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The Study of Nucleophlic and Electrohilic Reactions of Bis- and 3-Substituted Chroman-2, 4-Dions

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Authors' contributions

This work was carried out in collaboration between all authors. Author OAM designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors AAS and OVF managed the analyses of the study. Author AAS managed the literature searche. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: Here we study nucleophilic and electrophilic reactions of *bis*- and condensed 3-substituted chroman-2,4-dions to produce polychromeno (thio)pyrans and trioxaoxonium benzonaphthotetracene salts.
Place and Duration of Study: Saratov State University, Chemistry Institute, between September 2011 and July 2012.
Results: Reactions of phenylmethylene *bis*-chroman-2,4-dion, 3-substituted chroman-2, 4-dion with nucleophilic and electrophilic reagents were studied. Intramolecular O-heterocyclization to polyheteronuclear systems with key chromeno (thio) pyrano fragments of various saturation degrees is shown to be characteristic of the compounds studied. It is noted that phenylmethylene bis chroman-2,4-dion, under the action of phosphorus pentasulfide and hydrogen sulfide in situ, forms bis chromeno thiopyrans.
Conclusion: Optimal heterocyclization conditions for 3-substituted chroman-2,4-dion with boron trifluoride etherate to trioxaoxonium benzonaphthotetracene salts were found.

Keywords: Phenylmethylene bis-chromane-2,4-dion; 3-substituted chromane-2,4-dion; (thio) pyrano dichromenes; trioxaoxonium benzonaphthotetracene salts.

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1. INTRODUCTION

Much research in the field of the chemistry of heterocyclic compounds is now aimed at development of approaches to build systems containing pharmacophoric fragments close to natural ones. Of great interest among such systems are chromene-2-ones (coumarins), widespread in the flora.

Extensive literature data describe the biological action range of chromene-2-ones of both natural and synthetic origin. The structural variety of this class of compounds has allowed designing a number of high-effective and low-toxic medicines rendering the anticoagulation [1–3], antioxidant [4], antineoplastic [5–7], antivirus, AIDS-integrase inhibiting [8–10] action on their basis.

2. MATERIALS AND METHODS

IR spectra were recorded on an IR FSM 1201 Fourier spectrometer in KBr cuvettes. 1H NMR spectra were recorded on a Varian 400 spectrometer at 25ºC (400 MHz, CDC13 for compounds III, IV, V, and VIII; DMSO-d6 for compound VI), and on a Bruker MSL-400 (400 MHz, CDC13, DMSO-d6 for compound VII). TMS was the internal reference. The course of the reaction was controlled and the identity of the formed substances was verified by TLC on Silufol UV-254 plates, the eluent was 3:1:1hexan–ether–acetone, 2:2:1hexan–ethylacetate–acetone, iodine vapors as the developer.

The initial polyoxo compounds I a-c, II were obtained according to known techniques of crotonic condensation with subsequent Michael's condensation [16,17]. The yield of 3, 3'-((4-R)-phenylmethylene) *bis*-(3,4,4a, 8a-tetrahydro-2H-chromene-2,4-dione I a-c was 1.85 g (75%), colorless crystals, mp 208–209ºC [16]. The yield of 3-(6-oxo-6H, 7H-chromeno [4,3-b]chromene-7-yl) -2H-chromene-2,4 (3H)-dione II was 0.82 g (43%), colorless crystals, mp 246–247ºC [16].

2.1 General procedure of synthesis 13b-hydroxy-7-(4-R)-phenyl-7,7a-dihydro-6H-pyrano[3,2-s:5,6-s']dichromen-6,8(13bH)-dion (III a-c)

4-R-Phenylmethylene *bis*-chromane-2,4-dion I a-c (1 g, 2.4 mmol) was dissolved in a mixture of glacial acetic acid (30 ml) and acetic anhydride (10 ml) under heating and boron trifluoride etherate (0.34 ml, 2.4 mmol) was added. The reaction mixture was boiled for twelve hours. After cooling, the precipitated crystals were filtered and washed with diisopropyl ether.

2.2 General procedure of synthesis 7-(4-R)-phenyl-6H-pyrano[3,2-s:5,6-s']dichromene-6,8-(7H)-dion (IV a-c) and 7-(4-R)-phenyl-6H-pyrano[3,2-s:5,6-s']dichromene-6,8(13bH)-dion (V a-c)

They were obtained similarly to variant B with the use of 4-R-phenylmethylene *bis*-chromane-2,4-dion I a-c (1 g, 2.4 mmol) and phosphorus pentachloride (0.51 g, 2.4 mmol).

2.3 7 General procedure of synthesis (4-R)-phenyl-6H-thiopyrano[3,2-s:5,6-s']dichromene-6,8(7H)-dion (VI a-c)

2.3.1 Method A

When 4-R-phenylmethylene *bis*-chromane-2,4-dion I a-c (1 g, 2.4 mmol) in xylol (20 ml) interacted with phosphorus pentasulfide (0.6 g, 2.4 mmol), 7-(4-R)-phenyl-6H-thiopyran[3,2-s:5,6-s']dichromene-6,8(7H)-dion VI a-c resulted.

2.3.2 Method B

4-R-Phenylmethylene *bis*-chromane-2,4-dion I a-c (1 g, 2.4 mmol) with zinc sulfide (0.41 g, 4.3 mmol) were dissolved in a mixture of acetic anhydride (10 ml) and glacial acetic acid (20 ml), the mixture being stirred under heating (70–80ºC) until the reagents are fully dissolved. The vessel was cooled down to 20–30ºC and hydrochloric acid (6 ml, ρ = 1.19 mg/ml, 0.2 mmol) was added. Mixing at a constant temperature in a tight mode followed. The inorganic precipitate was removed, and water was added to the filtrate. The precipitated colorless crystals of compound VI were filtered and washed with water until neutral reaction of the medium.

2.4 11a-Hydroxy-5-oxo-5H,11aH-6,11,12-trioxa-17-oxonium benzo[a]naphtho [1,2,3fg]tetracene tetrafluoroborate (VII) and 11a-hydroxy-4bH,5H,11aH 6,11,12,17 tetraoxabenzo[a]naphtha[1,2,3fg]tetracene-5-one (VIII)

2.4.1 Method A

3-(6-Oxo-6H,7H-chromeno[4,3-b]chromene-7-yl)-2H-chromene-2,4 (3H)-dion II (1 g, 2.4 mmol) was dissolved in a 3:1 mixture of glacial acetic acid (30 ml) and acetic anhydride (10 ml) under heating and boron trifluoride etherate (0.5 ml, 3.6 mmol) was added. The reaction mixture was boiled for two hours. After cooling, the precipitated crystals of 11a hydroxy-5-oxo-5H,11aH-6,11,12-trioxa-17-oxonium benzo[a]naphtha[1,2,3-fg]tetracene tetrafluoroborate VII were filtered and washed with diisopropyl ether.

The filtrate with 11a-hydroxy-4bH, 5H,11aH-6,11,12,17-tetraoxabenzo[a]naphtha[1,2,3-fg]tetracene-5-one VII was evaporated and treated with hexane.

2.4.2 Method B

3-(6-Oxo-6H,7H-chromeno[4,3-b]chromene-7-yl)-2H-chromene-2,4(3H)-dion II (1 g, 2.4 mmol) was dissolved in dichloromethane (20 ml) under heating and phosphorus pentachloride (0.51 g, 2.4 mmol) was added; the reaction mixture was boiled for six hours. The precipitated crystals were washed with water.

2.4.3 Method C

3-(6-Oxo-6H,7H-chromeno[4,3-b]chromene-7-yl)-2H-chromene-2,4(3H)-dion II (1 g, 2.4 mmol) and xylol (20 ml) were mixed under heating (70–80ºC). The mixture was cooled and phosphorus pentasulfide (0.6 g, 2.4 mmol) was added within 20–30ºC. Mixing with heating up to 60–70ºC in a tight mode followed. The inorganic precipitate was filtered, and the filtrate was evaporated.

2.4.4 Method D

Similarly to 2.3.2, at interaction of 3-(6-oxo-6H,7H-chromeno[4,3-b]chromene-7-yl)-2H-chromene-2,4(3H)-dion II (1 g, 2.4 mmol) and zinc sulfide (0.47 g, 4.8 mmol) in the presence of hydrochloric acid (6 ml, ρ = 1.19 mg/ml, 0.2 mmol).

3. RESULTS AND DISCUSSION

3,3'-(4-R-Phenylmethylene)bis(3,4,4a, 8a-tetrahydro-2H-chromene-2,4-dion) I a-c [11] and 3-(6-oxo-6H, 7H-chromeno [4,3-b]chromene-7-yl)-2H-chromen-2,4(3H) - dion II structurally similar to the known anticoagulant preparation Dicoumarol™ [2] are of particular interest in this aspect. Besides, the 1,3- and 1,5-position of carbonyl groups in the considered compounds, their various (ketonic and lactonic) character bring some features into their behavior, determining the diversity of their transformations in nucleophilic and electrophilic reactions.

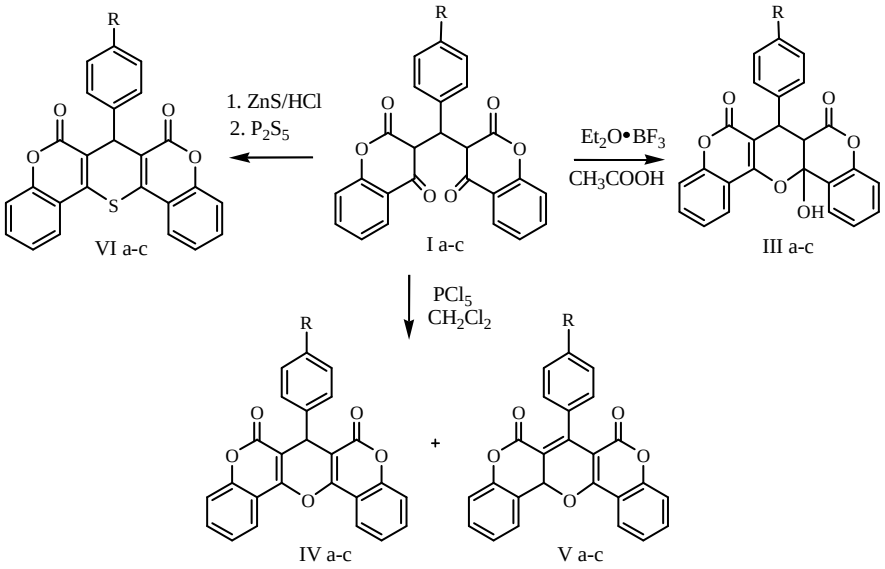
Due to the above, it seemed promising to study features of the transformations of 4-R-phenylmethylene *bis*-chromane-2,4-dion I a-c and its condensed analog II under the influence of electrophilic (boron trifluoride etherate and phosphorus pentachloride) and nucleophilic (zinc sulfide and phosphorus pentasulfide) reagents.

Intramolecular O-heterocyclization is shown to follow the interaction of 4-R-phenylmethylene *bis*-chromane-2,4-dion I a-c with boron trifluoride etherate as well as with phosphorus pentachloride. However, the reaction with phosphorus pentachloride does not stop at the stage of hemiketal formation, i.e. 13b-hydroxy-7-(4-R)-phenyl-7,7a-dihydro-6H-pyrano[3,2-s:5,6-s']dichromene-6,8-(13bH)-dion III a-c but proceeds with further dehydration to 7-(4-R)-phenyl-6H-pyrano[3,2-s:5,6-s'] dichromene-6,8 (7H)-dion IV a-c and 7-(4-R)-phenyl-6H-pyrano[3,2-s:5,6-s']dichromene-6,8(13bH)-dion V a-c isolated as an isomeric mixture of substances.

1,5-Dicarbonyl compounds are known to form 4H-thio (pyran) chromene under the action of hydrogen sulfide in an acidic medium [12], which, as a result of disproportionation, is converted to the corresponding thio (pyrylium) chromylium salts [13]. Phosphorus pentasulfide most often promotes O-heterocyclization of dioxo compounds [14].

In the case of 4-R-phenylmethylene *bis*-chromane-2,4-dion I a-c under the action of both phosphorus pentasulfide and in situ hydrogen sulfide (ZnS/HCl), according to the classical scheme of 4H-thiopyran formation, S-heterocyclization occurs to the earlier unknown 7-(4-R)-phenyl-6H-thiopyran[3,2-s:5,6-s']dichromen-6,8-(7H)-dion VI a-c with a 67% yield (Table 1).

For 3-(6-oxo-6H,7H-chromeno [4,3-b] chromene-7-yl)-2H-chromene-2,4 (3H)-dion II in similar conditions (boiling with boron trifluoride etherate in a mixture of glacial acetic acid and acetic anhydride) the reaction proceeds more deeply to form 11a-hydroxy-5-oxo-5H, 1aH-6,11,12-trioxa-17-oxonium benzo[a] naphtha [1,2,3-fg] tetracene tetrafluoroborate VI along with 11a-hydroxy-4bH,5H, 11aH-6,11,12,17-tetraoxobenzo[a]naphtha [1,2,3-fg] tetracene-5-one VIII (Table 1), which is also isolated as the unique product when phosphorus pentachloride is used. The structures of compounds III a-c - VIII were confirmed on the basis of spectroscopic data (Table 2).



I-V a R=H; I-V b R= OCH_3; I-V c R= Cl

Table 1. Comparison of yield of compounds III a-c – VIII obtained by different methods

Compd no.	M.Pt (ºC)	Yield (%)			
		Method A	Method B	Method C	Method D
IIIa	280¬–281			86	
IIIb	273-274			78	
IIIc	288-289			83	
VIa	215–216	67	53		
VIb	208-209	63	51		
VIc	220-221	58	45		
VII	234–235			25	
VIII	118–119	11	57	37	42

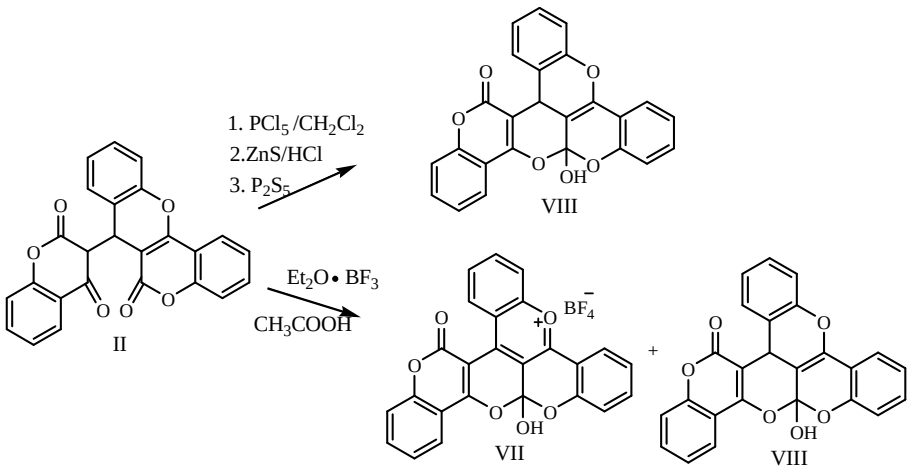


Table 2. Spectroscopic data of compounds III a-c – VIII

Compd No	R	IR, ν, cm–1	1H NMR **(400 MHz)**, δ, ppm (J, Jz)	^{13}C NMR (100.62 MHz) δ, ppm
III a-c	H	1718 (C=O), 3415 (OH).	2.21 s (1H, OH); 4.14 d (J 4 Hz); 5.07 d (J 4 Hz); 7.08–7.87 m (13H, Harom).	26.2 (C^{7}), 62.3 (C^{7a}), 91.2 (C^{6a}), 95.6 (C^{13b}) 117.5-128.4 (C^{1}-C^{4}, C^{10}-C^{13}, $C^{2'}$-$C^{6'}$), 139.3 ($C^{1'}$), 141.6 (C^{4a}, C^{9a}), 150.2 (C^{14a}, C^{13b})
	Cl	1720 (C=O), 3380 (OH). 565 (Cl)	2.25 s (1H, OH); 4.16 d (J 4 Hz); 5.15 d (J 4 Hz); 7.12–8.07 m (12H, Harom).	
	OCH_3	1717 (C=O), 3425 (OH).	2.18 s (1H, OH); 2.45 s (3H CH_3); 4.10 d (J 4 Hz); 5.00 d (J 4 Hz); 6.98–7.67 m (12H, Harom).	26.8 (CH_3), 31.2 (C^{7}), 65.3 (C^{7a}), 90.5 (C^{6a}), 94.2 (C^{13b}) 117.8-131.2 (C^{1}-C^{4}, C^{10}-C^{13}, $C^{2'}$-$C^{6'}$), 140.3 ($C^{1'}$), 145.5 (C^{4a}, C^{9a}), 153.3 (C^{14a}, C^{13b})
IV a-c V a-c (mixed)	H	1706 (C=O), 1180 (=C–O–C).	7.15–8.39 m (13H, Harom) (mixed) 4.88 s (1H, CH) (IV a); 5.08 s (1H, CH) (V a).	120.1-128.8 (C^{1}-C^{4}, C^{10}-C^{13}, $C^{2'}$-$C^{6'}$), 140.5 ($C^{1'}$), 151.5 (C^{4a}, C^{9a}), 155.3 (C^{14a}) (mixed) 43.5 (C^{7}), 156.3 (C^{13b}) (IV a-c) 67.6 (C^{7}), 151.0 (C^{13b}) (V a-c)
	Cl	1715 (C=O), 1210 (=C–O–C), 583 (Cl).	7.24–8.60 m (12H, Harom) (mixed) 4.89 s (1H, CH) (IV a); 5.17 s (1H, CH) (V a).	
	OCH_3	1710 (C=O), 1203 (=C–O–C).	2.41 s (3H CH_3); 7.10–8.43 m (12H, Harom) (mixed) 4.85 s (1H, CH) (IV a); 5.12 s (1H, CH) (V a).	26.5, 28.3 (CH_3) 121.1-135.6 (C^{1}-C^{4}, C^{10}-C^{13}, $C^{2'}$-$C^{6'}$), 141.3 ($C^{1'}$), 155.1 (C^{4a}, C^{9a}), 158.3 (C^{14a}) (mixed) 44.5 (C^{7}), 160.3 (C^{13b}) (IV a-c) 68.1 (C^{7}), 153.1 (C^{13b}) (V a-c)
VI a-c	H	1723–1688 (C=O), 1086–1107 (=C–O–C)	6.11 s (1H, CH); 7.18–8.11 m (13H, Harom).	43.5 (C^{7}), 121.1-128.5 (C^{1}-C^{4}, C^{10}-C^{13}, $C^{2'}$-$C^{6'}$), 142.6 ($C^{1'}$), 150.3 (C^{4a}, C^{9a}), 152.4 (C^{14a}, C^{13b})
	Cl	1723–1688 (C=O), 1086–1107 (=C–O–C), 568 (Cl)	6.13 s (1H, CH); 7.21–8.18 m (12H, Harom).	
	OCH_3	1723–1688 (C=O), 1086–1107 (=C–O–C)	2.38 s (3H CH_3); (6.08 s (1H, CH); 7.15–8.21 m (12H, Harom).	28.5 (CH_3) 45.5 (C^{7}), 118.1-125.5 (C^{1}-C^{4}, C^{10}-C^{13}, $C^{2'}$-$C^{6'}$), 144.2 ($C^{1'}$), 150.3 (C^{4a}, C^{9a}), 153.6 (C^{14a}, C^{13b})
VII		1721 (C=O), 3429 (OH), 1060 (BF_4^-)	4.88 s (1H, OH); 7.08–7.83 m (12H, Harom).	91.6 (C^{4c}), 114.0 (C^{11a}), 117.5-129.8 (C^{1}-C^{4a}, C^{7}-C^{10a}, C^{12}-C^{16a}, C^{16c}), 141.1 (C^{4b}), 150.2-160.0 (C^{6a}, C^{12a}, C^{16b}, C^{17a}), 159.5 (C^{10b}), 160.3 (C^{5})
VIII		1724 (C=O), 3424 (OH).	2.10 s (1H, OH); 5.57 s (1H, CH); 6.98–8.06 m (12H, Harom).	12.6 (C^{4b}), 96.6 (C^{4c}), 107.9 (C^{11a}), 114.2-129.0 (C^{1}-C^{4a}, C^{7}-C^{10a}, C^{12}-C^{16a}, C^{16c}), 146.2-157.1 (C^{6a}, C^{12a}, C^{16b}, C^{17a}), 162.0 (C^{10b}), 162.8 (C^{5})

4. CONCLUSION

Therefore, in the considered reactions of the complex-built polyoxo compound II, unlike its symmetric analog, the reagents used by us did not show their nucleophilic properties, with hemiketalization into product VIII in both cases). This fact confirms the general tendency of substratum II to intramolecular O-heterocyclization under the influence of both nucleophilic and electrophilic reagents [15].

The obtained products represent a new type of polyheteronuclear systems (ensembles) promising for finding their possible practical applications.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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