23] series based on the polyfunctional derivatives of salicylic aldehyde. The aim of this study was to synthesize a similar highly modified spiropyran of the indoline series containing several reactive substituents and study its photochromic properties.

2. Results and Discussion

The target methyl 5′-chloro-8-formyl-5-hydroxy-1′,3′,3′-trimethyl-spiro[chromene-2,2′-indoline]-6-carboxylate **1** was obtained via the cyclocondensation reaction of 5-chloro-1,2,3,3-tetramethyl-3*H*-indolium perchlorate **2** and methyl 3,5-diformyl-2,4-dihydroxybenzoate **3** after their mixture in *i*-PrOH and chloroform was heated in the presence of triethylamine (Scheme 1).



Scheme 1. The synthesis of methyl 5′-chloro-8-formyl-5-hydroxy-1′,3′,3′-trimethyl-spiro[chromene-2,2′-indoline]-6-carboxylate **1**.

The structure of 5′-chloro-8-formyl-5-hydroxy-1′,3′,3′-trimethyl-spiro[chromene-2,2′-indoline]-6-carboxylate **1** was confirmed by ^{1}H, ^{13}C NMR, IR, and UV spectroscopy, as well as LC-MS and elemental analysis. It should be noted that due to the presence of two formyl and two hydroxyl groups in the molecule of initial aldehyde **3**, the formation of three structural isomers (**1**, **4**, and **5**) during synthesis was potentially possible (Scheme 1). However, the ^{1}H and ^{13}C NMR spectra indicated the presence of a single isolated product, whereas the analysis of the 2D NMR spectra (^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC and ^{1}H-^{15}N HMBC) enabled us to identify it as structure **1** and to assign all the signals in the ^{1}H and ^{13}C NMR spectra to the corresponding atoms in the molecule.

Thus, the protons H-3 and H-4 appeared in the ^{1}H NMR spectrum as characteristic doublet signals with *J*-constants of 10.6 Hz at 5.72 and 7.27 ppm, respectively, and showed correlations in the ^{1}H-^{1}H COSY NMR spectrum (Figure S3). These data indicate the *cis*-configuration of the corresponding vinylic fragment of the 2*H*-chromene moiety and confirm the spirocyclic structure of molecule **1**. The characteristic signal of the spiro carbon atom C-2 appeared at 107.28 ppm in the ^{13}C NMR spectrum and correlated with the proton signals of H-3, H-4, N-C$\underline{H}_3$, and 3′-C$\underline{H}_3$ groups in the ^{1}H-^{13}C HMBC (Figure S5). The presence of a characteristic cross-peak of the proton H-7 with the carbon atom of the aldehyde group (C-8a) in the ^{1}H-^{13}C HMBC spectrum excluded the possibility of structure **5,** while the observed cross-peak of the –OH hydrogen and the carbon atom C-6 attached to the -COOMe group made the realization of structure **4** impossible. The signal of a single nitrogen atom was found at 92.5 ppm and showed strong correlations with the signals of hydrogen atoms H-3, H-7′ and of the N-CH3 group in the 1H-15N HMBC spectrum (Figure S6). All these facts together confirmed the formation of compound **1** as a single product, which is consistent with the previously obtained data for spiropyrans of the 1,3-benzoxazine series derived from the same aldehyde [22].

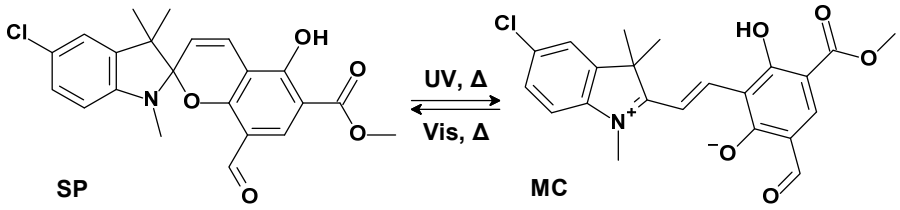
The photochromic properties of spiropyran **1** were studied in acetonitrile solution at room temperature. The obtained spectral and photokinetic parameters are summarized in Table 1.

Table 1. Spectral and kinetic properties of spiropyran **1** in acetonitrile, T = 293 K.

Compound	Isomer	Absorption λ_{max}, nm ($\varepsilon \cdot 10^{-3}$, $M^{-1} \cdot cm^{-1}$)	τ, s	Fluorescense λ_{max}, nm (Φ_{fl})
1	SP	202 (33.4); 253 (47.1); 299 ^{sh} (11.2); 341 ^{sh} (3.5)	-	-
	MC	402; 536	105	611 (0.01)

^{sh} shoulder.

Under ambient conditions, compounds were predominantly found to exist in the closed SP form with the presence of trace amounts of the open MC isomer (Scheme 2). The cyclic-form SP was characterized by intensive absorption bands with maxima in the range of 202–341 nm, while the MC demonstrated two low-intensity absorption maxima in the visible region at 402 and 536 nm (Figure 1). Moreover, the open MC isomer of **1** possessed fluorescence in the red region of the visible spectrum with a maximum at 611 nm and a quantum yield value of 0.01 (Figure S9). After irradiation with UV light (365 nm), an increase in the intensity of the absorption bands with maxima at 402 and 536 nm was observed due to photoinduced isomerization of spiropyran and the enhancement of its MC-form concentration (Figure 1). The reverse reaction of thermal relaxation occurred spontaneously after the termination of irradiation and returned the system to its initial equilibrium state (Figure S10). The lifetime of the open form (τ) was found to be 105 s, which significantly exceeded the lifetime values of similar compounds substituted by several carbonyl-containing groups [22,24]. It should be noted that the irradiation of the initial solution with visible light (546 nm) led to full discoloration due to the photoinitiated cyclization of the MC form. However, the system also returned to the thermal equilibrium state after stopping the irradiation. Thus, it can be concluded that spiropyran **1** demonstrates the properties of a photochromic "balance", as previously described by us [8].



Scheme 2. The photoisomerization scheme of spiropyran **1**.

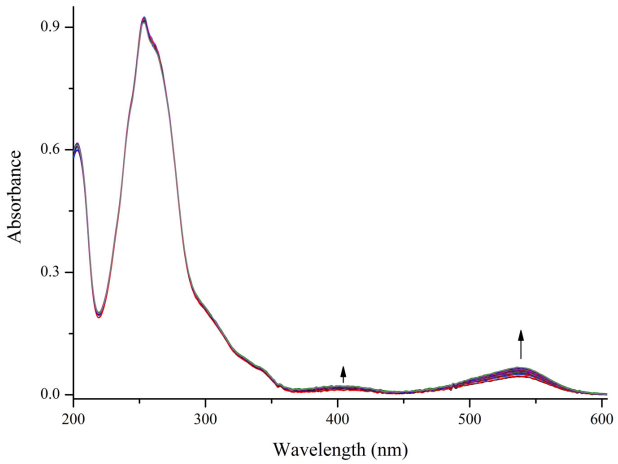


Figure 1. Changes in the absorption spectrum of the compound **1** upon UV irradiation (λ_{irr} = 313 nm) in acetonitrile, $C = 2.18 \times 10^{-5}$ M, T = 293 K.

In summary, we obtained a new highly functionalized spiropyran of the indoline series containing hydroxy, methoxycarbonyl, and formyl groups in the 2*H*-chrome moiety. The molecular structure of the product was confirmed by a set of physicochemical methods. The use of various two-dimensional NMR techniques made it possible to establish the occurrence of only one of the three possible reaction paths, leading to the formation of a single target compound **1**. The obtained spiropyran demonstrated the properties of the photochromic "balance" in acetonitrile solution at room temperature. Its MC form has shown enhanced lifetime value in comparison with similar compounds and exhibited fluorescent properties. The presence of several reactive substituents with different functionality, in combination with photochromic activity and fluorescent properties, makes the target compound a promising candidate for use as a switching molecule in photopharmacology, drug delivery, etc.

3. Materials and Methods

All reagents were purchased from Alfa Aesar and Merck and were used as received. Organic solvents used were purified and dried according to standard methods. Aldehyde **3** was obtained according to the method previously developed by us [22].

^{1}H, ^{13}C, ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, and ^{1}H-^{15}N HMBC NMR spectra were recorded on a Bruker AVANCE-600 (600 MHz) spectrometer at the Center for Collective Use "Molecular Spectroscopy" of Southern Federal University. The signals were assigned relative to the signals of residual protons of the deuteriosolvent $CDCl_3$ (δ = 7.26 ppm). The IR spectra of the compounds were recorded on a Varian Excalibur 3100 FT-IR spectrometer using a partial internal reflection method. The mass spectra were recorded on an Agilent 6470 Triple Quadrupole Jetstream LC/MS spectrometer. The electronic absorption spectra were recorded on an Agilent–8453 spectrophotometer equipped with the thermostatic cell. The irradiation of solutions with the filtered light of a high-pressure Hg lamp was performed on a Newport 66902 equipment. Photoluminescent spectra were recorded with a Varian Cary Eclipse fluorescence spectrophotometer. UV/Vis and fluorescence spectra were recorded using standard 1 cm quartz cells. Acetonitrile of the spectroscopic grade (Aldrich) was used to prepare solutions. The quantum yields of fluorescence were determined by the Parker–Rees [25] method, which used an ethanol solution of cresyl violet acetate (Φ_{fl} = 0.54) as the standard (λ_{ex} = 540 nm) [26].

Elemental analysis was carried out by a conventional method [27]. Melting points were determined on Fisher–Johns apparatus (Thermo Fisher Scientific, Waltham, WA, USA).

Methyl 5′-chloro-8-formyl-5-hydroxy-1′,3′,3′-trimethyl-spiro[chromene-2,2′-indoline]-6-carboxylate 1. In total, 308 mg (1 mmol) of 5-chloro-1,2,3,3-tetramethyl-3*H*-indolium perchlorate **2** and 224 mg (1 mmol) of methyl 3,5-diformyl-2,4-dihydroxy-benzoate **3** were dissolved in a mixture of 10 ml of *i*-PrOH and 5 ml of $CHCl_3$. Then, 0.15 of Et_3N was added and the reaction mixture was refluxed for 2 h. After the solvent was evaporated under vacuum conditions, the residue was purified by column chromatography on SiO_2 (eluent—$CHCl_3$) and recrystallization from acetone to furnish the target product as light purple amorphous solid. Yield = 120 mg (29%). Mp 202–204 °C. IR spectrum, ν, cm^{-1}: 2961, 2855, 1672, 1645, 1605, 1578, 1484, 1436, 1345, 1307, 1271, 1231, 1174, 1094, 1082, 1027, 984, 930, 893, 811, 796, 772, 735, 661, 610, 572, 482, 452. ^{1}H NMR (ppm): δ 11.72 (s, 1H, -OH), 9.91 (s, 1H, -CHO), 8.26 (s, 1H, H-7), 7.27 (d, *J* = 10.6 Hz, 1H, H-4), 7.10 (dd, *J* = 8.2, 2.1 Hz, 1H, H-6′), 7.00 (d, *J* = 2.1 Hz, 1H, H-4′), 6.42 (d, *J* = 8.2 Hz, 1H, H-7′), 5.72 (d, *J* = 10.6 Hz, 1H, H-3), 3.92 (s, 3H, -COOCH_3), 2.72 (s, 3H, N-CH_3), 1.29 (s, 3H, C(3′)-CH_3), 1.19 (s, 3H, C(3′)-CH_3). ^{13}C NMR (ppm): δ 186.82 (CHO), 170.45 (C<u>O</u>OCH$_3$), 162.29 (C-5), 161.82 (C-9), 146.32 (C-8′), 138.20 (C-9′), 131.51 (C-7), 127.67 (C-6′), 124.74 (C-5′), 123.39 (C-4), 122.22 (C-4′), 117.36 (C-3), 116.24 (C-8), 108.10 (C-7′), 107.48 (C-10), 107.28 (C-2), 106.12 (C-6), 52.60 (COO<u>C</u>H$_3$), 52.27 (C-3′), 29.06 (N-CH_3), 25.76 (C-<u>C</u>H$_3$), 20.11 (C-<u>C</u>H$_3$). MS (m/z): 414.2 $[M+H]^+$. Anal. calcd (%) for $C_{22}H_{20}ClNO_5$: C, 63.85; H, 4.87; Cl, 8.57; N, 3.38. Found: C, 63.79; H, 4.90; Cl, 8.53; N, 3.35.

Supplementary Materials: The following supporting information can be downloaded online. Figures S1–S6: The NMR spectra of compound **1**. Figure S7: The IR spectrum of compound **1**; Figure S8: mass-spectrum of compound **1**. Figure S9: The UV/Vis, fluorescence emission, and fluorescence excitation spectra of compound **1**. Figure S10: Kinetic curve of the thermal recyclization reaction of compound **1**.

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