Reactions of Substituted Xanthotoxin with Nitriles and Hydrazines


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Substituted Xanthotoxin

4-Bromoxanthotoxin reacts with cyanoacetamide to form 4-bromo-5,6-dihydroxanthotoxin, which on hydrolysis with cold hydrochloric acid leads to the formation of cyanoacetamide derivative, but hydrolysis by boiled hydrochloric acid gives the acetic acid derivative.

Thio-, and 4-nitroxanthotoxin react with malononitrile in presence of piperidine by addition to give thio- and 4-nitro-5,6-dihydroxanthotoxin-5-[1',3',3'-tricyano-2-aminopropene(2)] respectively, while in presence of ammonia leads to the formation of 5-malononitrile derivatives.

The reaction of hydrazine and phenyl hydrazine with thio- and 4-bromothioxanthotoxin leads to the formation of the hydrazones.

Also thio- and 4-bromothioxanthotoxin reacts with anhydrous aluminium chloride in benzene by cleavage of the furan ring and the formation of 6-(1,2-diphenylethyl)-7,8-dihydroxythioxanthotoxin and 5-bromo-6-(1,2-diphenylethyl)-7,8-dihydroxythioxanthotoxin, respectively.

Because of the wide spread and increasing interest in xanthotoxin (9-methoxy-7H-furo[3,2-g][1]benzopyran-7-one) for its pharmacological action [1–3], this study was undertaken to investigate some of the chemical properties of the compound and to prepare new derivatives for biological testing.

In this study the reactions of substituted xanthotoxin: 4-bromo- (1), thio- (1b), and 4-nitroxanthotoxin (1c) [4, 5], (which were prepared by bromination, thionation and nitration of xanthotoxin), with cyanoacetamide and malononitrile under different condition were investigated.

![Chemical structure](image)

Thus, whereas 4-bromoxanthotoxin (4-bromo-9-methoxy-7H-furo[3,2-g][1]benzopyran-7-one) (1a) reacted with cyanoacetamide in presence of piperidine by adding to the double bond of the pyrone ring to form 5,6-dihydro-4-bromoxanthotoxin-5-cyanoacetamide (2a).

The structure of 2a has been confirmed by its infrared spectrum, which shows the presence of C=O vibration at 1740 and 1745 cm⁻¹ characteristic for -COOH group.

Hydrolysis of 2a with cold hydrochloric acid leads to the formation of 4-bromo-5,6-dihydroxanthotoxin-5-cyanoacetic acid (2b), while hydrolysis with boiling hydrochloric acid gave 4-bromo-5,6-dihydroxanthotoxin-5-acetic acid (2c).

The infrared spectra of 2c and 2b show bands at 1740 and 1745 cm⁻¹ characteristic for –COOH group.

In a similar manner thioxanthotoxin (1b) reacts also by addition with cyanoacetamide to give 5,6-dihydrothioxanthotoxin-5-cyanoacetamide (3).

Malononitrile reacts with thioxanthotoxin (1b) and 4-nitroxanthotoxin (1c) in presence of piperidine to form thio- (4a) and 4-nitroxanthotoxin-5-[1',3',3'-tricyano-2-aminopropene(2)] (4b), respec-
tively, probably by dimerization of malononitrile in alkaline medium to form 5 which then adds to the double bond of the pyrone ring.

The infrared spectra of 4a and 4b reveals the presence of C= N group (2235, and 2230 cm⁻¹). Bands at 1645 and 1635 cm⁻¹ characteristic for -NH of NH₂ group stretching respectively.

The asymmetric and symmetric N-H stretching mode for the compounds 4a and 4b appears at 3365 and 3350 cm⁻¹ and 3295 and 3290 cm⁻¹, respectively. Also compound 4a shows a band at 1740 cm⁻¹ (the carbonyl group of the lactone ring) and 4b shows bands at 1120 cm⁻¹ (≥C=S).

Experimental

Melting points were not corrected. PMR were obtained at 60 MHz in CDCl₃ or TFA, with TMS as internal standard. Mass Spectra were run at 70 eV. The infra-red were carried out in potassium bromide on a Unicam infrared spectrophotometer Model SP 1000.

Preparation of 5,6-dihydro-4-bromoxanthotoxin-5-cyanoacetamide (2a)

A mixture of 2 g of 4-bromoxanthotoxin (1a) and 1 g of cyanoacetamide in 25 ml ethanol and piperidine (1 ml) was refluxed for 6 h (crystallization started while hot), leave to cool. Filter the solid that separated and crystallize from chloroform as colourless crystals, m.p. 292 °C with decomposition (yield is ca. 80%). It is soluble in dilute sodium hydroxide solution.
Analysis for C_{15}H_{10}BrO_{5}N_{2} (379)
Calcd C 47.49 H 2.90 Br 21.11 N 7.39.
Found C 47.62 H 3.03 Br 21.35 N 7.57.

PMR (TFA) δ 4.50 s (3H, OCH_{3}), 3.4 m (4H, aliphatic), 7.08 d (1H, J = 2 Hz, C-3), and 7.70 d (1H, J = 2 Hz, C-2).
Low resolution MS, m/e M+ 379(40), 377(40), 363(27), 361(29), 309(100), and 299(20).

5,6-Dihydro-4-bromoxanthotoxin-5-cyanoacetic acid (2b)
A mixture of 5,6-dihydro-4-bromoxanthotoxin-5-cyanoacetamide (2a) (0.7 g) and 8 ml of cold concentrated hydrochloric acid was vigorously shaken for 4 h, then left at room temperature overnight. Filter the solid and crystallize from acetone as colourless crystals, m.p. 275 °C; yield is ca. 67%. It dissolves in aqueous sodium hydroxide to form a yellow colouration, it is also soluble in sodium bicarbonate solution.

Analysis for C_{15}H_{10}BrNO_{5} (380)
Calcd C 47.37 H 2.63 N 3.68 Br 21.05.
Found C 47.21 H 2.42 N 3.83 Br 20.85.

PMR (TFA) δ 3.45 m (4H, aliphatic), 4.43 s (3H, OCH_{3}), 6.98 d (1H, J = 2 Hz, C-3) and 7.85 d (1H, J = 2 Hz, C-2).
Low resolution MS, m/e M+ 380(100), 356(98), 354(15), 337(17), 300(22), and 296(38).

5,6-Dihydro-4-bromoxanthotoxin-5-acetic acid (2c)
0.5 g of 1a was refluxed with 8 ml of concentrated hydrochloric acid for 2 h, then left to cool. Filter the precipitate and wash with n-hexane, crystallize the solid from dilute ethanol as deep yellow crystals, m.p. 170 °C with decomposition; yield is ca. 80%.

Analysis for C_{14}H_{11}BrO_{6} (355)
Calcd C 47.32 H 3.10 Br 22.54.
Found C 47.01 H 3.25 Br 22.63.

PMR (TFA) δ 3.43 m (5H, aliphatic), 4.40 s (3H, OCH_{3}), 6.90 d (1H, J = 2 Hz, C-3) and 7.80 d (1H, J = 2 Hz, C-2).
Low resolution MS, m/e M+ 355(100), 354(55), 337(17), 323(12), 300(22), and 296(38).

5,6-Dihydrothioxanthotoxin-5-cyanoacetamide (3)
As in case of 2a, 2 g of thioxanthotoxin (1b) and 1 g of cyanoacetamide in 25 ml of ethanol and piperidine (1 ml), gave 55% of 3 as deep yellow crystals m.p. 283 °C with decomposition from chloroform. It is soluble in sodium hydroxide solution.

Analysis for C_{15}H_{10}O_{5}N_{2} (316)
Calcd C 56.96 H 3.80 N 8.86 S 10.13.
Found C 57.31 H 3.91 N 8.57 S 10.42.

Preparation of 5,6-dihydrothioxanthotoxin-5-
[1',3',3'-tricyano-2'-aminopropene(2)] (4a)
A mixture of 2 g of thioxanthotoxin (1b) and 3 ml of malononitrile in 25 ml of ethanol and few drops of piperidine was refluxed for one hour, then left to cool filter the solid that obtained and crystallize from acetone as deep orange crystals, m.p. > 300 °C; yield is ca. 80%.

Analysis for C_{15}H_{12}O_{5}N_{5}S (364)
Calcd C 59.34 H 3.30 N 15.38 S 8.79.
Found C 59.55 H 3.08 N 15.22 S 9.01.

5,6-Dihydro-4-nitroxanthotoxin-5-
[1',3',3'-tricyano-2'-aminopropene(2)] (4b)
In a similar manner 2 g of 4-nitroxanthotoxin (1c) and 3 ml of malononitrile in 25 ml ethanol and few drops of piperidine, led to the formation of 4b as brown crystals from acetone, m.p. 255 °C with decomposition; yield is ca. 60%.

Analysis for C_{15}H_{10}O_{6}N_{5} (393)
Calcd C 54.96 H 2.80 N 17.81.
Found C 54.73 H 3.01 N 17.93.

Hydrolysis of 4a with sodium hydroxide solution (6a)
0.3 g of 4a was refluxed with 3 ml of 10% sodium hydroxide solution for one hour, cool then dilute with water (10 ml) and neutralize with acetic acid. Filter the solit that separated and crystallize from ethanol to give the known compound [10] as colourless crystals (mixed m.p. gave no depression); yield is ca. 40%.

Hydrolysis of 4b with sodium hydroxide solution (6a)
In a similar manner as in case of 5a, 1 g of 4b when refluxed with 10 ml of 10% sodium hydroxide solution led to the formation of 6b, from acetone as yellow crystals, m.p. > 300 °C; yield is ca. 45%.

Analysis for C_{15}H_{13}NO_{7} (411)
Calcd C 52.55 H 3.16 N 17.03.
Found C 52.83 H 3.22 N 16.86.

Preparation of 5,6-dihydro-4-bromoxanthotoxin-5-
malononitrile (7a)
A mixture of 3 g of 4-bromoxanthotoxin (1a) and 3 ml of malononitrile in 24 ml ammonia was refluxed for 1/2 h, cooled, the solid filtered, washed with hot benzene and crystallize from ethanol and few drops of acetone as colourless crystals, m.p. 270 °C; yield is ca. 90%.

Analysis for C_{15}H_{12}BrN_{2}O_{4} (361)
Calcd C 49.86 H 2.49 Br 22.16 N 7.76.
Found C 50.12 H 2.65 Br 22.33 N 7.95.

5,6-Dihydrothioxanthotoxin-5-malononitrile (7b)
In a similar manner as in case of 7a, a mixture of 3 g of thioxanthotoxin (1b) and 3 ml of malono-
nitrile gave 85% of 7b as orange crystals from acetone, m.p. 242 °C.  
Analysis for C_{15}H_{10}N_{2}O_{3}S (298)  
Caled C 60.40 H 3.36 N 9.39 S 10.74,  
Found C 60.11 H 3.52 N 9.64 S 11.03.

5,6-Dihydro-4-nitroxanthotoxin-5-malononitrile (7c)  
3 g of 1c and 3 ml of malononitrile in benzene furnished 82% of 5,6-dihydro-4-nitroxanthotoxin-5-malononitrile (7c) as yellow crystals from acetone, m.p. 232 °C.  
Analysis for C_{15}H_{9}N_{3}O_{6} (327)  
Caled C 55.05 H 2.75 N 12.84,  
Found C 54.83 H 2.93 N 13.03.

Preparation of xanthotoxin-7-hydrazone (9a)  
1 g of 1b and 0.9 ml of hydrazine hydrate was refluxed for 24 h in 50 ml of 95% ethanol. The solution was diluted with water and cooled. The product was collected and crystallized from petrol ether (b.p. 60–80 °C), m.p. 135 °C; yield is ca. 70%. It gave no colour with ferric chloride solution.  
Analysis for C_{12}H_{10}N_{2}O_{3} (230)  
Caled C 62.61 H 4.44 N 12.17,  
Found C 62.43 H 4.57 N 13.03.

PMR (CDCl_{3}), δ 7.20 s (5H, aromatic), 7.46 d (1H, J = 2 Hz, C-2), 6.64 d (1H, J = 2 Hz, C-3), 6.76 d (1H, J = 10 Hz, C-5), 6.16 d (1H, J = 10 Hz, C-6), and 7.85 s (1H, NH). MS m/e M+, 230(100), 214(60), 201(80), 225(60), and 170(40).

Preparation of 4-bromoxanthotoxin-7-hydrazone (9b)  
As in case of 9a, a mixture of 1 g of 4-bromoxanthotoxin (1a) and 0.9 ml of hydrazine hydrate in ethanol gave a yellow crystals of 9b from petrol ether (b.p. 60–80 °C), m.p. 117 °C; yield is ca. 68%.  
Analysis for C_{18}H_{14}BrN_{2}O_{3} (385)  
Caled C 56.10 H 3.37 Br 20.78 N 7.27,  
Found C 56.23 H 3.42 Br 20.41 N 7.54.

6-(1,2-Diphenylethyl)-7,8-dihydroxythiocoumarin (10a)  
A mixture of 1 g of thioxanthoxin (1b) and 2 g of anhydrous aluminium chloride in 100 ml of dry benzene was refluxed for 30 min. The benzene was decanted and evaporated to dryness. The residue was acidified and recrystallized from ethanol, yield is ca. 65%; m.p. 212 °C. It gave a greenish brown colour with aqueous ferric chloride solution.  
Analysis for C_{24}H_{20}O_{3}S (388)  
Caled C 74.22 H 5.15 S 8.24,  
Found C 74.51 H 5.43 S 8.41.

PMR (CDCl_{3}), δ 7.21 s (5H, aromatic), 7.16 d (1H, J = 2 Hz, C-2), 6.76 d (1H, J = 2 Hz, C-3), 6.92 d (1H, J = 10 Hz, C-5), 6.37 d (1H, J = 10 Hz, C-6), and 7.85 s (1H, NH). MS m/e M+, 385(80), 354(40), 331(70), 293(60), and 281(100).

Preparation of xanthotoxin-7-phenylhydrazone (9c)  
A mixture of 1 g of thioxanthotoxin (1b) and 0.8 ml of phenylhydrazine in 50 ml of ethanol was refluxed for 24 h, diluted with water, left to cool and filtered. The product was collected and recrystallized from ethanol as orange crystals, m.p. 133 °C; yield is ca. 63%.  
Analysis for C_{18}H_{14}N_{2}O_{3} (306)  
Caled C 62.61 H 4.44 N 12.17,  
Found C 62.43 H 4.57 N 13.03.

PMR (CDCl_{3}), δ 7.20 s (5H, aromatic), 7.46 d (1H, J = 2 Hz, C-2), 6.64 d (1H, J = 2 Hz, C-3), 6.76 d (1H, J = 10 Hz, C-5), 6.16 d (1H, J = 10 Hz, C-6), and 7.20 s (1H, NH). MS m/e M+, 306(100), 214(60), 201(80), 225(60), and 170(40).