Nitrophenyl Derivatives of the Furazan and Furoxan Ring Systems

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The preparation of some nitrophenyl derivatives of the furazan and furoxan ring systems is reported. The results of an antimicrobial screening on these compounds are also briefly discussed.

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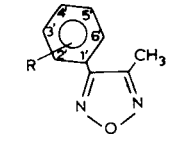
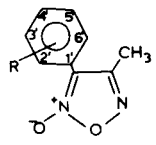
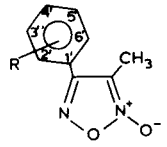
In previous work [1] we showed that some of the nitro furazans and nitro furoxans display antimicrobial properties. In the present paper we report principally on the synthesis of some nitrophenyl derivatives which are phenyl analogs (cyclic vinyl analogs) of nitrofurazan and nitrofuroxan systems (compounds **2, 4, 2a, 4a, 2b, 4b**). The results of an antimicrobial screening on these products are also briefly discussed.





1, R = H, 2, R = 2'-NO_2, 1a, R = H, 2a, R = 2'-NO_2

3, R = 3'-NO_2 4, R = 4'-NO_2, 3a, R = 3'-NO_2, 4a, R = 4'-NO_2



1b, R = H, 2b, R = 2'-NO_2

3b, R = 3'-NO_2, 4b, R = 4'-NO_2

All of the derivatives were obtained by nitration of the corresponding methyl-phenyl-furazan **1** and furoxans **1a, 1b**.

Generally speaking little attention has been paid to the systematic study of the nitration of the benzene ring of the phenyl substituted heteroaromatic compounds; this is principally due to a lack of satisfactory methods of analysis of the mixture produced in the reaction. In a recent study Blackhall *et al.*, clearly discussed this problem [2].

In particular the nitration of the benzene ring of phenyl furazan has been studied by De Munno *et al.* [3] and more recently by some Soviet workers [4]. Similar studies have been carried out on 3-phenylfuroxan [5] and, earlier, on diphenylfuroxan [6]. This early work is probably inaccurate for the reason mentioned above. From these papers we can conclude that the furazanyl moiety not bearing electron withdrawing groups specifically orients the nitration toward the *para*-position otherwise it is *meta*-directing. In more drastic reaction conditions 2',4'-dinitro-derivatives or 3',5'-dinitro-derivatives are afforded respectively. The 3-furoxanyl group is *ortho-para* directing. Under more drastic conditions 2',4'-dinitro-derivatives are produced.

In our nitration conditions (90% nitric acid, −5°) **1** gives, after 15 minutes, a mixture (yield 98%) of three derivatives that can be resolved by preparative tlc on silica gel (tlc, 70:30, petroleum ether (40-60°)/tetrahydrofuran). The three isomeric products so obtained have ir, nmr, mass spectra and analytical data in keeping with the structures **2** (3-(2'-nitrophenyl)-4-methylfurazan), **3** (3-(3'-nitrophenyl)-4-methylfurazan), **4** (3-(4'-nitrophenyl)-4-methylfurazan), respectively. A quantitative analysis of the mixture by tlc gave the results reported in Table 1.

Table 1

Isomers Ratio (%) [a] Obtained in the Mononitration of **1, 1a, 1b**

Compound	*ortho*	*meta*	*para*
1	30	13	57
1a	29	3	68
1b	29	16	55

[a] Each percentage was averaged over four different measures.

These data are only partially in accordance with the data of the Soviet workers and of De Munno *et al.* In fact, in our hands, the *para*-isomer is afforded in a higher percentage but it accounts only for 57% of the nitrated product, the *ortho* and *meta* isomers were also present. The nitration of **1b** gives similar results. The reaction mixture obtained after 15 minutes (yield 95%), analysed by methods similar to those discussed above, showed that the mixture was composed of three isomeric mono-nitro-derivatives **2b** (3-methyl-4-(2'-nitrophenyl)furoxan), **3b** (3-methyl-4-(3'-nitrophenyl)furoxan), **4b** (3-methyl-4-(4'-nitrophenyl)furoxan) in the ratios reported in Table 1.

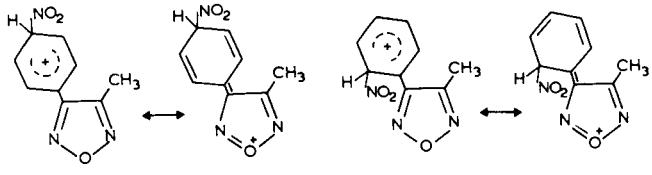
The results of the nitration of **1a** are very similar to those obtained in the nitration of 3-phenylfuroxan [5]. After nitration for 15 minutes a mixture (yield 97%) composed by **2a** (4-methyl-3-(2'-nitrophenyl)furoxan), **3a** (4-methyl-3-(3'-nitrophenyl)furoxan) and **4a** (4-methyl-3-(4'-nitrophenyl)furoxan), in the ratios given in Table 1, was formed.

Mechanistic interpretation of these results is not simple. In trying to explain the attack on all the positions of the benzene ring in **1** and **1b**, with a predominant *ortho-para* orientation, we suggest that the reaction, at least in 90%

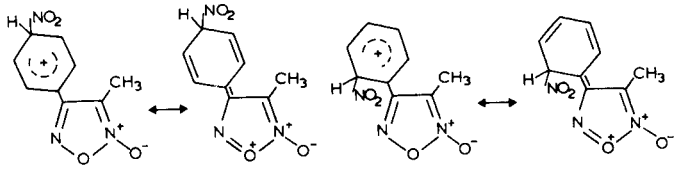
nitric acid, may involve principally the free bases [7].

The mesomeric stabilization of the Wheland intermediates, pictured in the Schemes 1 and 2, accounts for the dominant *ortho-para* directing effect of the heterocyclic rings.

Scheme 1

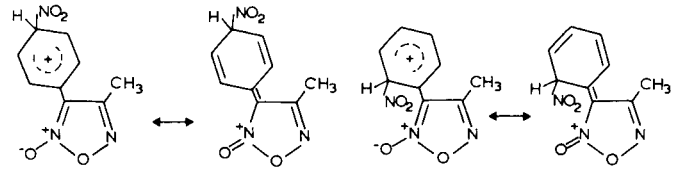


Scheme 2



The results obtained on the nitration of **1a** suggest that this molecule is nitrated *via* the free base. The highly dominant *ortho-para* orientation could be due to the direct resonance between the *ortho-para* sites and the $^{+}N—O^{-}$ moiety, which effectively stabilizes the σ-complex (see Scheme 3).

Scheme 3



All *ortho* and *para* nitro-compounds were screened for their antimicrobial properties against the same microorganisms and with the same procedures reported previously [1]. All products were inactive (MIC >50 μg) [12]. Thus, while the direct link of the furazan and furoxan carriers to the nitro group gives active compounds [1], the interposition of an *ortho* or *para* phenylene structure removes the antimicrobial action.

Obviously the modification by "cyclic vinylogy" of the nitrofurazan and nitrofuroxan models, deeply alters their physical chemical and/or chemical properties responsible for the activity.

EXPERIMENTAL

The melting points were recorded on a capillary melting point apparatus and are uncorrected. The ^{1}H nmr spectra were recorded on a Varian T-60 instrument in deuteriochloroform with tetramethylsilane as the internal standard. The ir spectra were measured on a Perkin-Elmer 257 spectrometer. Mass measurements were carried out on a Varian CH7 MAT mass spectrometer.

3-Methyl-4-phenylfurazan **1** [9].

3-Methyl-4-phenylfuroxan **1b** mp 95° from ethanol (lit [11] mp 95.2-95.8° from ethanol) was prepared by the action of nitrous acid on *trans*-1-phenyl-1-propene (commercial product from Fluka), according to the procedure reported [10] for the preparation of the *p*-methoxy analogue.

Compound **1b** was heated at 135° for two hours and gave a mixture of **1a** and **1b** (**1a/1b** = 0.56) which was resolved by column chromatography (silica gel 60 E. Merck, eluent: petroleum ether (40-60°) containing chloroform 0-40%); pure **1a** was so obtained mp 62° from ethanol (lit [11] mp 61.6-62.4° from ethanol).

Nitration of **1**, **1a** and **1b**. General Method.

Starting products **1**, **1a**, **1b**, (1.00 g, 6.25 and 5.68 mmoles, respectively) was added with stirring, to 90% nitric acid (5.0 ml), at -5°. After 15 minutes the reaction solution was poured into ice and extracted with chloroform. The organic layer was washed with water, dried with magnesium sulfate and evaporated *in vacuo* at room temperature. The mixture

Table 2

Spectral Data for The Nitrated Products

Compound	IR (cm^{-1})	NMR	Mass Spectrum
2	1520, 1345 (NO_2)	2.27 (3H, s, 3-CH_3), 7.42-7.97 (3H, m, 4', 5', 6'-H), 8.07-8.47 (1H, m, 3'-H)	205 (M^+), 175 (M^+-NO), 134 (M^+-NO-CH_3CN)
3	1535, 1342 (NO_2)	2.62 (3H, s, 3-CH_3), 7.72 (1H, t, 5'-H, J = 8 Hz); 7.97-8.53 (2H, m, 4', 6'-H), 8.58 (1H, t, 2'-H, J = 2.5 Hz)	205 (M^+), 175 (M^+-NO), 164 (M^+-CH_3CN)
4	1520, 1345 split (NO_2)	2.62 (3H, s, 3-CH_3), 7.77-8.57 (4H, A'$_2$B'$_2$ system, -C_6H_4)	205 (M^+), 175 (M^+-NO), 164 (M^+-CH_3CN), 134 (M^+-NO-CH_3CN)
2a	1610 (furox), 1530, 1345 (NO_2)	2.30 (3H, s, 4-CH_3), 7.40-7.97 (3H, m, 4', 5', 6'-H), 8.17-8.43 (1H, m, 3'-H)	221 (M^+), 161 (M^+-N_2O_2)
3a	1580 (furox) 1530, 1350 (NO_2)	2.62 (3H, s, 4-CH_3), 7.73 (1H, t, 5'-H, J = 8 Hz), 8.07-8.50 (2H, m, 4', 6'-H), 8.63 (1H, t, 2'-H, J = 2.5 Hz)	221 (M^+), 191 (M^+-NO), 161 (M^+-N_2O_2)
4a	1590 split (furox), 1520, 1340 (NO_2)	2.62 (3H, s, 4-CH_3), 7.88-8.55 (4H, A$_2$'B$_2$' system, -C_6H_4)	221 (M^+), 191 (M^+-NO), 161 (M^+-N_2O_2), 131 (M^+-N_2O_2-NO)
2b	1615 (furox) 1520, 1348 (NO_2)	2.05 (3H, s, 3-CH_3), 7.50-8.00 (3H, m, 4', 5', 6'-H), 8.18-8.43 (1H, m, 3'-H)	221 (M^+), 161 (M^+-N_2O_2)
3b	1600 (furox), 1520, 1350 (NO_2)	2.42 (3H, s, 3-CH_3), 7.75 (1H, t, 5'-H, J = 8 Hz), 7.95-8.45 (2H, m, 4', 6'-H), 8.55 (1H, t, 2'-H, J = 2.5 Hz)	221 (M^+), 191 (M^+-NO), 161 (M^+-N_2O_2)
4b	1595 (furox) 1520, 352 (NO_2)	2.40 (3H, s, 3-CH_3), 7.78-8.55 (4H, A'$_2$B'$_2$ system, -C_6H_4)	221 (M^+), 191 (M^+-NO), 161 (M^+-N_2O_2), 131 (M^+-N_2O_2-NO)

Table 3

Physical and Analytical Data of the Nitrated Products

Compound No.	Mp, °C	Solvent of crystallization	Molecular formula	Analyses % Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
2	43	ethanol	$C_9H_7N_3O_3$	52.69	3.44	20.48	52.61	3.55	20.54
3	78-79	ethanol	$C_9H_7N_3O_3$	52.69	3.44	20.48	52.40	3.56	20.66
4	60-61	ethanol	$C_9H_7N_3O_3$	52.69	3.44	20.48	52.52	3.54	20.41
2a	97-98	ethanol-water	$C_9H_7N_3O_4$	48.88	3.19	19.00	48.96	3.24	18.76
3a	95-96	ethanol-water	$C_9H_7N_3O_4$	48.88	3.19	19.00	48.90	3.38	18.78
4a	70-71	ethanol	$C_9H_7N_3O_4$	48.88	3.19	19.00	48.58	3.24	19.00
2b	81-82	ethanol-water	$C_9H_7N_3O_4$	48.88	3.19	19.00	48.78	3.27	19.01
3b	76-77	ethanol-water	$C_9H_7N_3O_4$	48.88	3.19	19.00	48.51	3.21	19.06
4b	94-95	ethanol	$C_9H_7N_3O_4$	48.88	3.19	19.00	48.57	3.25	19.09

of *ortho, meta* and *para* nitro derivatives so obtained, was quantitatively resolved by preparative tlc (plates of silica gel 60 F_{254} E. Merck, 2 mm, double eluted, eluent: petroleum ether (40-60°)-tetrahydrofuran 70:30, Rf *para* > Rf *meta* > Rf *ortho*). The results are reported in Table 1. Spectral, physical and analytical data are reported in Table 2 and 3 respectively.

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[12] MICs against *Trichophyton mentagrophytes* (De Carls) of all the compounds lie in the range 12.5 - 50 μg/ml with the exception of **4b** (MIC > 50 μg/ml).