Synthesis and Structure of some IminesContaining Furoxan Ring Derived from Isosafrole

Nguyen Huu Dinh , Ngo Thi Ly, and Le Thi Thanh Van

Department of Chemistry, Hanoi Pedagogic University
Caugiay, Hanoi, Vietnam
Received April 26, 2004

A series of 14 imines containing furoxan and benzene rings has been prepared starting from isosafrole. The structure of reported compounds have been confirmed by elemental analysis, EI MS, UV, IR, and NMR spectroscopy. It is shown that, on treatment with $Na_2S_2O_4$, the nitro group on the benzene ring was reduced to amino group, but the N→O group of the furoxan ring was not. The ^1H- and ^{13}C NMR signals are assigned based on their spin-spin splitting patterns, in some cases, NOESY and HMBC spectra are used. The NOESY spectra indicate that for reported imines, the benzene and the furoxan rings could not be co-planar; the imine group has *E*-configuration.

J. Heterocyclic Chem., **41**, 1015 (2004).

Introduction.

Wide-ranging biological activity has been claimed for furoxan derivatives. Some are depressants of the central nervous system, or of frog flesor muscle reflexes, or are reported as potential antitrypanosomal drugs [1], hypoxic cytotoxins [2,3], vasodilatory activities [4,5,6,7]. The compounds with furoxan structure (1,2,5-oxadiazole-N-oxide) have been shown to possess NO - mimetic pharmacological activities [8,9]. Recently, great attention has been paid to new chemical species that give rise to nitric oxide under physiological conditions. These prompted the synthesis of many new furoxan derivatives and the study of their pharmacological activities.

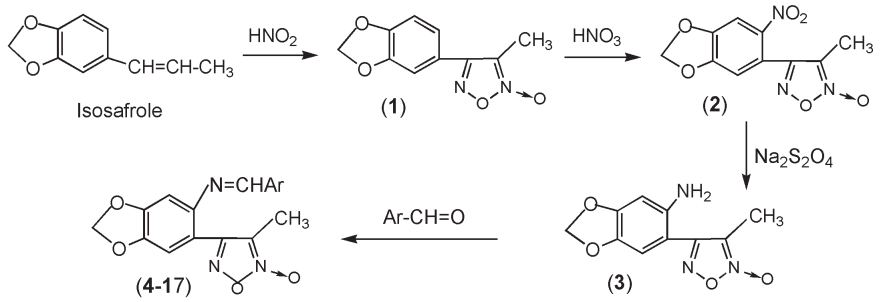
In this paper we report on the preparation and structure of some imines containing furoxan and benzene ring.

Results and Discussion.

The title compounds have been prepared starting from isosafrole as shown in Scheme 1. Compound **1** has been prepared by reaction of isosafrole with nitrous acid [10]. Compound **2** is obtained by nitration of **1** (see experimental). When **2** was treated with iron, tin , zinc or tin(II) chloride in the presence of hydrochloric or acetic acids at 20-80 °C we have not obtain the expected amine, hence, the starting nitro compound is not reduced under these conditions. Of the sulfur compounds that were tested, sodium dithionite in alkaline medium is effective for reducing **2**. Because the furoxan ring was not stable in strong alkaline medium, sodium dithionite and sodium hydroxide were dissolved in water whereas **2** was dissolved in toluene. The components of the resulting two-phase mixture were forced into contact by vigorously stirring. The yield of the amine **3** was limited about 30% due to partial decomposition of the furoxan ring. The condensation of **3** with aromatic aldehydes was carried out in boiling ethanol for 8-10 h with or without acidic catalyst to give the imines **4**-**17** as yellow crystals. The structures of compounds were confirmed by UV-, IR- and NMR spectroscopy (see Table 1, 2, 3, and 4).

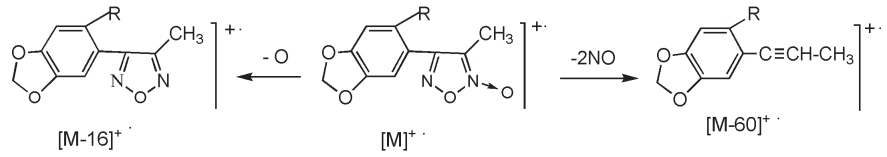
The EI mass spectra of **1**, **2**, **3**, **4** and **17** were recorded. In The EIMS spectra of examined compounds show peaks with m/z values that are in good agreement with their molecular weight. The peak corresponding to the loss of an oxygen atom, $[M-16]^{+\cdot}$, is very weak, but the peak corresponding to the loss of two NO molecules, $[M-60]^{+\cdot}$, is always very intense (86-100%). These primary fragmentations are characteristic for 3-methyl-4-aryl furoxans as shown in Scheme 2.

Scheme 1



Ar: C_6H_5 (**4**), $C_6H_5CH=CH$ (**5**), 4-$NO_2C_6H_4$ (**6**), 3-$NO_2C_6H_4$ (**7**), 2-$NO_2C_6H_4$ (**8**), 2-HOC_6H_4 (**9**), 2-$CH_3OC_6H_4$ (**10**), 4-$CH_3OC_6H_4$ (**11**), 4-HO-3-$CH_3OC_6H_3$ (**12**), 3,4-$OCH_2OC_6H_3$ (**13**), 4-$(CH_3)_2NC_6H_4$ (**14**), 2-pyridyl (**15**), 3-pyridyl (**16**), 2-furyl (**17**).

Scheme 2



The UV spectra of examined compounds show 3 or 4 absorption bands in the 201-384 nm range (logε 3.1-4.6). Compound **1** absorbs at 301 nm, while nitro-, amino-, and imine-derivatives (**2**, **3** and **4**-**17**) have a band in the region near 342-384 nm. This red shift is associated with the extension of conjugation in the molecules **2**-**17** compared with **1**.

The NMR data of the examined compounds were most informative with respect to their structures. The numeration of the examined compounds for analysis NMR spectra is shown on formula A, B, and C (see Figure 1). The resonances of the parent 3-benzo[1,3]dioxol-5-yl-furoxan moiety (H-3 through H-10) are listed in Table 1. The resonances of aromatic substituted imine moiety (H-12 through H-19) are listed in Table 2. In most cases, the assignment of proton signals are based on their spin-spin splitting patterns, however in some cases they are also based on NOESY spectra. For example, due to the cross peak between H-17 (-CH=N-) and H-6 in the NOESY spectrum of **4** (formula B, Ar = C_6H_5), the singlet at 7.35 ppm was assigned to H-6 and next singlet at 7.17 ppm was assigned to H-3.

The IR spectrum of **3** shows two N-H stretching bands corresponding to a primary amine (3485 and 3388 cm^{-1}). In the ^1H NMR spectrum, the resonance of the NH_2-group appears as a broadened singlet at 5.4 ppm. The EIMS spectrum of **3** shows its molecular weight is 235 (41.5%). These indicate that, when **2** is treated with $Na_2S_2O_4$, the nitro group on benzene ring is reduce and the N→O group on the furoxan ring is not.

For imines **4**-**17**, the chemical shift of H-3, H-7, H-10 are nearly the same for all compounds, while chemical shift of H-6 and H-12 through H-19 changed significantly from one to another. In general, groups that are electron withdrawing (-NO_2, hetero atom) cause down-field shifts, electron donating substituents (OCH_3, OCH_2O, NMe_2) cause up-field shifts. There are some exceptions, *e.g.* the -OH group in **9** causes the chemical shift of H-6 and H-17 to be the largest in comparison with those of the other

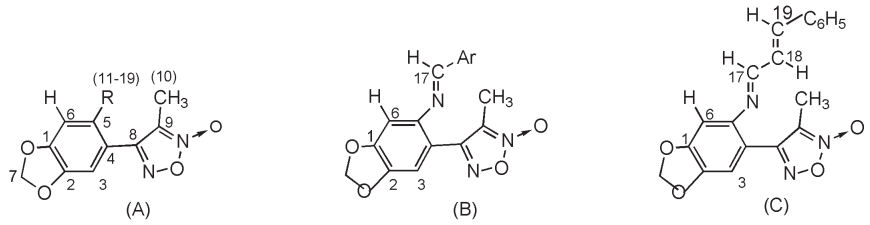


Figure 1

Gasco and colleges [11] have shown that the chemical shift of a ring methyl group adjacent to the N-oxide oxygen of furoxans occurs in the region 2.30-2.33 ppm, while a ring methyl group remote from it occurs in the 2.50-2.53 ppm region. The signal of the ring methyl group (H-10) of **1**-**17** appears as a singlet in the 2.00-2.28 ppm range (Table 1) indicating that the methyl group is at position 3 of the furoxan ring.

In the ^1H NMR spectrum of **1** (Formula A, R=H), there are 3 signals of 3 aromatic protons: 7.31 (d, ^4J=1.5 Hz, H-3); 7.27 (dd, ^3J=8, ^4J=1.5, H-5); 7.13 (d, ^3J=8 Hz, H-6). In the spectrum of **2** (R=NO_2) there are 2 singlets at 7.94 and 7.38 ppm, corresponding to 2 aromatic protons *para* positions relative to one another. This indicates that, the nitro group is introduced into position 5 (Formula A).

compounds. It is possible that the *ortho*-OH group forms intramolecular hydrogen bonding with imine nitrogen atom.

It is interesting that the NOESY spectrum of **1** yields cross peaks between the methyl group (H-10) and both H-3 and H-5 (Figure 2). This demonstrates that the furoxan and the benzene rings rapidly rotate on the NMR time scale. In the NOESY spectra of the imines **4**, **5**, **6**, **12**, **15** and **17** there are cross peaks between H-10 and H-3 (H-5 has been replaced). However, free rotation of the furoxan

Table 1

Resonance Signals of 3-Benzo[1,3]dioxol-5-yl-furazan Moiety (H-3 through H-10) of Compounds **1**-**17** (δ, ppm, J Hz)

Compd	H-3	H-6	H-7	H-10	Other
1	7.31; d; ^{4}J 1.5	7.13; d; ^{3}J 8	6.15; s	2.28; s	7.27; dd; H-5
2	7.38; s	7.94; s	6.38; s	2.02; s	-
3	6.80; s	6.46; s	5.94; s	2.12; s	5.4; s; NH_2
4	7.17; s	7.35; s	6.19; s	2.06; s	-
5	7.13; s	7.24; s	6.17; s	2.05; s	-
6	7.20; s	7.42; s	6.22; s	2.05; s	-
7	7.20; s	7.38; s	6.21; s	2.08; s	-
8	7.19; s	7.27; s	6.21; s	2.00; s	-
9	7.22; s	7.48; s	6.22; s	2.01; s	-
10	7.15; s	7.22; s	6.18; s	2.05; s	-
11	7.14; s	7.28; s	6.18; s	2.04; s	-
12	7.14; s	7.27; s	6.18; s	2.07; s	-
13	7.14; s	7.27; s	6.18; s	2.03; s	-
14	7.10; s	7.23; s	6.15; s	2.03; s	-
15	7.20; s	7.47; s	6.21; s	2.06; s	-
16	7.19; s	7.37; s	6.21; s	2.06; s	-
17	7.15; s	7.31; s	6.18; s	2.07; s	-

and the benzene rings is impossible since the van der Waals repulsions between groups -CH_3 and -N=CHAr, thus the two rings could not be coplanar. The cross peaks between H-17 (imine proton) and H-6 in the NOESY spectra of the examined imines (**4**, **5**, **6**, **12**, **15** and **17**) indicate that imine group (-N=CH-) has *E*-configuration (Formula B). In addition, the large value of the coupling constant

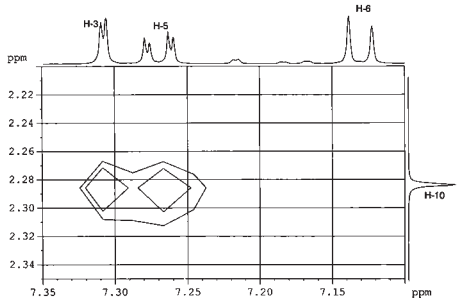


Figure. 2- A part of NOESY spectrum of compound **1**.

Table 2

Resonance Signals of Aromatic Substituted Imine Moiety (H-12 through H-19) of Compounds **4**-**17** (δ,ppm, J Hz)

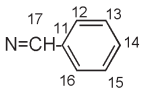
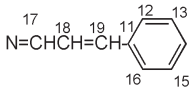
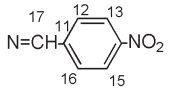
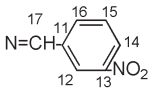
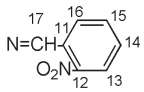
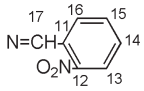
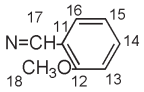
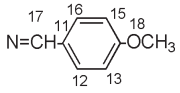
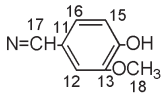
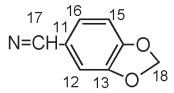
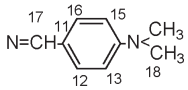
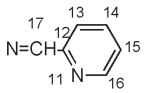
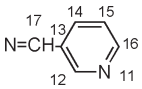
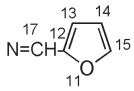
No	R	H-12	H-13	H-14	H-15	H-16	H-17	Others
4		7.79; dd ^{3}J 7.5, ^{4}J 2	7.53; m	7.51; m	7.53; m	7.79; dd ^{3}J 7.5, ^{4}J 2	8.76; s	-
5		7.70; dd ^{3}J 8, ^{4}J 1	7.42;t ^{3}J 7.5	7.40;t ^{3}J 8	7.42 ^{3}J 7.5	7.70 ^{3}J 8, ^{4}J 1	8.52;d ^{3}J 8.5	7.12; dd; H18 7.15; d; H19 J 15; 8.5
6		8.02; d J 8.5	8.36; d J 8.5	-	8.36; d J 8.5	8.02; d J 8.5	8.93; s	-
7		8.57; t J 1.5	-	8.35; d J 8	7.81; d J 8	8.19; d J 8	8.94; s	-
8		-	7.94; dd ^{3}J 8, ^{4}J 1	7.56;td ^{3}J 8, ^{4}J 1.5	7.84;td ^{3}J 8, ^{4}J 1	8.03;td ^{3}J 8, ^{4}J 1	8.92; s	-
9		-	6.92; d	7.40; td J 8	6.98; td ^{3}J 8, ^{4}J 2	7.60; d ^{3}J 8, ^{4}J 2	9.03; s ^{3}J 7.5	12.22; s; OH
10		-	7.16; d J 7.5	7.52; td ^{3}J 7.5, ^{4}J 1.5	7.04; t J 7.5	7.73; dd ^{3}J 8; ^{4}J 3	8.91; s	3.89; s; H18
11		7.73; d J 8.5	7.07; d J 9	-	7.07; d J 9	7.73; d J 8.5	8.66; s	3.83; s; H18
12		7.31; d J 1.5	-	-	6.90; d J 8.5	7.25; dd ^{3}J 8; ^{4}J 1.5	8.59; s	9.85; s; OH 3.79; s; H18

Table 2 (continued)

No	R	H-12	H-13	H-14	H-15	H-16	H-17	Others
13		7.22; d J 1.5	-	-	7.06; d J 8	7.34; dd ^{3}J 8 ^{4}J 1.5	8.63; s	6.12; s; H18
14		7.59; d J 9	6.78; d J 9	-	6.80; d J 9	7.59; d J 9	8.52; s	3.00; s; H18
15		-	7.86; d -	7.95; t J 7.5	7.52; t J 7.5	8.72; d J 5.5	8.74; s J 4	
16		8.93; d J 1.5		8.12; td ^{3}J 8, ^{4}J 2	7.55;dd ^{3}J8, ^{4}J 1.5	8.70;dd ^{3}J 8, ^{4}J 1.5	8.84; s	-
17			7.12; d J 3.5-	6.71; dd ^{3}J 3.5, ^{4}J 1.5	7.96; m	-	8.57; s	-

between H-18 and H-19 of **5** (15 Hz, Table 2) shows also *E*-configuration for –CH=CH- (formula C).

The ^{13}C NMR data are given in Table 3 and 4. Assignment of the ^{13}C signals are based on their chemical shift and HMBC spectra of the examined compounds (**1, 2, 3, 6, 7, 12, 15, 16, 17**). For example, HMBC spectrum of **7** is presented in Figure 3.

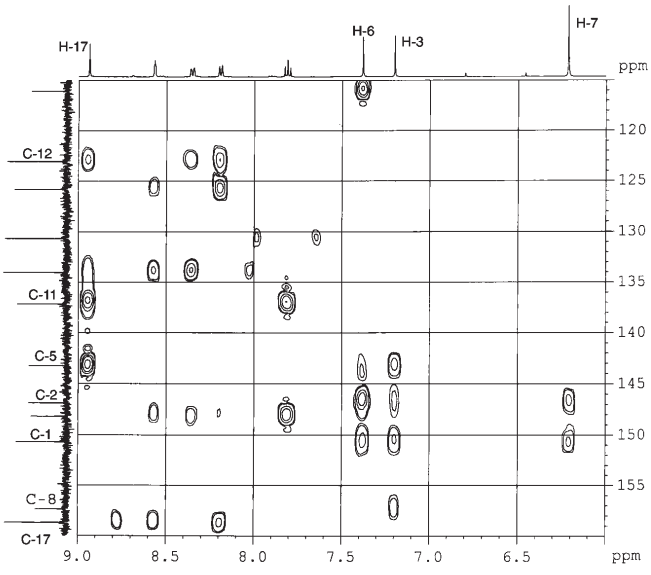


Figure 3. A part of HMBC spectrum of compound **7**.

Because the signals of the protons H-3, H-6, H-7, H-10 and H-17 are always assigned unambiguously, the signals of ring carbons are thus identified. For example, in Figure 3, two cross peaks of H-7 (6.21 ppm) show that the two signals at 150.7 and 146.9 ppm correspond to C-1 and C-2; the cross peaks of H-3 (7.20 ppm) show signals of C-8 (157.4), C-1 (150.7), C-5 (146.9); the cross peaks of H-6 (7.38 ppm) show signals of C-1, C-2, C-4; the cross peaks of H-17 (8.94 ppm) show signals of C-5, C-11, C-12; the cross peaks of C-17 (158.7 ppm), in turn, show signals of H-12, H-16; and so on.

Chemical shift of C-1÷C-10 significantly changed from **1** to **2** and **3,** but little changed from **4** to **17** (Table 3). It is interesting that the imine group (-N=CH-) causes up-field shifts for C-6 of **4**÷**17** as well as group -NH_2 - for C-6 of **3**. These groups make chemical shift of C-6 smaller than those of C-7 for **3**÷**17.** As expected, for **4**÷**17**, the ^{13}C of imine group (C-17) resonated at lowest field (Table 4).

EXPERIMENTAL

IR spectra were recorded on a IMPACK- 410 NICOLET spectrometer in KBr discs at 400-4000 cm^{-1}. The UV spectra were recorded in ethanol at concentration 10^{-4}–10^{-5} *M* using UV-Vis Cintra spectrometer. The EI mass spectra of examined compounds were recorded using a 5989B Hewlett-Packard mass spectrometer. NMR spectra were recorded on a Bruker AVANCE 500 MHz spectrometer, all at 298-300 K, in d_6-DMSO with TMS as the internal standard.

3-Methyl-4-(3,4-methylendioxyphenyl)furoxan (**1**).

Isosafrole (16.2 g, 0.1 mol) was dissolved in 50 ml of acetic acid. To this solution $NaNO_2$ (15.1 g, 0.12 mol) was added in portions over 4 hours and stirred at 25-30 °C for an additional hour. The reaction mixture was added into 100 ml of water. The organic layer was separated and washed with water. The residual semisolid was dissolved in 50 ml of hot ethanol and allowed to cool to room temperature. The resulting yellow precipitate was collected, recrystallized from ethanol and then from benzene. The light yellow needle crystals were dried in vacuum at 50 °C

Table 3

Resonance signals of the 3-Benzo[1,3]dioxol-5-yl-furazan Moiety (C-1 through C-10) of Compounds **1**-**17** (δ, ppm)

Comp.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1	149.6	148.0	108.9	119.7	122.4	107.4	101.8	156.9	112.8	8.85
2	150.1	152.3	110.6	116.3	142.3	105.9	104.5	156.1	113.5	7.45
3	150.2	138.5	108.4	100.2	143.7	97.1	100.9	157.0	113.7	8.9
4	150.7	146.3	109.3	115.4	144.2	99.3	102.4	157.7	114.2	8.75
5	150.7	146.1	109.2	115.5	144.5	98.7	102.3	157.8	114.5	9.03
6	150.8	147.1	109.5	116.4	143.4	99.3	102.6	157.4	114.2	8.96
7	150.7	146.9	109.4	116.1	143.3	99.3	102.5	157.4	114.1	8.71
8	150.7	147.0	109.5	115.9	143.6	99.3	102.6	156.8	114.0	8.52
9	150.7	146.7	109.3	115.1	141.8	99.3	102.6	156.8	113.8	8.23
10	150.7	146.1	109.2	115,0	145.0	99.4	102.3	157.7	114.2	8.75
11	150.7	145.9	109.2	115.0	144.6	99.2	102.3	157.8	114.3	8.78
12	150.7	145.8	109.1	115.1	144.4	99.0	102.3	157.97	114.3	8.91
13	150.7	146.0	109.2	115.2	144.3	99.2	102.3	157.7	114.2	8.75
14	152.5	150.7	109.1	114.5	145.2	98.9	102.0	158.1	114.4	8.83
15	150.8	147.0	109.3	116.3	143.1	99.3	102.5	157.5	114.2	8.7
16	150.7	147.0	109.3	115.8	143.8	99.3	102.5	157.5	114.2	8.7
17	150.8	146.4	109.2	115.9	143.9	98.7	102.4	157.8	114.6	9.1

Table 4

Resonance signals of the Aromatic Substituted Imine Moiety (C-11 through C-19) of Compounds **4**-**17** (δ, ppm)

Comp.	C-11	C-12	C-13	C-14	C-15	C-16	C-17	C-18	C-19
4	135.7	128.9	128.6	131.8	128.6	128.9	160.7	-	-
5	135.2	127.7	128.8	128,3	128.8	127.7	162.1	129.7	145.2
6	141.2	129.6	124.2	148.9	124.2	129.6	158.8	-	-
7	137.2	123.1	148.2	125.8	130.7	134.1	158.7	-	-
8	130.0	149.1	124.4	132.1	133.5	129.0	157.2	-	-
9	119.4	162.7	116.6	133.6	119.3	132.3	159.8	-	-
10	120.8	155.8	112.1	133.5	123.6	126.7	159.4	55.8	-
11	128.6	130.5	114.5	162.2	114.5	130.5	159.9	55.4	-
12	127.6	110.4	147.97	150.6	115.6	124.0	159.7	55.3	-
13	130.4	108.6	148.1	150.5	105.9	126.1	159.8	101.8	-
14	128.1	130.2	111.5	123.3	111.5	130.2	159.8	40.0	-
15	-	153.8	121.2	137.3	125.8	149.8	160.4	-	-
16	-	152.1	131.3	134.8	124.3	150.4	158.6	-	-
17	-	147.8	118.1	112.7	147.1	-	151.7	-	-

for 2 hours. The yield 19.9 g (90%), mp 124 °C. ir (KBr): 3002, 2906 (C-H), 1596, 1501 (ring); uv (ethanol), λmax, nm/logε: 301/3.89, 269/3.87, 202 (shoulder); ms: m/z 220(M^+), 190(M^+-NO), 160(M^+-2NO); ^{1}H nmr and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{10}H_8N_2O_4$: C, 54.54; H, 3.84; N, 12.72. Found: C, 54.14; H, 3.98; N, 12.55.

3-Methyl-4-(4,5-methylendioxy-2-nitrophenyl)furoxan (**2**).

To a stirred solution of 11 g (0.05 mol) of **1** in 40 ml of acetic acid, at room temperature was slowly added a mixture of HNO_3 (12 ml, D = 1.41 g/ml) and H_2SO_4 (20 ml, D= 1.84 g/ml). The reaction mixture was stirred at 50-60 °C for 3 hours after which the reaction mixture was allowed to cool to room temperature. The solid was collected and washed with water, a Na_2CO_3 solution, and then with water to neutralize. The resulting precipitate was recrystallized from ethanol, and the resulting yellow needle crystals were dried in vacuum at 50 °C for 2 hours. The yield 8.2 g (62%), mp 140-2 °C. ir (KBr): 3058, 2986 (C-H), 1619, 1524 (ring); uv (ethanol), λmax, nm/logε: 342/3.66, 251/4.26, 210 (shoulder); ms: m/z 265(M^+), 235 (M^+-NO), 205 (M^+-2NO); ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{10}H_7N_3O_6$: C, 45.28; H, 2.64; N, 15.85. Found: C, 45.52; H, 2.34; N, 15.62.

4-(2-Amino-4,5-methylendioxyphenyl)-3-methylfuroxan (**3**).

To a vigorously stirred solution of 13.25 g (0.05 mol) of **2** in 150 ml of toluene, at 80 °C was slowly added a solution of $Na_2S_2O_4$ (52.2 g, 0.3 mol) and NaOH (12 g, 0.3 mol). The reaction mixture was stirred at 80 °C for 2 additional hours at which time the reaction mixture was allowed to cool to room temperature. The organic layer was extracted, washed with water and dried with Na_2SO_4. Evaporation of toluene *in vacuo* gave a yellow residue, which was recrystallized from 60% by volume aqueous ethanol. The resulting light yellow needle crystals were dried in vacuum at 50 °C for 2 hours. The yield 3.53 g (30%), mp 158-159 °C. ir (KBr): 3485, 3388, 1641 (NH_2), 3040, 2908 (C-H), 1597, 1502 (ring); uv (ethanol), λmax, nm/logε: 354/3.70, 256/4.23, 205/4.40 ; ms: m/z 235 (M^+), 205 (M^+-NO), 175 (M^+-2NO); ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{10}H_9N_3O_4$: C, 51.06; H, 3.83; N, 17.87. Found: C, 51.32; H, 3.54; N, 17.61.

General Procedure for the Preparation of Imines **4**-**17**.

A solution of 1 mmol of **3** and 1 mmol of an aromatic aldehyde dissolved in 20 ml of ethanol (for the preparation of **9**-**14**, 0.1 ml acetic acid was also added) was refluxed over 8-10 hours. The mixture was allowed to stand at room temperature. The resulting yellow precipitate was collected and recrystallized.

4-(2-Benzylidenamino-4,5-methylendioxyphenyl)-3-methylfuroxan (**4**).

This compound was obtained as yellow needles (from ethanol); The yield 0.22 g (69%), mp 207 °C; ir (KBr): 3080, 2970 (C-H), 1629, 1604, 1577 (ring); uv (ethanol), λmax, nm/logε: 350/3.19, 263/3.53, 208/3.54; ms: m/z 323 (M^+), 307 (M^+-O), 293 (M^+-NO), 263 (M^+-2NO); ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{17}H_{13}N_3O_4$: C, 63.16; H, 4.02; N, 13.00. Found: C, 62.87; H, 3.88; N, 13.38.

3-Methyl-4-(2-xynamylydenamino-4,5-methylendioxyphenyl)-furoxan (**5**).

This compound was obtained as yellow needles (from ethanol); the yield 0.27 g (77%), mp 161 °C; ir (KBr): 3064, 3021, 2941 (C-H), 1627 (C=C), 1615, 1581, 1501 (ring); uv (ethanol), λmax, nm/logε: 363/4.37, 302/4.50, 210/4.24 ; ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{17}H_{15}N_3O_4$: C, 65.33; H, 4.30; N, 12.07. Found: C, 64.97; H, 4.07; N,12.35.

3-Methyl-4-[2-(4-nitrobenzylyden)amino-4,5-methylendioxyphenyl]furoxan (**6**).

This compound was obtained as deep-yellow needles (from dioxane-ethanol); the yield 0.33 g (90%), mp 224 °C; ir (KBr): 3108, 2972, 2911 (C-H), 1610,1501 (ring); uv (ethanol), λmax, nm/logε:382/3.23, 274/3.56, 204/3.71; ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{17}H_{12}N_4O_6$: C, 55.43; H, 3.26; N, 15.22. Found: C, 55.06; H, 3.14; N, 15.54.

3-Methyl-4-[2-(3-nitrobenzylyden)amino-4,5-methylendioxyphenyl]furoxan (**7**).

This compound was obtained as yellow needles (from dioxane-ethanol); The yield 0.34 g (92%), mp 227 °C; ir (KBr): 3099, 3082, 2921 (C-H), 1603,1500 (ring); uv (ethanol), λmax, nm/logε: 358/3.16, 261/3.62, 231/3.69, 202/3.97; ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{17}H_{12}N_4O_6$: C, 55.43; H, 3.26; N, 15.22. Found: C, 55.67; H, 3.01; N, 14.87.

3-Methyl-4-[2-(2-nitrobenzylyden)amino-4,5-methylendioxyphenyl]furoxan (**8**).

This compound was obtained as yellow needles (from dioxane-ethanol); the yield 0.35 g (95%), mp 164 °C; ir (KBr): 3112, 3082, 2921, (C-H), 1614, 1564 (ring); uv (ethanol), λmax, nm/logε: 363/3.80, 274/4.22, 239/4.23, 207/4.26; ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{17}H_{12}N_4O_6$: C, 55.43; H, 3.26; N, 15.22. Found: C, 55.72; H, 3.41; N, 14.82.

4-[2-(2-Hydroxybenzylyden)amino-4,5-methylendioxyphenyl]-3-methylfuroxan (**9**).

This compound was obtained as yellow needles (from dioxane-ethanol); the yield 0.26 g (77%), mp 196 °C; ir (KBr): 3115, 3063, 2986, 2915 (C-H), 1619, 1599, 1505 (ring); uv (ethanol), λmax, nm/logε: 364/3.58, 269/3.74, 236/3.71, 209/3.82; ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{17}H_{13}N_3O_5$: C, 60.18; H, 3.83; N, 12.39. Found: C, 59.86; H, 3.51; N, 12.67.

4-[2-(2-Methoxybenzylyden)amino-4,5-methylendioxyphenyl]-3-methylfuroxan (**10**).

This compound was obtained as light-yellow needles (from ethanol); the yield 0.25 g (70%), mp 176 °C; ir (KBr): 3003, 2969, 2906 (C-H), 1607, 1594, 1500 (ring); uv (ethanol), λmax, nm/logε: 354/4.06, 266/4.24, 210/4.28; ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{18}H_{15}N_3O_5$: C, 61.18; H, 4.25; N, 11.90. Found: C, 61.57; H, 4.51; N, 11.86.

4-[2-(4-Methoxybenzylyden)amino-4,5-methylendioxyphenyl]-3-methylfuroxan (**11**).

This compound was obtained as yellow plates (from ethanol); the yield 0.26 g (74%), mp 172 °C; ir (KBr): 3024, 2961, 2917(C-H), 1629, 1603, 1568, (ring); uv (ethanol), λmax, nm/logε: 384/3.96, 280/4.02, 223/3.99, 208/4.00; ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{18}H_{15}N_3O_5$: C, 61.18; H, 4.25; N, 11.90. Found: C, 61.65; H, 4.05; N, 11.68.

4-[2-(3-Methoxy-4-hydroxybenzylyden)amino-4,5-methylendioxyphenyl]-3-methylfuroxan (**12**).

This compound was obtained as yellow light-yellow needles (from toluene); the yield 0.29 g (79%), mp 215 °C; ir (KBr): 3373 (OH), 3014, 2937, 2898 (C-H), 1627, 1593, 1509, (ring); uv (ethanol), λmax, nm/logε: 355/3.65, 273/3.43, 245/3.59, 215/3.56; ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{18}H_{15}N_3O_6$: C, 58.53; H, 4.06; N, 11.38. Found: C, 58.89; H, 4.21; N, 11.63.

3-Methyl-4-[2-(3,4-methylendioxybenzylyden)amino-4,5-methylendioxyphenyl]furoxan (**13**).

This compound was obtained as yellow needles (from toluene); the yield 0.26 g (71%), mp 119 °C; ir (KBr): 3082, 3018, 2912 (C-H), 1603, 1501, (ring); uv (ethanol), λmax, nm/logε: 352/4.38, 274/4.28, 240/4.43, 205/4.54; ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{18}H_{13}N_3O_6$: C, 58.86; H, 3.54; N, 11.44. Found: C, 59.16; H, 3.21; N, 11.67.

3-Methyl-4-[2-(4-dimethylaminobenzylyden)amino-4,5-methylendioxyphenyl]furoxan (**14**).

This compound was obtained as yellow crystals (from toluene); the yield 0.25 g (68%), mp 211 °C; ir (KBr): 3110, 3006, 2909 (C-H), 1611, 1593, 1582, (ring); uv (ethanol), λmax, nm/logε: 381/3.93, 320/3.50, 242/3.69, 204/3.84; ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{19}H_{18}N_4O_4$: C, 62.29; H, 4.92; N, 15.30. Found: C, 61.96; H, 5.21; N, 15.67.

3-Methyl-4-[2-(2-pyridylmethylen)amino-4,5-methylendioxyphenyl]furoxan (**15**).

This compound was obtained as yellow needles (from ethanol); the yield 0.30 g (93%), mp 182 °C. ir (KBr): 3050, 2906 (C-H),

1603, 1568, 1503, (ring); uv (ethanol), λmax, nm/logε: 358/3.82, 260/4.09, 204/4.16; ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{16}H_{12}N_4O_4$: C, 59.26; H, 3.70; N, 17.28. Found: C, 59.66; H, 3.61; N, 16.97.

3-Methyl-4-[2-(3-pyridylmethylen)amino-4,5-methylendioxyphenyl]furoxan (**16**).

This compound was obtained as yellow needles (from ethanol); the yield 0.29 g (90 %), mp 185 °C; ir (KBr): 3058, 2988, 2902 (C-H), 1610, 1584 (ring); uv (ethanol), λmax, nm/logε: 357/4.29, 258/4.60, 208/4.53; ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{16}H_{12}N_4O_4$: C, 59.26; H, 3.70; N, 17.28. Found: C, 59.57; H, 3.51; N, 17.47.

4-[2-(2-Fufurylyden)amino-4,5-methylendioxyphenyl]-3-methylfuroxan (**17**).

This compound was obtained as yellow needles (from ethanol); the yield 0.28 g (90 %), mp 218 °C; ir (KBr): 3156,3081, 2977, 2910 (C-H), 1629, 1602, 1505 (ring); uv (ethanol), λmax, nm/logε: 352/4.17, 282/4.26, 204/4.14; ms: m/z 313 (M^+), 297 (M^+-O), 283 (M^+-NO), 253 (M^+-2NO); ^{1}H- and ^{13}C nmr see Table 1, 2, 3 and 4.

Anal. Calcd. for $C_{15}H_{11}N_3O_5$: C, 57.69; H, 3.53; N, 13.46. Found: C, 57.26; H, 3.65; N, 13.67.

REFERENCES AND NOTES

[1] C. Hugo, D. M. Rossanna, G. Mercedes, R. Mariela, S. Patricia, S. Gustavo, D. Ana, P. Gonzalo, Q. Celia and O-A. Claudio; *J. Med. Chem.*, **42**, 1941 (1999).

[2] C. Hugo, G. Mercedes, R. Mariela, S. Gustavo, D. C. A. Lopez, E. Olga, M. Antonio, S. Leopoldo, M. Alvaro and M. A. Bruno *Archiv der Pharmazie*, **333** 387 (2000).

[3] A. Monge, A. L. de Cerain, O. Ezpeleta, *Die Pharmazie*, **53**, 698 (1998).

[4] A. M. Gasco, A. Di Stilo, G. Sorba, A. Gasco R. Ferioli, G. C. Folco, M. Civelli and P. Caruso *Eur. J. Med. Chem*., **28**, 433 (1993).

[5] R. Ferioli, A. Fazzini, G. C. Folco, R. Fruttero, R. Canvino, A. Gasco, S. Bongani and M. Civelli *Pharmacol. Res*., **28**, 203 (1993).

[6] C. Medana, G. Ermondi, R. Fruttero, A. Di Stilo, C. Ferretti and A. Gasco, *J. Med. Chem*., **37**, 4412 (1994).

[7] R. Ferioli, G. C. Polco, C. Ferretti, A. M. Gasco, C. Medana, R. Fruttero, M. Civelli and A. Gasco, *British Journal of Pharmacology*, **114**, 816 (1995).

[8] R. Calvino, R. Fruttero, D. Ghigo, A. Bosia, G. P. Pescarmona and A. Gasco, *J. Med. Chem.*, **35**, 3296 (1992).

[9] D. Ghigo, R. Heller, R. Calvino, P. Alessio, R. Fruttero, A. Gasco, A. Bosia and G. P. Pescarmona, *Biochem. Pharmacol*., **43**, 1281 (1992).

[10] G. Ponzio and C. Satta, *Gazz. Chim. Ital*., **60**, 150 (1930).

[11] A. Gasco, G. R. Mortarini and E. Menziani *J. Heterocyclic Chem.*, **9**, 837 (1972).