New Organic Nitrates. I. Synthesis of 1,3-Benzoxazine-2,4-dione, 1,3-Benzoxazine-2-thion-4-one, 1,3-Benzothiazine-2,4-dione and Quinazoline-2,4-dione Derivatives

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The preparation and the physico-chemical characterization of new heterocyclic organic nitrates containing 1,3-benzoxazine-2,4-dione, 1,3-benzoxazine-2-thion-4-one, 1,3-benzothiazine-2,4-dione and quinazoline-2,4-dione moieties, are reported.

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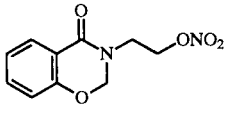
Introduction.

Since glyceryl trinitrate (GTN) was first used in angina pectoris in 1879, organic nitrates have remained a basic class of drugs for the treatment of several cardiovascular diseases. In the first half of the twentieth century, a number of organic nitrate molecules were prepared and used in managing ischaemic heart diseases and for the control of hypertension. In the last few years the search for new organic nitrates with reduced side-effects and improved oral bioavailability has greatly intensified [1].

Our interest in the cardiovascular field prompted us to synthesize new derivatives with a pharmacodynamic profile different from that of GTN, containing the 1,3-benzoxazin-4-one moiety [2]. Particularly, ITF 296, 3-[2-(nitrooxy)ethyl]-2*H*-1,3-benzoxazin-4(3H)-one (Figure 1), was selected for the pharmacological development showing good oral activity in rats [3]. In this paper we report the synthesis of the new ITF 296 analogues **4a-e, 8, 10** and **15** (Figure 2).



ITF 296

Figure 1

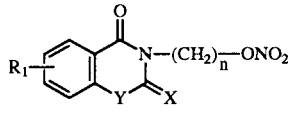


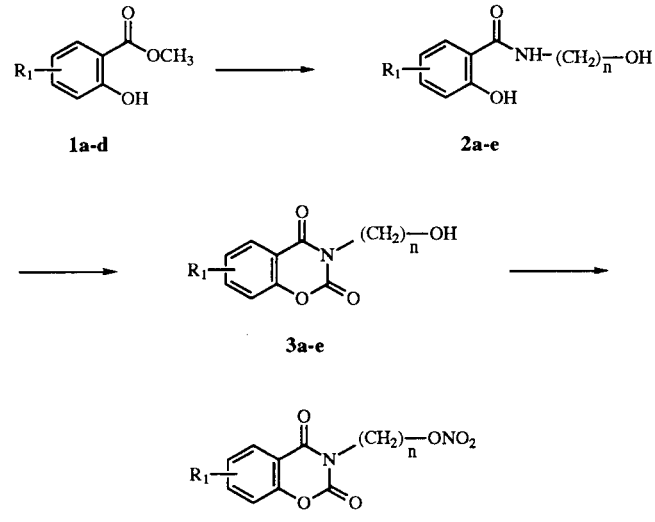
Figure 2

Chemistry.

The synthesis of compounds **4a-e** was carried out according to Scheme 1. Particularly, derivatives **4a-d** were prepared starting from commercial methyl salicylates **1a-d** which were heated at 170° in the presence of ethanolamine distilling off methanol. The known compounds **2a-d** [2,4] thus obtained were cyclized at room temperature using 1,1'-carbonyldiimidazole in dichloromethane in the presence of sodium methylate to give 1,3-benzoxazine-2,4-diones **3a-d**. A solution of compounds **3a-d** and tetrabutylammonium nitrate in a mixture of dichloromethane, pyridine and *N,N*-dimethylformamide was treated with trifluoromethanesulfonic anhydride [5] obtaining the desired nitroesters **4a-d.** The same synthetic route was adopted for the preparation of compound **4e** starting from known derivative **2e** [6] which was obtained from methyl salicylate and 3-amino-1-propanol.

Analytical data of compounds **3a-e** and their ^{1}H-nmr are reported in Table 1. Analytical data and ^{1}H-nmr of organic nitrates **4a-e** are given in Table 2. Scheme 2 illus-

Scheme 1



Compounds **1-4**	R_1	n
a	H	2
b	5-CH_3	2
c	6-OCH_3	2
d	7-Cl	2
e	H	3

Table 1

Compound	Yield (%)	MP, °C crystallization solvent	Molecular Formula	Analysis ,% (Calcd./Found) C	H	N	^{1}H-NMR, (δ) ppm DMSO-d_6
3a	83	124-125° (ethyl acetate)	$C_{10}H_9NO_4$	57.97 57.86	4.38 4.35	6.76 6.82	7.97 (dd, 1H), 7.82 (dt, 1H), 7.44 (t, 1H), 7.42 (d, 1H), 4.83 (t, 1H), 3.98 (t, 2H), 3.62 (q, 2H)
3b	30	[a]	$C_{11}H_{11}NO_4$	59.73 60.00	5.01 4.98	6.33 6.30	7.68 (t, 1H), 7.27 (d, 2H), 4.81 (t, 1H), 3.96 (t, 2H), 3.60 (q, 2H),2.69 (s, 3H)
3c	11	131-132° (dichloromethane)	$C_{11}H_{11}NO_5$	55.70 55.73	4.67 4.72	5.90 5.96	7.42-7.38 (m, 3H), 4.85 (t, 1H), 3.96 (t, 2H), 3.86 (s, 3H), 3.61 (q, 2H)
3d	11	[a]	$C_{10}H_8ClNO_4$	49.71 49.60	3.34 3.36	5.80 5.75	8.01 (d, 1H), 7.73 (d, 1H), 7.53 (dd, 1H), 4.87 (t, 1H), 3.94 (t, 2H), 3.63 (q, 2H)
3e	97	80-81° (*n*-hexane)	$C_{11}H_{11}NO_4$	59.73 59.68	5.01 4.96	6.33 6.39	7.99 (dd, 1H), 7.83 (dt, 1H), 7.49-7.42 (m, 2H), 4.80 (t, 1H), 3.98 (m, 4H), 2.06 (m, 2H)

[a] Compounds obtained as amorphous solids.

Table 2

Compound	Yield (%)	MP, °C crystallization solvent	Molecular formula	Analysis, % (Calcd./Found) C	H	N	^{1}H-NMR, (δ) ppm DMSO-d_6
4a	17	88-89° (*n*-hexane)	$C_{10}H_8N_2O_6$	47.63 47.62	3.20 3.20	11.11 11.01	8.01 (dd, 1H), 7.85 (dt, 1H), 7.51-7.43 (m, 2H), 4.78 (m, 2H), 4.28 (m, 2H)
4b	42	75-76° (*n*-hexane)	$C_{11}H_{10}N_2O_6$	49.62 49.59	3.79 3.77	10.52 10.50	7.68 (t, 1H), 7.27 (d, 2H), 4.77 (m, 2H), 4.25 (m, 2H), 2.69 (s, 3H)
4c	67	141-142° (*n*-hexane)	$C_{11}H_{10}N_2O_7$	46.81 46.78	3.57 3.54	9.92 9.93	7.43-7.36 (m, 3H), 4.78 (m, 2H), 4.28 (m, 2H), 3.86 (s, 3H)
4d	43	105-106° (*n*-hexane)	$C_{10}H_7ClN_2O_6$	41.90 41.86	2.46 2.43	9.78 9.77	8.01 (d, 1H), 7.73 (d, 1H), 7.53 (dd, 1H), 4.77 (t, 2H), 4.27 (t, 2H)
4e	16	72-73° (*n*-hexane)	$C_{11}H_{10}N_2O_6$	49.63 49.66	3.79 3.75	10.53 10.52	8.00 (dd, 1H), 7.83 (dt, 1H), 7.46 (t, 1H), 7.44 (d, 1H), 4.61 (t, 2H), 4.00 (t, 2H), 2.06 (q, 2H)
8	57	121-122° (ethyl acetate)	$C_{10}H_8N_2O_5S$	44.78 44.79	3.01 3.01	10.44 10.48	8.03 (dd, 1H), 7.91 (dt, 1H), 7.58-7.49 (m, 2H), 4.91 (m, 2H), 4.75 (m, 2H)
10	34	109-110° (*n*-hexane)	$C_{10}H_8N_2O_5S$	44.79 44.75	3.01 3.03	10.44 10.34	8.29 (s, 1H), 7.79 (dt, 1H), 7.65 (d, 1H), 7.56 (t, 1H), 4.78 (m, 2H), 4.43 (m, 2H)
15	70	192-193° (ethyl acetate)	$C_{10}H_9N_3O_5$	47.81 47.54	3.61 3.57	16.73 16.55	8.41 (s, 1H), 8.18 (dd, 1H), 7.86 (dt, 1H), 7.71 (d, 1H), 7.58 (t, 1H), 4.89 (t, 2H), 4.40 (t, 2H)

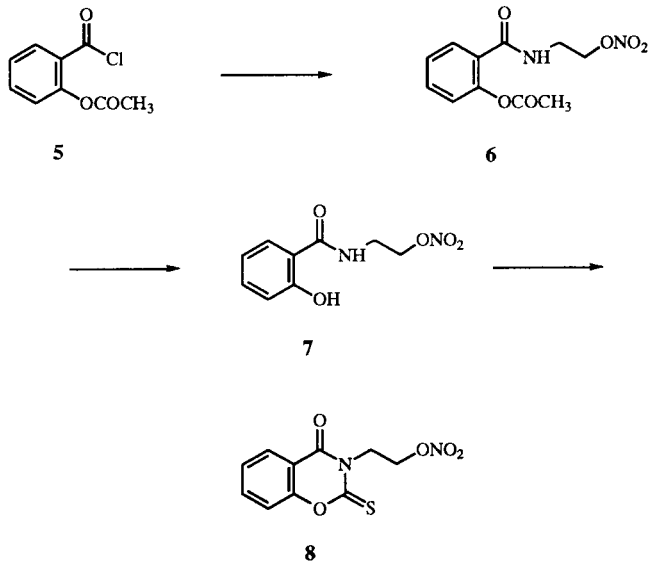
trates the synthetic approach used in the preparation of derivative **8**. Already reported nitroester **7** [7] was prepared in a two-step synthesis starting from salicyloyl chloride. Compound **7** was dissolved in tetrahydrofuran and treated at room temperature with 1,1'-thiocarbonyldiimidazole in the presence of sodium methylate to give 1,3-benzoxazine-2-thion-4-one **8**.

The synthetic routes, described in Schemes 1 and 2, can be used indifferently for the preparation of derivatives **4a-e** and **8**.

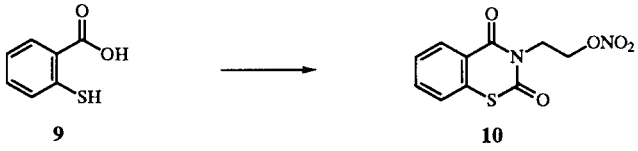
In Scheme 3 is reported the one-pot synthesis of 1,3-benzothiazine-2,4-dione **10**. Thiosalicylic acid **9** was treated at room temperature with 2-nitrooxyethylamine nitrate in chloroform in the presence of 1,1'-carbonyldiimidazole. The amidic intermediate thus obtained was directly cyclized taking advantage of the presence of 1,1'-carbonyldiimidazole to give the desired compound **10**.

The preparation of derivative **15** was carried out as shown in Scheme 4. As previously reported [8] starting

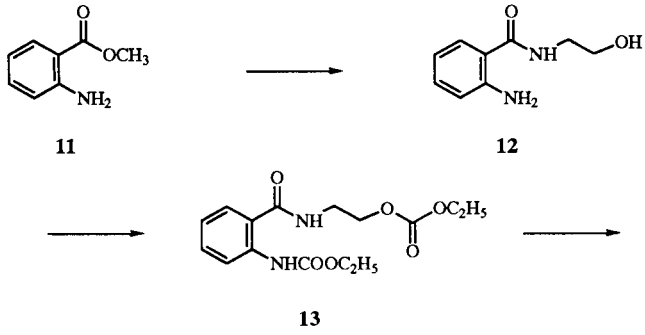
Scheme 2

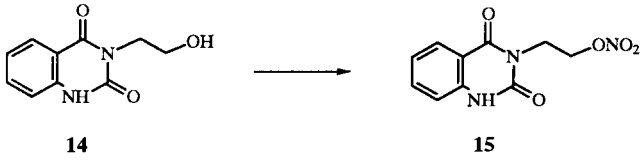


Scheme 3



Scheme 4





from methyl anthranilate we prepared 1*H*,3*H*-quinazoline-2,4-dione **14** in a three-step synthesis. A solution of derivative **14** and tetrabutylammonium nitrate in a mixture of dichloromethane, pyridine and *N*,*N*-dimethylformamide was treated with trifluoromethanesulfonic anhydride to obtain desired nitroester **15**. Analytical data of nitroester compounds **8**, **10** and **15** and their ^{1}H-nmr are shown in Table 2.

The nitroesters obtained show good *in vitro* vasorelaxing activity and are now under *in vivo* pharmacological evaluation for their anti-ischemic properties.

EXPERIMENTAL

General.

Melting points were determined in open capillary tubes on a Büchi 530 melting point apparatus and were uncorrected. Thin-layer chromatography was performed on silica gel glass backed plates (5719) purchased from E. Merck & Co., and flash chromatography was performed on silica gel 60 (230-400 mesh ASTM) (E. Merck & Co). The ^{1}H-nmr spectra were recorded at 200 MHz (Varian Gemini 200); chemical shifts are given in ppm (δ) referenced to DMSO-d_6 (2.50 ppm). Elemental analysis were carried out on Perkin Elmer 240.

2,3-Dihydro-3-(2-hydroxyethyl)-6-methoxy-1,3-benzoxazine-2,4-dione (**3c**).

To a solution of compound **2c** (10.5 g, 0.05 mole) in dichloromethane (100 ml) sodium methylate (0.274 g, 0.005 mole) was added portionwise and successively 1,1'-carbonyldiimidazole (8.2 g, 0.05 mole) dissolved in dichloromethane (80 ml) was added dropwise at room temperature. The solution obtained was stirred at room temperature for 3 hours and then treated with water. The organic layer was separated and concentrated at reduced pressure to give a crude residue that was dissolved in a mixture of tetrahydrofuran-1*N* hydrochloric acid 2:1 (430 ml). The solution was stirred at room temperature for 2 hours, concentrated at reduced pressure, diluted with water and extracted with dichloromethane. The organic phase was separated, dried with anhydrous sodium sulphate and evaporated under reduced pressure to give pure derivative **3c** after recrystallization from dichloromethane (72%, mp 131-132°).

Compounds **3a-b** and **3d-e** were similarly prepared starting from corresponding derivatives **2a-b** and **2d-e**. Derivatives **3b** and **3d** were purified by silica gel chromatography eluting with *n*-hexane-ethyl acetate 8:2.

2,3-Dihydro-6-methoxy-3-(2-nitrooxyethyl)-1,3-benzoxazine-2,4-dione (**4c**).

To a solution of derivative **3c** (1.2 g, 0.005 mole), tetrabutylammonium nitrate (3.05 g, 0.01 mole) and pyridine (0.81 ml, 0.01 mole) in dichloromethane (30 ml) and dimethylformamide (30 ml) cooled at -50°, a solution of trifluoromethanesulfonic anhydride (1.64 ml, 0.01 mole) in dichloromethane (17 ml) was added dropwise. The reaction mixture was stirred at 40° for 1 hour and then poured into water. The organic layer was separated, washed with 1% hydrochloric acid, water, aqueous sodium bicarbonate and water and then dried with sodium sulfate. After the evaporation of the solvent at reduced pressure, the obtained residue was purified by silica gel chromatography eluting with dichloromethane to give pure compound **4c** after recrystallization from *n*-hexane (67%, 141-142°).

Compounds **4a-b, 4d-e** and **15** were similarly prepared starting from corresponding derivatives **3a-b, 3d-e** and **14**.

2,3-Dihydro-3-(2-nitrooxyethyl)-1,3-benzoxazine-2-thion'-4-one (**8**).

To a solution of compound **7** (13 g, 0.054 mole) in tetrahydrofuran (500 ml) sodium methylate (0.295 g, 0.005 mole) and then 1,1'-thiocarbonyldiimidazole (9.73 g, 0.054 mole) were added portionwise at room temperature. The reaction mixture was stirred at room temperature for 6 hours and evaporated at reduced pressure. The residue was treated with water and extracted with ethyl acetate which was separated, dried with sodium sulphate and evaporated at reduced pressure. The solid residue was crystallized from ethyl acetate to give pure **8** (57%, 121-122°).

2,3-Dihydro-3-(2-nitrooxyethyl)-1,3-benzothiazine-2,4-dione (**10**).

To a suspension of thiosalicylic acid **9** (5 g, 0.032 mole) in chloroform (100 ml) a solution of 1,1'-carbonyldiimidazole (10.52 g, 0.064 mole) in chloroform (50 ml) was added dropwise at room temperature and the reaction mixture was stirred for 1 hour. A solution of nitrooxyethylamine nitrate (5.48 g, 0.032 mole) and triethylamine (6.3 ml, 0.048 mole) in chloroform (50 ml) was then added dropwise at room temperature. The obtained mixture was stirred for 5 hours and washed with water; the organic layer was separated, dried with sodium sulphate and evaporated under reduced pressure to give pure compound **10** after crystallization from *n*-hexane (34%, 109-110°).

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