Xanthone Analogues of Milrinone

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The xanthone analogues of milrinone have been prepared. The new compounds do not retain the inotropic activity of the parent compound.

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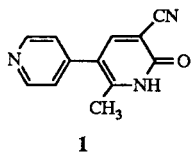
Digitalis glycosides have been the principal agents used to treat congestive heart failure for more than a century in spite of their low therapeutic index [1,2]. Sympathomimetic agents such as dopamine and dobutamine are orally inactive and may lead to tachyphylaxis due to β-receptor regulation. These circumstances have led to the development of noncatecholamine and nonglycoside cardiotonic agents such as milrinone, enoxinone and imazodam [3,4]. In this note we have investigated the possibility of using the xanthone nucleus as a supporting moiety for the pyridone ring of milrinone **1**. The xanthone ring represents a valuable supporting moiety in medicinal chemistry research; by a suitable functionalization indeed, a number of important biological activities may be singled out [5-11]. With this in mind the possible four isomers of xanthone have been taken into account, as in the general formula **2**, *i.e.* the pyridone nucleus occupies alternatively the positions 1, 2, 3 or 4 of the xanthone moiety.

Scheme



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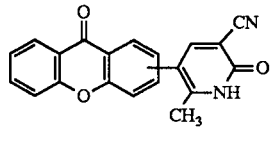


2a-d

Compounds **2a-d** have been prepared in four steps starting from xanthen-9-one carboxaldehydes [11] following the scheme:

Experiments on atrial muscle isolated from guinea-pig hearts were designed to determine whether exposure of myocardium to the new compounds would induce dose-dependent inotropic and/or chronotropic effects. [For experimental details see *Eur. J. Med. Chem.*, **22**, 473-477 (1987)].

The inotropic and chronotropic activity was evaluated in the left atria driven at 1 Hz and in the spontaneously beating right atria.

None of the tested compounds elicited any appreciable response both on the developed tension of the left atrium and on the frequency of the right atrium.

EXPERIMENTAL

1-(Xanthen-9-on-3-yl)-2-nitropropene **3c**.

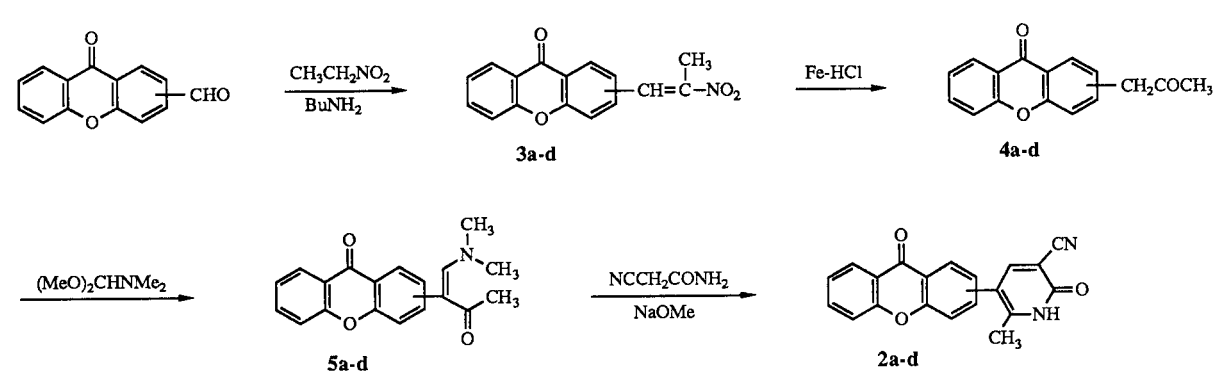
A solution of xanthen-9-one-3-carboxaldehyde (9.2 g, 0.04 mole) and *n*-butylamine (2.92 g, 0.04 mole) in benzene (200 ml) was heated for 5 hours removing water azeotropically, and then evaporated to dryness. An excess of nitroethane (9 ml) in acetic acid (30 ml) was added and the mixture was heated under reflux for 10 minutes. After cooling the reaction mixture was poured into water and the separated solid was collected and crystallized from ethanol to give 7.75 g (67%) of the compound, mp 192-195°; ^{1}H nmr (deuteriochloroform): 2.55 (s, 3H), 7.4-8.47 (m, 8H); ms: 281 (M^+).

Anal. Calcd. for $C_{16}H_{11}NO_4$: C, 68.33; H, 3.94; N, 4.98. Found: C, 68.45; H, 3.77; N, 4.90.

By the same procedure the following compounds have been prepared:

1-(Xanthen-9-on-1-yl)-2-nitropropene **3a**.

Scheme



3a-d **4a-d** **5a-d** **2a-d**

This compound was obtained in a yield of 73%, mp 175-178° (ethanol); ^{1}H nmr (deuteriochloroform): 2.3 (s, 3H), 7.2-8.9 (m, 8H); ms: 281 (M^+).

Anal. Calcd. for $C_{16}H_{11}NO_4$: C, 68.33; H, 3.94; N, 4.98. Found: C, 68.09; H, 3.99; N, 4.75.

1-(Xanthen-9-on-2-yl)-2-nitropropene **3b**.

This compound was obtained in a yield of 75%, mp 150-153° (ethanol); ^{1}H nmr (deuteriochloroform): 2.5 (s, 3H), 7.4-8.76 (m, 8H); ms: 281 (M^+).

Anal. Calcd. for $C_{16}H_{11}NO_4$: C, 68.33; H, 3.94; N, 4.98. Found: C, 68.12; H, 3.82; N, 4.77.

1-(Xanthen-9-on-4-yl)-2-nitropropene **3d**.

This compound was obtained in a yield of 70%, mp 170-173° (ethanol); ^{1}H nmr (deuteriochloroform): 2.48 (s, 3H), 7.4-8.56 (m, 8H); ms: 281 (M^+).

Anal. Calcd. for $C_{16}H_{11}NO_4$: C, 68.33; H, 3.94; N, 4.98. Found: C, 68.41; H, 3.80; N, 4.92.

1-(Xanthen-9-on-3-yl)propanone **4c**.

To a stirred solution of **3c** (3.68 g, 0.013 mole) in ethanol (500 ml), concentrated hydrochloric acid (5 ml) and iron powder (3.7 g) was added portionwise during 2 hours. The reaction mixture was heated under reflux for 7 hours and more hydrochloric acid (10 ml) and iron (6 g) were added. The reaction mixture was filtered hot and evaporated to dryness. The residue was crystallized from toluene to give 1.8 g (55%) of the compound, mp 165-168°; ^{1}H nmr (deuteriochloroform): 2.27 (s, 3H), 3.88 (s, 2H), 7.16-8.45 (m, 7H); ms: 252 (M^+).

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.30; H, 4.66.

By the same procedure the following compounds have been prepared:

1-(Xanthen-9-on-1-yl)propanone **4a**.

This compound was obtained in a yield of 63%, mp 195-198° (toluene); ^{1}H nmr (deuteriochloroform): 2.48 (s, 3H), 4.38 (s, 2H), 7.04-8.32 (m, 7H); ms: 252 (M^+).

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.01; H, 4.86.

1-(Xanthen-9-on-2-yl)propanone **4b**.

This compound was obtained in a yield of 85%, mp 154-156° (ethanol); ^{1}H nmr (deuteriochloroform): 2.25 (s, 3H), 3.86 (s, 2H), 7.32-8.4 (m, 7H); ms: 252 (M^+).

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.11; H, 4.90.

1-(Xanthen-9-on-4-yl)propanone **4d**.

This compound was obtained in a yield of 62%, mp 174-177° (ethanol): ^{1}H nmr (deuteriochloroform): 2.32 (s, 3H), 4.08 (s, 2H), 7.32-8.42 (m, 7H); ms: 252 (M^+).

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.44; H, 4.63.

4-Dimethylamino-3-(xanthen-9-on-3-yl)-3-buten-2-one **5c**.

A solution of **4c** (1.8 g, 0.007 mole), *N,N*-dimethylformamide dimethyl acetal (0.51 g, 0.007 mole) in dry toluene (125 ml) was heated under reflux for 20 hours and then evaporated to dryness. The residue was crystallized from toluene to give 1.65 g (75%) of the compound, mp 197-200°; ^{1}H nmr (deuteriochloroform): 2.08 (s, 3H), 2.8 (s, 6H), 7.32-8.42 (m, 8H); ms: 307 (M^+).

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.36; H, 5.41; N, 4.50.

By the same procedure the following compounds have been prepared:

4-Dimethylamino-3-(xanthen-9-on-1-yl)-3-buten-2-one **5a**.

This compound was obtained in a yield of 60%, mp 136-140° (toluene); ^{1}H nmr (deuteriochloroform): 2.1 (s, 3H), 2.72 (s, 6H), 7.06-8.32 (m, 8H); ms: 307 (M^+).

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.00; H, 5.68; N, 4.30.

4-Dimethylamino-3-(xanthen-9-on-2-yl)-3-buten-2-one **5b**.

This compound was obtained in a yield of 70%, mp 153-155° (toluene); ^{1}H nmr (deuteriochloroform): 2.04 (s, 3H), 2.76 (s, 6H), 7.38-8.44 (m, 8H); ms: 307 (M^+).

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.04; H, 5.50; N, 4.28.

4-Dimethylamino-3-(xanthen-9-on-4-yl)-3-buten-2-one **5d**.

This compound was obtained in a yield of 65%, mp 158-162° (toluene); ^{1}H nmr (deuteriochloroform): 2.04 (s, 3H), 2.80 (s, 6H), 7.36-8.44 (m, 8H); ms: 307 (M^+).

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.41; H, 5.40; N, 4.66.

1,2-Dihydro-6-methyl-2-oxo-5-(xanthen-9-on-3-yl)nicotinonitrile **2c**.

A mixture of sodium methoxide [from sodium (0.04 g, 0.0017 mole)], **5c** (0.51 g, 0.0017 mole), cyanoacetamide (0.143 g, 0.0017 mole) in dry *N,N*-dimethylformamide (20 ml) was heated under reflux with stirring for 1 hour. The reaction mixture was evaporated to dryness and then crystallized from acetic acid to give 0.41 g (73%) of the compound, mp >300°; ^{1}H nmr (DMSO-d_6): 2.32 (s, 3H), 7.4-8.25 (m, 8H); ms: 328 (M^+).

Anal. Calcd. for $C_{20}H_{12}N_2O_3$: C, 73.17; H, 3.68; N, 8.53. Found: C, 73.40; H, 3.71; N, 8.53.

By the same procedure the following compounds have been prepared:

1,2-Dihydro-6-methyl-2-oxo-5-(xanthen-9-on-1-yl)nicotinonitrile **2a**.

This compound was obtained in a yield of 10%, mp >300° (acetic acid); ^{1}H nmr (DMSO-d_6): 2.0 (s, 3H), 7.2-8.2 (m, 8H); ms: 328 (M^+).

Anal. Calcd. for $C_{20}H_{12}N_2O_3$: C, 73.17; H, 3.68; N, 8.53. Found: C, 73.25; H, 3.60; N, 8.46.

1,2-Dihydro-6-methyl-2-oxo-5-(xanthen-9-on-2-yl)nicotinonitrile **2b**.

This compound was obtained in a yield of 30%, mp >300° (acetic acid); ^{1}H nmr (DMSO-d_6): 2.18 (s, 3H), 7.44-8.26 (m, 8H); ms: 328 (M^+).

Anal. Calcd. for $C_{20}H_{12}N_2O_3$: C, 73.17; H, 3.68; N, 8.53. Found: C, 72.98; H, 3.29; N, 8.40.

1,2-Dihydro-6-methyl-2-oxo-5-(xanthen-9-on-4-yl)nicotinonitrile **2d**.

This compound was obtained in a yield of 45%, mp >300° (acetic acid); ^{1}H nmr (DMSO-d_6): 2.16 (s, 3H), 7.42-8.26 (m, 8H);

ms: 328 (M^+).

Anal. Calcd. for $C_{20}H_{12}N_2O_3$: C, 73.17; H, 3.68; N, 8.54. Found: C, 73.01; H, 3.79; N, 8.33.

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