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 cyanoacetic acid derivative, but hydrolysis by boiled hydrochloric acid gives the acetic acid derivative.

Thio-, and 4-nitroxanthotoxin reacts with malononitrile in presence of piperidine by addition to give thio- and 4-nitro-5,6-dihydroxanthotoxin-5-[1',3',3'-tricyano-2-amino-propene-(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-dihydroxythiocoumarin and 5-bromo-6-(1,2-diphenylethyl)-7,8-dihydroxythiocoumarin, respectively.

Because of the wide spread and increasing interest in xanthotoxin (9-methoxy-7 H-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.

- a:** R = Br; X = O
b: R = H; X = S
c: R = NO₂; X = O

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 characteristic bands at 1165 and 1055 cm⁻¹ due to the in-plane bending vibrations of the α - and β -hydrogen atoms of the

furan ring [6]. The strong peak at 1750 cm⁻¹ is characteristic of an α,β -unsaturated- δ -lactone [7]. The amide I band occurs at 1645 cm⁻¹, while amide II appeared at 1635 cm⁻¹. The stretching vibration at 2255 cm⁻¹ shows the presence of C $\equiv$ N group (saturated alkyl nitrile) [8]

- a:** R = CN; R' = NH₂
b: R = CN; R' = OH
c: R = H; R' = OH

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-

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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 $C\equiv N$ group (2235 , and 2230 cm^{-1}). Bands at 1645 and 1635 cm^{-1} characteristic for $-NH$ of NH_2 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} ($>C=S$).

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a: $R = H$; $X = S$
b: $R = NO_2$; $X = O$

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Alkaline hydrolysis of **4a** and **4b** leads to opening of the pyrone ring and formation of the acids **6a** and **6b**, respectively.

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a: $R = H$
b: $R = NO_2$

In this investigation the reaction of 4-bromo- (**1a**), thio- (**1b**), and 4-nitroxanthotoxin (**1c**) with malononitrile in presence of ammonia gave the malononitrile derivatives **7a**, **7b**, and **7c**, respectively.

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a: $R = Br$; $X = O$
b: $R = H$; $X = S$
c: $R = NO_2$; $X = O$

It have been shown that the lactone ring of xanthotoxin was opened by the action of hydrazine hydrate and gave 6-hydroxy-7-methoxy-5-benzofuranacrylic acid hydrazide [5]. In this investigation the reaction of thio- (**1b**) and 4-bromothioxanthotoxin (**8**) with hydrazine hydrate and phenyl hydrazine in ethanol led to the condensation of the

hydrazines on the thiocarbonyl group and gave the hydrazones **9a**, **9b**, **9c**, and **9d** respectively.

8 **9**

a: $R = R' = H$
b: $R = Br$; $R' = H$
c: $R = H$; $R' = C_6H_5$
d: $R = Br$; $R' = C_6H_5$

The infrared spectra of **9a**, **9b**, **9c**, and **9d** shows the absence of $-OH$ and $>C=O$ groups and shows bands at 1633 , 1640 , 1635 , and 1630 cm^{-1} respectively, characteristic for $-C=N$ groups, also these compounds gave no colour with aqueous ferric chloride solution.

When **1b** and **8** were treated with aluminium chloride in benzene, cleavage of the furan moiety occurred with simultaneous addition of two moles of benzene to produce 6-(1,2-diphenylethyl)-7,8-dihydroxythiocoumarin (**10a**) and 5-bromo-6-(1,2-diphenylethyl)-7,8-dihydroxythiocoumarin (**10b**) respectively.

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a: $R = H$
b: $R = Br$

The infrared spectra of both compounds **10a** and **10b** shows the presence of $-OH$ group as a broad band (3280 – 3100 and 3170 – 3070 cm^{-1}).

Experimental

Melting points were not corrected. PMR were obtained at 60 MHz in $CDCl_3$ 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 C₁₅H₁₁BrO₅N₂ (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 [9] (TFA) δ 4.50 s (3H, OCH₃), 3.4 m (4H, aliphatic), 7.03 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 C₁₅H₁₀BrNO₆ (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, OCH₃), 6.98 d (1H, $J = 2$ Hz, C-3) and 7.85 d (1H, $J = 2$ Hz, C-2). MS m/e M⁺ 380(100), 356(98), 354(15), 337(27), 323(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%). It is soluble in sodium bicarbonate solution and in sodium hydroxide solution.

Analysis for C₁₄H₁₁BrO₆ (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, OCH₃), 6.90 d (1H, $J = 2$ Hz, C-3), and 7.80 d (1H, $J = 2$ Hz, C-2). MS m/e M⁺ 355(100), 337(33), 322(31), 295(50), and 280(25).

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 C₁₅H₁₂O₄N₂S (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 C₁₈H₁₂O₃N₄S (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 C₁₈H₁₁O₆N₅ (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 solid 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 C₁₈H₁₃N₅O₇ (411)

Calcd	C 52.55	N 3.16	N 17.03,
Found	C 52.83	N 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 C₁₅H₉BrN₂O₄ (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 $C_{15}H_{10}N_2O_3S$ (298)

Calcd	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 $C_{15}H_9N_3O_6$ (327)

Calcd	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 $C_{12}H_{10}N_2O_3$ (230)

Calcd	C 62.61	H 4.44	N 12.17,
Found	C 62.43	H 4.57	N 11.98.

PMR ($CDCl_3$), δ 0.83 s (2H, NH_2), 4.33 s (3H, OCH_3), 7.75 d (1H, $J = 2$ Hz, C-2), 6.71 d (1H, $J = 2$ Hz, C-3), 7.00 d (1H, $J = 10$ Hz, C-5) and 6.58 d (1H, $J = 10$ Hz, C-6). MS m/e M^+ , 230(100), 214(40), 215(40), and 286(50).

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 $C_{12}H_9BrN_2O_3$ (309)

Calcd	C 46.60	H 2.91	Br 25.89	N 9.06,
Found	C 46.96	H 3.07	Br 26.23	N 9.18.

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 $C_{18}H_{14}N_2O_3$ (306)

Calcd	C 70.59	H 4.90	N 9.15,
Found	C 70.84	H 5.01	N 8.93.

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).

4-Bromoxanthotoxin-7-phenylhydrazone (9d)

1 g of **8** and 0.9 ml of phenylhydrazine in ethanol gave 83% of **9d** as yellow crystals, m.p. 170 °C in 73% yield. It gave no colour with aqueous ferric chloride solution.

Analysis for $C_{18}H_{13}BrN_2O_3$ (385)

Calcd	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.

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).

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 $C_{24}H_{20}O_3S$ (388)

Calcd	C 74.22	H 5.15	S 8.24,
Found	C 74.51	H 5.43	S 8.41.

5-Bromo-6-(1,2-diphenylethyl)-7,8-dihydroxythiocoumarin (10b)

As in case of **10a** 1 g of 4-bromothioxanthotoxin (**8**) and 2 g of anhydrous aluminium chloride in benzene gave 70% of 5-bromo-6-(1,2-diphenylethyl)-7,8-dihydroxythiocoumarin (**10b**) as brown crystals from ethanol, m.p. 195 °C; yield is ca. 83%. It gave a green colour with aqueous ferric chloride solution.

Analysis for $C_{24}H_{19}BrO_3S$ (467)

Calcd	C 61.67	H 4.07	Br 17.13	S 6.85,
Found	C 61.93	H 4.23	Br 17.21	S 7.01.

PMR ($CDCl_3$), δ 3.65 m (3H, aliphatic) and 7.13 s (12H, aromatic). MS m/e M^+ , 467(10), 465(40), 374(68), and 287(100).

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