SYNTHESIS AND PHOTOCHROMIC PROPERTIES OF A NOVEL CHROMENE DERIVATIVE

P. S. Perevozhikova, T. M. Aliev, P. A. Nikitina, and N. E. Shepel

Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences
ul. Vavilova 28, Moscow, 119991 Russia
b Mendeleev University of Chemical Technology of Russia, Miusskaya pl. 9, Moscow, 125047 Russia

Abstract

A convenient synthetic approach to a novel 2,2-diphenyl-2H-chromene derivative is developed starting from vanillin or acetovanillone. The photochromic properties of the resulting chromene are studied. The kinetic characteristics of this compound show its potential for the design of new efficient DNA intercalators.

Key words: chromene, rearrangement, photochromic properties, activation energy, DNA intercalator.

Introduction

Small molecules that are able to recognize a DNA sequence are promising therapeutic agents and molecular tools for studying and regulating specific gene expression [1, 2]. Of particular interest is the investigation of DNA binding with organic molecules that can intercalate between two complementary base pairs, thereby changing its functioning. This process is of high importance for the search for new drugs for the treatment of various diseases, including different types of cancer.

In developing selective drugs for chemotherapy, special attention is given, in particular, to the photoactive derivatives of chromene [3]. Owing to the structural features, a chromene molecule in a closed form does not interact with DNA; however, upon irradiation, it undergoes a photochromic transformation into an open, planar merocyanine form that can coordinate with DNA, for example, of cancer cells [4].

It should be noted that there is only a limited number of reports devoted to the application of chromene derivatives as photoswitchable ligands for DNA. Therefore, the goal of this work was to synthesize a novel chromene derivative and to study its photochromic characteristics. A relatively stable open form of the resulting derivative opens the way to the investigation of its interaction with DNA, which will become a subject for further research.

Results and discussion

Syntheses

Chromene derivative 1 was chosen as a target compound. The introduction of electron-donating substituents at positions 6 and 7 of a benzopyran moiety leads to a bathochromic shift of an absorption band relative to that of the unsubstituted chromene, which can provide a greater color contrast between closed and open forms [5]. The presence of a bromine atom in the oxalkyl substituent ensures a possibility of further synthesis of chromene conjugates with other molecules, for example, styryl dyes that exhibit affinity to DNA. The length of this spacer can affect the simultaneous binding of both of the conjugate moieties with a DNA molecule.

As is known, one of the methods for synthesizing this type of chromenes is the interaction of phenols with diphenylpropargyl alcohol 2 in the presence of acids [6–10]. Compound 1 was obtained by reacting phenol 3 with 2 in the presence of p-toluenesulfonic acid upon heating in toluene (Scheme 1).

Scheme 1. Synthesis of chromene derivative 1.

The formation of a linear chromene instead of an angular one was confirmed by the presence of two singlets in the 'H NMR spectrum of chromene 1, which correspond to the protons at positions 5 and 8 of the benzopyran moiety.

Initial phenol 3 can be obtained in three stages starting from commercially available vanillin (4a, R = H) or acetovanillone (4b, R = Me) (Scheme 2).

Scheme 2. Synthesis of phenol 3.
At the first step, substituted phenols 4a,b were subjected to the O-alkylation upon prolonged refluxing with a double excess of 1,5-dibromopentane in the presence of potassium carbonate and potassium iodide in acetonitrile [11]. The next step was the Baeyer–Villiger oxidation (rearrangement). The interaction of 5a,b with m-chloroperbenzoic acid in dichloromethane under an argon atmosphere was accomplished according to the published procedure [12]. The hydrolysis of esters 6a,b was carried out by heating with 7% aq. hydrochloric acid. It should be noted that the hydrolysis of acetate ester 6b required a much higher temperature. At the same time, the hydrolysis of formic acid ester 6a afforded target phenol 3 in a higher yield.

**Photochromic properties**

It is well known that chromenes undergo structural transformations under the action of UV radiation, which afford two, the most stable isomers, the so-called transoid-cis (TC) and transoid-trans (TT) forms (Scheme 3) [13, 14]. These isomers feature high closure stability, which defines the total lifetime of the open form.

\[
\text{Scheme 3. Photochromic transformations of chromene derivatives.}
\]

The phototransformation can be monitored by UV-Vis spectroscopy. The open forms exhibit absorption bands in the visible region, which gradually disappear after the cessation of irradiation. Thus, the irradiation of a solution of chromene 1 leads to the growth of two bands in the spectrum with \(\lambda_{\text{max}} = 380\) and 470 nm (Fig. 1).

**Figure 1.** Absorption spectra of chromene 1 in MeCN (4x10^{-3} M) during irradiation (294 K, filtered light, \(\lambda = 313\) nm, Hg lamp, light beam power 1.06 mW/cm²). Spectrum labeled (A) was recorded before irradiation. Spectrum labeled (B) was recorded in 5 min of irradiation.

The stability of the photoinduced forms can be defined from kinetic characteristics of the thermal relaxation: the reaction rate constant \((k)\) and half-decoloration time \((\tau_1/2)\). The kinetics of the thermal relaxation of chromene 1 was studied at four temperatures: 294, 298, 303, and 313 K (Fig. 2).

As can be seen from Fig. 2a, the absorption spectrum at \(T = 294\) K did not conform to the initial form (Fig. 1, A), which may evidence the formation of a stable photoinduced form (TT). A temperature increase was accompanied by a decrease in the residual optical density in the visible region (Fig. 2b,c): the values of optical density at \(\lambda = 470\) nm in 3000 s after cessation of irradiation were 0.21 (294 K), 0.19 (298 K), 0.17 (303 K), and 0.08 (313 K). It is obvious that a temperature rise leads to the acceleration of both reverse processes. Owing to this, the stable open TT form converts to the less stable TC form, which finally leads to the complete closure of a pyran ring. During dark relaxation at \(T = 313\) K (Fig. 2d), the long-wave absorption
band disappears. At the same time, the absorption spectrum of the light-exposed solution kept in the dark became almost indistinguishable from that of the solution before irradiation.

The processes that take place after cessation of irradiation can be characterized by the following scheme of transformations:

\[ \text{TT} \xrightarrow{k_{\text{TT}}} \text{TC} \xrightarrow{k_{\text{TC}}} \text{CF}, \]

where TT and TC are the open forms of the chromene, CF is the closed (initial) form of the chromene. A total expression for the observed changes in the intensities of absorption bands of the open forms in time has a biexponential character and can be described by the following equation:

\[
A = A_0^{\text{TC}} \cdot e^{-k_{\text{TC}}t} + A_0^{\text{TT}} \cdot e^{-k_{\text{TT}}t},
\]

where \( k_{\text{TT}} \) and \( k_{\text{TC}} \) are the rate constants of sequential steps of the decoloration process, \( A_0^{\text{TC}} \) and \( A_0^{\text{TT}} \) are the initial absorbances of each form (at the beginning of the reverse reaction). The resulting kinetic characteristics for each temperature are summarized in Table 1.

Table 1. Kinetic characteristics of the thermal relaxation

<table>
<thead>
<tr>
<th>T, K</th>
<th>( k_{\text{TC}}, \text{s}^{-1} )</th>
<th>( t_{1/2}^{\text{TC}}, \text{s} )</th>
<th>( k_{\text{TT}}, \text{s}^{-1} )</th>
<th>( t_{1/2}^{\text{TT}}, \text{s} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>294</td>
<td>1.25 \times 10^{-3}</td>
<td>555 s</td>
<td>1.29 \times 10^{-5}</td>
<td>892 min</td>
</tr>
<tr>
<td>298</td>
<td>2.41 \times 10^{-3}</td>
<td>288 s</td>
<td>3.81 \times 10^{-5}</td>
<td>303 min</td>
</tr>
<tr>
<td>303</td>
<td>3.34 \times 10^{-3}</td>
<td>208 s</td>
<td>6.49 \times 10^{-5}</td>
<td>178 min</td>
</tr>
<tr>
<td>313</td>
<td>1.48 \times 10^{-2}</td>
<td>47 s</td>
<td>3.80 \times 10^{-4}</td>
<td>30 min</td>
</tr>
</tbody>
</table>

The temperature dependence of the rate constant of the thermal relaxation corresponds to the Arrhenius equation:

\[ k(T) = \nu \cdot e\left(-\frac{E_a}{RT}\right), \]

where \( E_a \) is the reaction activation energy, \( \nu \) is the preexponential factor, \( R \) is the universal gas constant, and \( T \) is the temperature.

The results of the investigation of the kinetics of thermal relaxation for both of the reactions are compared in Fig. 3 in the form of the Arrhenius plot. The dash lines in Fig. 3 represent the linear approximation of the data, and the line slopes were used to calculate the activation energies.

The closure of the open TC and TT forms can be accelerated not only by a temperature rise. While conducting the photochemical relaxation through irradiation with \( \lambda = 405 \) nm, the absorption spectrum of the open form also returns to its initial form (Fig. 4).

The application of NMR spectroscopy for the investigation of photochromic transformations allows one to unambiguously define the structures of the photoinduced forms and their stabilities. The irradiation of a solution of chromene \( \text{I} \) led to the appearance of signals of the open forms in the \(^1\text{H} \) NMR spectrum, which changed their intensity depending on the irradiation duration. A characteristic signal of the TC form is a peak of a proton at position 3 observed at 8.57 ppm. This shift is caused by a deshielding effect of the closely located carbonyl group (Fig. 5b). When irradiation was stopped, the reverse process was observed: the signals of the closed form increased and those of the open ones reduced (Fig. 5c). To fully escape the signals of the open form (TT), a solution after thermal relaxation was irradiated with \( \lambda_{\text{irr}} = 405 \) nm (Fig. 5d).

**Experimental**

**General remarks**

All the reagents were purchased from commercial sources and used without purification. The \(^1\text{H} \) and \(^1\text{C} \) NMR spectra were registered on a Bruker Avance TM 400 spectrometer at the operating frequencies of 400 and 100 MHz using deuterated solvents (CDCl\(_3\), CD2COCD2, CD-CN). The residual solvent signals were used as internal standards. The UV-Vis spectra were measured on an AvaSpec-2048 spectrophotometer. The irradiation was performed with a light diode (405 nm), a FIL-105 photographic flash (flash guide 34 at ISO 100, discharge energy 68 J), and a high-pressure mercury lamp (DRSh 120 W). The certain spectrum lines of the Hg lamp were separated using glass filters from a standard set of samples of color optical glasses (313 nm). The UV-Vis spectra of the colored form were registered during continuous irradiation of the samples with the filtered radiation of the mercury lamp to obtain the maximal concentration of the open forms. The dark relaxation was carried out in total darkness; the scanning light required for the registration of the UV-vis spectrum was turned off between measurements, its exposure time to the sample...
during spectrum registration composed less than 1 s per 1 spectrum (point on the kinetic curve). The elemental analyses were performed at the Laboratory of Microanalyses of INEOS RAS. The EI mass spectra were registered on a Finnigan Polaris Q instrument (ion trap). The energy of ionizing electrons was 70 eV. The melting points were measured on a PTP(M) apparatus.

**Syntheses**

6-[(5-Bromopentyl)oxy]-7-methoxy-2,2-diphenyl-2H-chromene (1). Phenol 3 (0.100 g, 0.35 mmol) and 1,1-diphenylprop-2-yn-1-ol (0.070 g, 0.35 mmol) were dissolved in toluene (6 mL) upon heating at 50–55 °C. Then, p-toluenesulfonic acid (0.010 g, 0.06 mmol) was added. The stirred reaction mixture was heated at 55–58 °C for 2.5 h and at 90 °C for further 4 h. The solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (eluent: CHCl3) to give 0.044 g of compound 1 as a viscous yellow oil. Yield: 26%. 1H NMR (CDCl3): δ 7.48 (d, 4H, H-Ar), 7.33 (t, 4H, H-Ar), 7.26 (t, 2H, H-Ar), 6.72 (s, 1H, H-Ar), 6.66 (s, 1H, H-Ar), 6.64 (d, 1H, CH, J = 10.2 Hz), 6.22 (d, 1H, CH, J = 10.2 Hz), 3.89 (t, 2H, CH2), 3.81 (s, 3H, CH3), 3.52 (t, 2H, CH2), 1.90–1.94 (m, 2H, CH2), 1.72–1.77 (m, 2H, CH2), 1.58–1.64 (m, 2H, CH2) ppm. 13C NMR (CDCl3): δ 150.8 (C-6), 146.9 (C-7), 145.3 (C-8a), 143.1 (2C-Ph), 128.2 (4C-Ph), 127.5 (2C-Ph), 126.7 (C-3), 126.6 (4C-Ph), 123.4 (C-4), 113.5 (C-5), 112.1 (C-4a), 101.6 (C-8), 81.9 (C-2), 69.2 (O-CH2), 55.6 (O-CH3), 34.3 (CH2-Br), 32.3 (–CH2–), 28.3 (–CH2–), 24.5 (–CH2–) ppm. MS (EI): m/z = 478, 480 (intensity ratio: 1:1.15) [M]+. Anal. Calcd for C32H28BrO6: C, 67.64; H, 5.68. Found: C, 67.92; H, 5.84%.

**General procedure for the synthesis of 4-[(5-bromopentyl)oxy]-3-methoxyphenol (3).** Ester 6a or 6b (1.2 mmol) was added to 7% aq. hydrochloric acid (40 mL). The stirred mixture was heated at 70–75 °C for 3 h and, then, cooled to room temperature and extracted with CH2Cl2 (50 mL). The organic layer was separated and dried over MgSO4. The solvent was removed under reduced pressure to give product 3 as a brown oil which crystallized in time. The reaction of ester 6a (0.38 g, 1.2 mmol) afforded 0.26 g (74%) of compound 3. The
After the reaction completion, the resulting mixture was washed with dichloromethane (30 mL) at 83 °C. The reaction mixture was stirred at 83 °C for 35 h. The reaction mixture was stirred at a calcium chloride tube for 35 h. The filtrate and washing liquid were combined. The solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (elucent: CHCl₃) to give 6.24 g of compound 5b as a yellow oil. Yield: 83%. ¹H NMR (CDCl₃): δ 9.87 (s, 1H, CH), 7.43–7.48 (m, 2H, H-3), 6.98 (d, 1H, H-1, J = 8.3 Hz), 4.14 (t, 2H, CH₂), 3.95 (s, 2H, CH₂), 3.72 (t, 2H, CH₂), 1.97 (q, 4H, 2CH₂), 1.68 (q, 2H, CH₂) ppm. ¹³C NMR (CDCl₃): δ 191.0 (C-10), 154.0 (C-4), 149.8 (C-3), 130.0 (C-1), 126.8 (C-6), 111.4 (C-5), 109.2 (C-2), 68.8 (O-CH₃), 56.0 (O-CH₃), 33.5 (C-CH₂-Br), 32.4 (C-CH₂), 28.1 (C-CH₂), 24.7 (C-CH₂) ppm. MS (EI): m/z = 300, 302 (intensity ratio: 1:1.6) [M⁺]. Anal. Calcd for C₁₃H₁₀BrO₃: C, 51.84; H, 5.69. Found: C, 51.68; H, 5.68%.

1-[4-(5-Bromopentyl)oxy]-3-methoxyphenyl)ethanone (5b). A solution of 1,5-dibromopentane (11.50 g, 0.050 mol) in acetonitrile (50 mL) was added to a mixture of vanillin 4a (3.80 g, 0.025 mol), potassium carbonate (5.18 g, 37.5 mmol), and potassium iodide (0.42 g, 2.5 mmol). The stirred mixture was refluxed with a calcium chloride tube for 35 h. The reaction mixture was stirred at 83 °C for 35 h. The filtrate and washing liquid were combined. The solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (elucent: CHCl₃) to give 2.05 g of compound 5b as an oil which crystallized in time. Yield: 49%. Mp: 32–34 °C. ¹H NMR (CDCl₃): δ 6.86 (d, 1H, H-1, J = 8.3 Hz), 6.62–6.65 (m, 2H, H-3), 4.02 (t, 2H, CH₂), 3.86 (s, 3H, CH₃), 3.46 (t, 2H, CH₂), 2.30 (s, 3H, CH₃), 1.94–1.98 (m, 2H, CH₂), 1.85–1.89 (m, 2H, CH₂), 1.62–1.66 (m, 2H, CH₂) ppm. ¹³C NMR (CDCl₃): δ 169.9 (C=O), 149.9 (C-3), 146.2 (C-1), 144.5 (C-4), 113.2 (C-5), 112.9 (C-6), 106.0 (C-2), 69.1 (O-CH₃), 56.0 (O-CH₃), 33.7 (C-CH₂-Br), 32.5 (C-CH₂), 28.4 (C-CH₂), 24.8 (C-CH₂) ppm. MS (EI): m/z = 330, 332 (intensity ratio: 1:0.94) [M⁺]. Anal. Calcd for C₁₃H₁₂O₃Br: C, 50.77; H, 5.78. Found: C, 50.96; H, 5.91%.

Conclusions

Two schemes for the synthesis of the new chromene derivative were developed that consist of four steps and utilize vanillin and acetovanillone as key precursors. Taking into account the higher yields at each step and availability of vanillin, the approach based on it seems to be optimal.

The photochromic properties of the resulting chromene derivative were explored at different temperatures. The kinetic studies revealed the high closure stability of its open form, which can be used for further investigation of the interaction with DNA.

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Corresponding author

P. S. Perevozchikova

E-mail: polina-krasnopevra@mail.ru

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Electronic supplementary information

Electronic supplementary information (ESI) available online: $^1$H, $^{13}$C NMR and mass spectra of compounds 1, 3, 5a,b, and 6a,b. For ESI, see DOI: 10.32931/io2102a

References


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