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Reactions of *N*-[(9-chloro-2,3-dihydro-1*H*-(chromen)xanthen-4-yl)methylene]-*N*-methylmethanaminium perchlorates with aromatic amines

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By interaction of N-[(9-chloro-1,2-dihydrocyclopenta[b]chromen-3-yl)methylene]-N-methylmethanaminium perchlorate and N-[(9-chloro-2,3-dihydro-1H-xanthen-4-yl)methylene]-N-methylmethanaminium perchlorate with aromatic amines (p-anisidine, p-aminophenol, p-aminobenzoic acid and aniline), Schiff bases were synthesized which are potential polydentant ligands for binding to transition metal ions. Depending on the amount of starting compounds, these reactions yield either a mixture of mono- and disubstitution products or a product with two aromatic amine fragments. Interaction of N-[(9-chloro-1,2-dihydrocyclopenta[b]chromen-3-yl)methylene]-N-methylmethanaminium perchlorate with p-aminobenzoic acid regardless of the ratio of starting materials leads to the formation of 4-{((3E,9Z)-3-{[(4-carboxyphenyl)amino]methylene}-2,3-dihydrocyclopenta[b]chromene-9(1H)-ylidene]amino}benzoic acid with low yield. The low reactivity of p-aminobenzoic acid can be explained by the reduced nucleophilicity of the nitrogen atom of the amino group due to the presence of an electron-accepting carboxyl group in the benzene nucleus. The regioselectivity of the reaction of perchlorate with p-aminobenzoic acid is explained by the intramolecular protonation of the primary intermediate azomethine due to the presence of a carboxyl group. In the resulting zwitterion, the positive charge is transferred to the nitrogen atom of the dimethylamino group. As a result of the charge transfer, the carbon atom associated with it becomes more electrophilic, which causes a second attack of p-aminobenzoic acid. The obtained compounds can be used in the synthesis of complex compounds.

Keywords: xanthene derivatives, chromen derivatives, Schiff bases, aromatic amines, polydentate ligands.

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Introduction

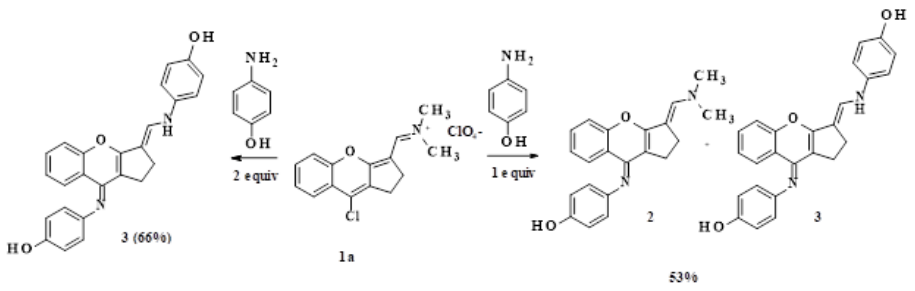
Today, a large number of fluorescent probes based on xanthenes are known, which contain fragments of Schiff bases in the structure [1,2]. The structure of Schiff bases is very well suited as a ligand for the identification of metal ions and quantitative analysis of ion content. There is a series of Schiff's xanthene bases for the detection of Cu^{2+} [3], Hg^{2+} [4], Fe^{3+} [5], Zn^{2+} [6,7], Ca^{2+} [8,9] ions. The number of publications indicates the further development in the biochemical and biomedical sciences of the use of xanthene derivatives as attractive sensory systems for intracellular detection.

We have developed an effective method for the synthesis of xanthene formyl derivatives by rearrangement of spiro derivatives of 1,3-benz(naphtho)oxazines(dioxins) [10–13]. As a result of chemical modification of formyl-derived xanthenes, Knovenagel reaction products [14], Schiff bases and azines [15] were obtained, and their photophysical properties were studied. The synthesized compounds demonstrated the presence of fluorescence in solutions with high Stokes shifts, high molar extinction coefficients and moderate quantum yields. The obtained results proved the prospects of continuing research in this area.

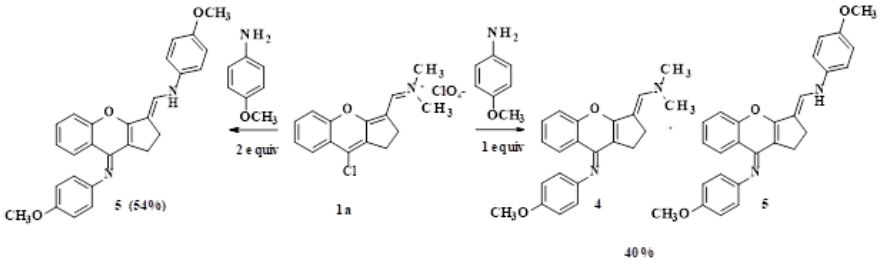
Results and discussion

A logical continuation of the research was the synthesis of Schiff bases by the reaction of N-[(9-chloro-2,3-dihydro-1H-(chromen)xanthen-4-yl) methylene]-N-methylmethanaminium perchlorate 1a,b [13] with N-nucleophiles in order to obtain potential polydentant ligands for binding to transition metal ions. The interaction of halogen derivatives of xanthene 1a,b with aromatic amines, such as p-aminophenol, p-anisidine, p-aminobenzoic acid and aniline, leads to the formation of Schiff bases. Depending on the amount of starting compounds in these reactions, either a mixture of products or a product with two fragments of aromatic amine is formed.

The interaction of perchlorate 1a with an equivalent amount of p-aminophenol for one day gave a mixture of products with structures 2 and



Scheme 1



Scheme 2

3 in the ratio according to chromato-masses 14.7% (retention time 0.755 min) and 85.3% (retention time 0.775 min), respectively. Upon interaction of compound 1a with a twofold excess of aromatic amine under similar conditions, only the product of disubstitution 3 is formed (Scheme 1). In the ^{1}H NMR spectrum, the presence of OH groups is confirmed by peaks with a chemical shift of 9.55 and 10.0 ppm. Proton signals of the enamine group =CH–NH correspond to peaks with a chemical shift of 8.05 and 10.12 ppm, respectively.

Reaction of salt 1a with one equivalent of p-anisidine by short heating and subsequent reaction at room temperature for one day also leads to the formation of a mixture of products 4 and 5, and the reaction with excess aromatic amine gave one product with structure 5 (Scheme 2).

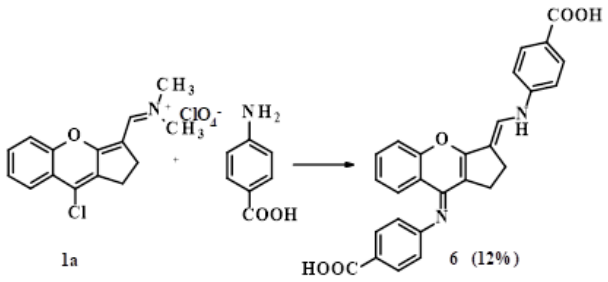
The reaction of chlorine-substituted xanthene 1a with p-aminobenzoic acid was also performed. It was found that the interaction of the starting compounds in a ratio of 1:1, as well as the use of excess amine formed xanthene dye 6 with low yield (Scheme 3). The low reactivity of p-aminobenzoic acid can be explained by the reduced nucleophilicity of the nitrogen atom of the amino group, due to the presence of an electron-accepting carboxyl group in the benzene nucleus. Based on experimental data, it can be assumed that azomethine is an intermediate product of the reaction, similar to products 2 and 4. When reacting with p-aminobenzoic acid, the resulting azomethine can be intramolecularly protonated due to the presence of a carboxyl group. In the resulting zwitter ion, the positive charge is transferred to the nitrogen atom of the dimethylamino group. As a result of the charge transfer, the carbon atom connected to it becomes more electrophilic, which causes the second attack by p-aminobenzoic acid.

According to the obtained results, the increase in the excess of aromatic amine leads to the formation of exclusively substitution products of the two end groups in the original chlorine derivatives of xanthene. Thus, due to the interaction of salt 1b with a threefold excess of aniline, xanthene dye 7 was synthesized (Scheme 4).

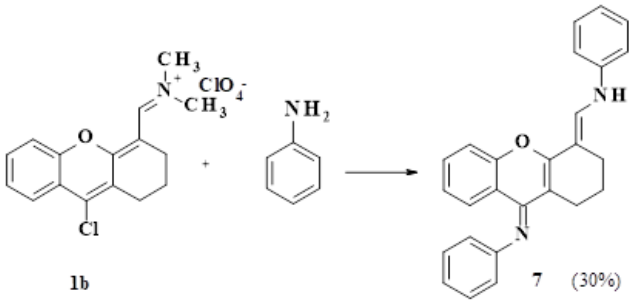
The structure of product 7 was determined by ^{1}H NMR spectroscopy and mass spectrometry, the gross formula was confirmed by elemental analysis. The mass spectrum of compound 7 with ionization in the FAB mode is characterized by the presence of a peak of the protonated molecule with m/z 279 $[M+H]^+$ with an intensity of 100%.

Conclusions

The interaction of N-[(9-chloro-2,3-dihydro-1H-(chromen)xanthen-4-yl)methylene]-N-methyl-methanaminium perchlorates with aromatic amines was studied. As a result of the interaction of an equimolar amount of starting compounds, a mixture of products is formed with substitution of only chlorine atom and chlorine atom and dimethylamino group on aromatic amine, while under the action of twice the excess substituted aniline only a disubstitution product is formed.



Scheme 3



Scheme 4

Experimental section

The ^{1}H NMR and ^{13}C NMR spectra were obtained by using a BrukerAvance II 400 instrument (400.13 MHz and 100.62 MHz for ^{1}H and ^{13}C, respectively) in DMSO-d_6 using residual solvent peak (δ 2.49 ppm and 39.50 ppm for ^{1}H and ^{13}C, respectively) as a reference. Elemental analysis was performed by means of a LECO CHNS-900 instrument. The reactions and the purity of the obtained compounds were monitored by TLC on Merck Silicagel 60 F-254 plates with 10:1 $CHCl_3$–i-PrOH as eluent. Chromato-masses of the reaction mixture of compounds 2 and 3 were determined on an Agilent 1100 instrument by liquid chromatography with DAD and ELSD Sedex 75 detectors coupled with an LC-MS VL spectrometer with electrospray ionization. Melting points were determined using an Electrothermal 9100 Digital Melting Point apparatus and were uncorrected.

General method of obtaining compounds 2–6

Perchlorate 1a or 1b (0.7 mmol) is dissolved in boiling acetonitrile (5 ml), and the corresponding aromatic amine (0.7 mmol or 1.4 mmol) is added. The reaction mixture is refluxed for 5 min and leave at room temperature for one day. The precipitate is filtered off and purified by crystallization from DMF.

4-{[(3E,9Z)-3-[(Dimethylamino)methylene]-2,3-dihydrocyclopenta[b]chromene-9(1H-ylidene]amino}phenol (2) and 4-{[(3E,9Z)-3-{[(4-hydroxyphenyl)amino]methylene}-2,3-dihydrocyclopenta[b]chromene-9(1H)-ylidene]amino}phenol (3)

Yield 0.2 g, dark-red powder, mp>360^{0}C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 10.33 (1H, s, OH); 10.13 (1H, d, ^{3}J=13.7, NH); 9.94 (2H, br.s., OH); 8.48 (1H, d, ^{3}J=8.3, H Ar); 8.39 (1H, d, ^{3}J=8.3, H Ar); 8.05 (1H, d, ^{3}J=13.7, CH); 7.79 (1H, t, ^{3}J=7.8, H Ar); 7.66–7.74 (3H, m, H Ar); 7.48–7.57 (3H, m, H Ar); 7.11–7.25 (6H, m, H Ar); 6.78–6.89 (6H, m, H Ar); 3.20 (6H, s, $2CH_3$); 2.80–2.84 (2H, m, CH_2); 2.59–2.61 (2H, m, CH_2); 2.16–2.19 (2H, m, CH_2). MS (ESI), m/z (I_{rel}, %): 333 $[M+H]^+$ (100), 397 $[M+H]^+$ (22). Found, %: C 75.99; H 6.18; N 8.29. $C_{21}H_{20}N_2O_2$. Calculated, %: C 75.88; H 6.06; N 8.43.

4-{[(3E,9Z)-3-{[(4-hydroxyphenyl)amino]methylene}-2,3-dihydrocyclopenta[b]chromene-9(1H)-ylidene]amino}phenol (3)

Yield 66%, dark-brown powder, mp>360^{0}C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 10.12 (1H, d, ^{3}J=13.7, NH); 10.00 (1H, br.s., OH); 9.55 (1H, br.s., OH); 8.48 (1H, d, ^{3}J=8.3, H Ar); 8.05 (1H, d, ^{3}J=13.7, CH); 7.79 (1H, t, ^{3}J=7.8, H Ar); 7.68–7.70 (1H, m, H Ar); 7.53–7.55 (1H, m, H Ar); 7.24 (2H, d, ^{3}J=8.8, H Ar); 7.18 (2H, d, ^{3}J=8.8, H Ar);

6.88 (2H, d, ^3J=8.8, H Ar); 6.79 (2H, d, ^3J=8.3, H Ar); 2.59–2.62 (2H, m, CH_2); 2.17–2.19 (2H, m, CH_2). MS (ESI), *m/z* (I_{rel}, %): 397 $[M+H]^+$ (100). Found, %: C 75.85; H 5.20; N 7.09. $C_{21}H_{20}N_2O_2$. Calculated, %: C 75.74; H 5.08; N 7.07.

N-[(3E,9Z)-3-[(Dimethylamino)methylene]-2,3-dihydrocyclopenta[b]chromene-9(1H)-ylidene]-4-methoxyaniline (4) and (4-methoxyphenyl)[3E,9Z)-3-{[(4-methoxyphenyl)amino]methylene}-2,3-dihydrocyclopenta[b]chromene-9(1H)-ylidene]amine (5)

Yield 0.2 g, dark-red powder, mp>360^{0}C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.93 (1H, s, CH); 8.55 (1H, d, ^3J=7.8, H Ar); 7.82 (1H, t, ^3J=7.8, H Ar); 7.73 (1H, d, ^3J=7.8, H Ar); 7.56 (1H, t, ^3J=7.8, H Ar); 7.39 (1H, d, ^3J=8.3, H Ar); 7.93 (1H, d, ^3J=8.3, H Ar); 3.81 (3H, s, CH_3); 3.20 (6H, s, $2CH_3$); 3.73–3.75 (6H, m, $2CH_3$); 2.63–2.65 (2H, m, CH_2), 2.17–2.19 (2H, m, CH_2). MS (ESI), *m/z* ($I_{від}$, %): 347 $[M+H]^+$ (33), 425 $[M+H]^+$ (100). Found, %: C 76.42; H 6.27; N 8.23. $C_{22}H_{22}N_2O_2$. Calculated, %: C 76.28; H 6.40; N 8.09.

(4-methoxyphenyl)[3E,9Z)-3-{[(4-methoxyphenyl)amino]methylene}-2,3-dihydrocyclopenta[b]chromene-9(1H)-ylidene]amine (5)

Yield 54%, red powder, mp>360^{0}C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.21 (1H, d, ^3J=13.2, NH); 8.53 (1H, d, ^3J=8.3, H Ar); 8.14 (1H, d, ^3J=13.2, CH); 7.83 (1H, t, ^3J=7.8, H Ar); 7.73 (1H, d, ^3J=8.3, H Ar); 7.57 (1H, t, ^3J=7.8, H Ar); 7.38 (1H, d, ^3J=8.8, H Ar); 7.33 (1H, d, ^3J=8.8, H Ar); 7.03 (1H, d, ^3J=8.8, H Ar); 6.94 (1H, d, ^3J=8.8, H Ar); 3.82 (3H, s, CH_3); 3.73 (3H, s, CH_3); 2.60–2.63 (2H, m, CH_2); 2.14–2.18 (2H, m, CH_2). MS (ESI), *m/z* ($I_{від}$, %): 425 $[M+H]^+$ (100). Found, %: C 76.51; H 5.85; N 6.73. $C_{27}H_{24}N_2O_3$. Calculated, %: C 76.39; H 5.70; N 6.60.

4-{((3E,9Z)-3-{[(4-Carboxyphenyl)amino]methylene}-2,3-dihydrocyclopenta[b]chromene-9(1H)-ylidene]amino}benzoic acid (6)

Yield 12%, dark-red powder, mp>360^{0}C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 11.41 (1H, s, COOH); 10.41 (1H, d, ^3J=13.2, NH); 7.55 (1H, d, ^3J=8.3, H Ar); 8.34 (1H, d, ^3J=13.2, CH); 8.05 (2H, d, ^3J=8.3, H Ar); 7.92 (2H, d, ^3J=8.3, H Ar); 7.84 (1H, d, ^3J=8.3, H Ar); 7.61–7.67 (2H, m, H Ar), 7.52 (2H, d, ^3J=8.3, H Ar); 7.48 (2H, d, ^3J=8.3, H Ar); 2.73–2.75 (2H, m, CH_2); 2.29–2.31 (2H, m, CH_2). MS (ESI), *m/z* ($I_{від}$, %): 453 $[M+H]^+$ (100). Found, %: C 71.78; H 4.35; N 6.33. $C_{26}H_{22}N_2O$. Calculated, %: C 71.67; H 4.46; N 6.19.

N-[(4E,9Z)-4-(anilinomethylene)-1,2,3,4-tetrahydro-9H-xanthen-9-ylidene]aniline (7)

Perchlorate 1b (0.7 mmol) is dissolved in boiling acetonitrile (5 ml), the aniline (2.1 mmol) is added. The reaction mixture is refluxed for 5 min and leave at room temperature for one day. The precipitate is filtered off and purified by crystallization from DMF. Yield 30%, red powder, mp 265–267^{0}C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.57–8.59 (1H, m, H Ar); 8.05 (1H, d, ^3J=8.3, NH); 7.98 (1H, d, ^3J=8.3, CH); 7.83 (1H, t, ^3J=7.8, H Ar); 7.51–7.53 (2H, m, H Ar); 7.40–7.48 (5H, m, H Ar); 7.29–7.35 (4H, m, H Ar); 7.16 (1H, t, ^3J=7.3, H Ar); 2.59–2.61 (2H, m, CH_2); 2.25–2.29 (2H, m, CH_2); 1.70–1.75 (2H, m, CH_2). MS (FAB), *m/z* ($I_{від}$, %): 379 $[M+H]^+$ (100). Found, %: C 82.65; H 5.99; N 7.27. $C_{26}H_{22}N_2O$. Calculated, %: C 82.51; H 5.86; N 7.40.

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Реакції N-[(9-хлоро-2,3-дигідро-1H-(хромен)ксантен-4-іл)метилен]-N-метилметанімінію перхлоратів з ароматичними амінами

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Взаємодією N-[(9-хлоро-1,2-дигідроциклопента[b]хромен-3-іл)метилен]-N-метилметанімінію перхлорату і N-[(9-хлоро-2,3-дигідро-1H-ксантен-4-іл)метилен]-N- метилметанімінію перхлорату з ароматичними амінами (п-анізидин, п-амінофенол, п-амінобензойна кислота та анілін) отримано основи Шиффа, які є потенційними полідентантними лігандами для зв'язування з йонами перехідних металів. В залежності від стехіометричної кількості вихідних сполук в цих реакціях утворюється або суміш продуктів моно- та дизаміщення, або продукт з двома фрагментами ароматичного аміну. Реакція N-[(9-хлоро-1,2-дигідроциклопента[b]хромен-3-іл)метилен]-N-метилметанімінію перхлорату з п-амінобензойною кислотою незалежно від кількості вихідних реагентів приводить до утворення 4-{((3E,9Z)-3-{[(4-карбоксифеніл)аміно]метилен}-2,3-дигідроциклопента-[b]хромен-9(1H)-іліден]аміно}бензойної кислоти з низьким виходом. Низьку реакційну здатність п-амінобензойної кислоти можна пояснити зниженою нуклеофільністю атома нітроґену аміногрупи, за рахунок наявності електроноакцепторної карбоксильної групи в бензольному ядрі. Регіоселективність реакції перхлорату з п-амінобензойною кислотою пояснюється внутрішньомолекулярним протонуванням первинного проміжного азометину за рахунок наявності карбоксильної групи. В отриманому цвіттеріоні позитивний заряд переноситься на атом азоту диметиламіногрупи. В результаті перенесення заряду пов'язаний з ним атом вуглецю стає більш електрофільним, що викликає другу атаку п-амінобензойної кислоти. Одержані сполуки можуть широко використовуватись у синтезі комплексних сполук.
Ключові слова: похідні ксантену, похідні хромену, основи Шиффа, ароматичні аміни, полідентантні ліганди.

Reactions of N-[(9-chloro-2,3-dihydro-1H-(chromen)xanthen-4-yl)methylene]-N-methylmethanaminium perchlorates with aromatic amines

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By interaction of N-[(9-chloro-1,2-dihydrocyclopenta[b]chromen-3-yl)methylene]-N-methyl-methanaminium perchlorate and N-[(9-chloro-2,3-dihydro-1H-xanthen-4-yl)methylene]-N-methylmethanaminium perchlorate with aromatic amines (p-anisidine, p-aminophenol, p-aminobenzoic acid and aniline), Schiff bases were synthesized which are potential polydentant ligands for binding to transition metal ions. Depending on the amount of starting compounds, these reactions yield either a mixture of mono- and disubstitution products or a product with two aromatic amine fragments. Interaction of N-[(9-chloro-1,2-dihydrocyclopenta[b]chromen-3-yl)methylene]-N-methyl-methanaminium perchlorate with p-aminobenzoic acid regardless of the ratio of starting materials leads to the formation of 4-{((3E,9Z)-3-{[(4-carboxy-phenyl)amino]methylene}-2,3-dihydrocyclopenta[b] chromene-9(1H)-ylidene]amino}benzoic acid with low yield. The low reactivity of p-aminobenzoic acid can be explained by the reduced nucleophilicity of the nitrogen atom of the amino group due to the presence of an electron-accepting carboxyl group in the benzene nucleus. The regioselectivity of the reaction of perchlorate with p-aminobenzoic acid is explained by the intramolecular protonation of the primary intermediate azomethine due to the presence of a carboxyl group. In the resulting zwitterion, the positive charge is

transferred to the nitrogen atom of the dimethylamino group. As a result of the charge transfer, the carbon atom associated with it becomes more electrophilic, which causes a second attack of p-aminobenzoic acid. The obtained compounds can be used in the synthesis of complex compounds.

Keywords: xanthene derivatives; chromen derivatives; Schiff bases; aromatic amines; polydentate ligands.

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