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5-METHYL-2-FURYLGLYOXAL, 5-METHYL-4-NITRO-2-FURYLGLYOXAL, AND THEIR DERIVATIVES. NITRATION OF 2-(5-METHYL-2-FURYL)QUINOXALINE

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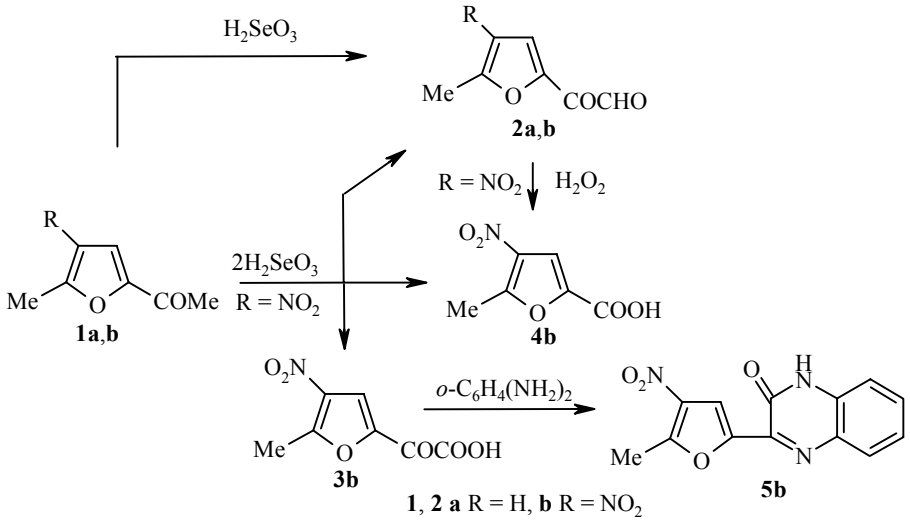
The oxidation of 2-acetyl-5-methyl-4-R-furans (R = H, NO_2) by selenious acid was studied. Derivatives substituted at the C=O groups of the corresponding glyoxals were obtained. The nitration of 2-(5-methyl-2-furyl)quinoxaline was carried out at $C_{(4')}$. Oxidative splitting of the β-nitrofuryl group occurs at the $C_{(4)}$–$C_{(5)}$ and $C_{(5)}$–O bonds.

Keywords: 2-acetyl-5-methyl-4-R-furans (R = H, NO_2), glyoxals, 2-(5'-methyl-2-furyl)quinoxaline, nitric acid nitration, oxidation, H_2SeO_3.

The α-methyl groups of ketones and methyl groups in the α-position relative to the heteroatom of heterocyclic compounds may be oxidized by selenium dioxide to formyl or carboxylic acid groups [1]. 5-R-2-Furylglyoxals (R = H, NO_2) were thereby obtained from the corresponding methyl ketones [2], while the 5-methyl group in 1-methyl-(5-methyl-3-furyl)benzimidazole was oxidized to a formyl group [3].

In the present work, we compared the reactivity of the methyl groups of the ring and ketone part of 2-acetyl-5-methylfuran (**1a**) and 2-acetyl-5-methyl-4-nitrofuran (**1b**) relative to oxidation by selenious acid and also obtained oxidation products of these compounds with transformed carbonyl groups.

The oxidation of **1a** and **1b** by an equimolar amount of H_2SeO_3 proceeds selectively at the ketone group to give 5-methyl-2-furylglyoxal (**2a**) and 5-methyl-4-nitro-2-furylglyoxal (**2b**), respectively.



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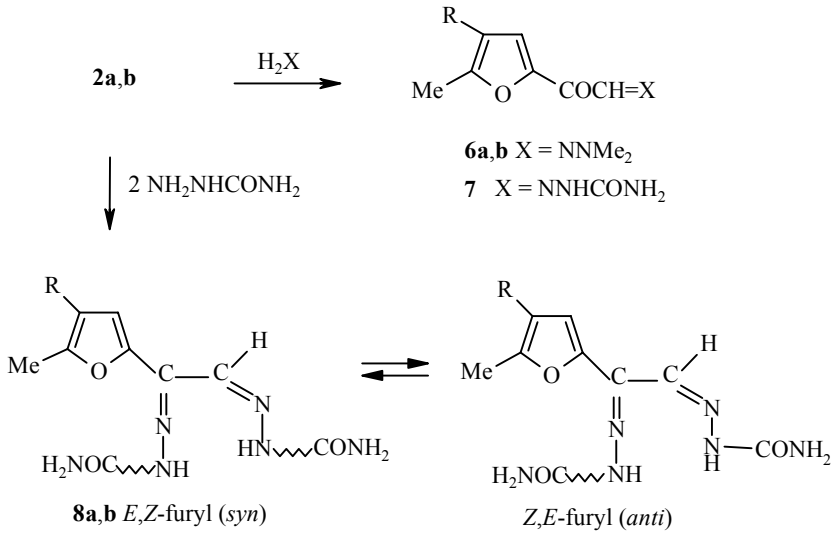
The ^{1}H NMR spectrum of glyoxal **2a** after vacuum distillation showed a trace of the monohydrate form. Glyoxal **2a** readily polymerizes to give a glassy mass. In contrast to 2-furylglyoxal, which forms a crystalline monohydrate upon heating at reflux with water (1:4 ratio) in high yield, 5-methyl derivative **2a** after heating at reflux with water (1:2 ratio) does not crystallize out in the hydrate form upon maintenance of the solution over a week at 3-5°C.

Nitro ketone **1b** did not react completely under the conditions selected. ^{1}H NMR spectroscopy indicated that the crude product contained 15 mol % starting ketone, 80 mol % glyoxal hydrate **2b**·H_2O, and 3 mol % 5-methyl-4-nitro-2-furylglyoxylic acid (**3b**) along with traces of anhydrous glyoxal and 5-methyl-4-nitro-2-furancarboxylic acid (**4b**).

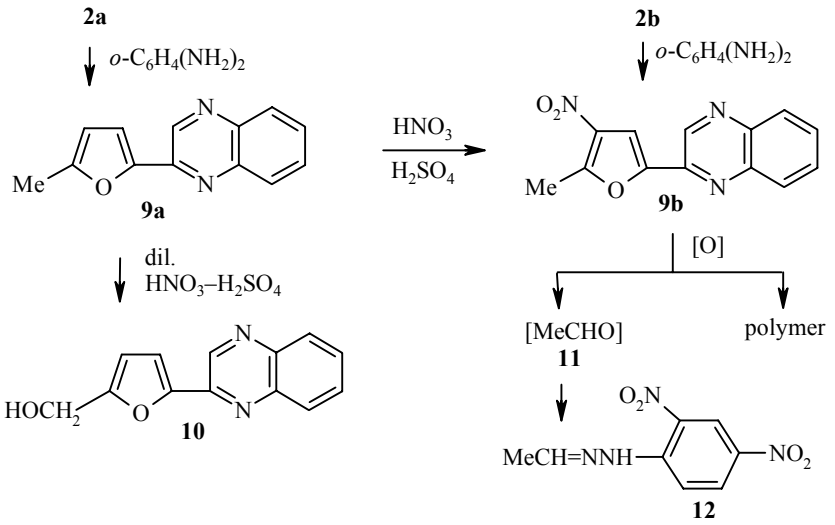
The action of two molar equivalents of H_2SeO_3 on ketone **2b** under the same conditions led to a mixture containing 50 mol % glyoxylic acid **3b**, 15 mol % glyoxal **2b**, and 15 mol % carboxylic acid **4b** contaminated by products of reaction with the trisubstituted furan ring as indicated by ^{1}H NMR spectroscopy. This mixture was not studied in detail. The presence of nitroglyoxylic acid **3b** was shown by treatment of the mixture with *o*-phenylenediamine, subsequent heating of the precipitate obtained with ethanol at reflux to remove the 5-methyl-4-nitro-2-furyl derivatives of quinoxaline and benzimidazole, and recrystallization of the residue from DMF to give 3-(5-methyl-4-nitro-2-furyl)quinoxal-2-one (**5b**). The signals for the quinoxalone fragment of **5** are found in the same regions as for 3-(5-nitro-2-furyl)quinoxal-2-one [4].

Furancarboxylic acid **4b** was obtained by oxidation of glyoxal **2b** using hydrogen peroxide by analogy to 5-nitro-2-furylglyoxal [2].



Glyoxals **2a** and **2b** were characterized by their conversion into aldehydo-N,N-dimethylhydrazones **6a** and **6b** and bissemicarbazones **8a** and **8b**. Glyoxal **2a** reacts with one molar equivalent of semicarbazide to form aldehydosemicarbazone **7a**, while glyoxal **2b** reacts with one molar equivalent of semicarbazide to give bissemicarbazone **8b**, i.e., an analogy is seen with 2-furylglyoxal and its 5-nitro derivative [2].

^{1}H NMR spectroscopy indicated that nitrobissemicarbazone **8b** has two isomers, namely, with *E,Z*- and *Z,E*-configuration of the furyl group in 2:1 ratio. The configuration of the aldehydosemicarbazone group was established relative to the position of the CH=N proton in accord with the data for other semicarbazones and thiosemicarbazones [5-7] and oximes [7], while the configuration of the ketosemicarbazone group was determined relative to the chemical shift of ring 3-H by analogy to the chemical shifts of the same proton in the *E*- and *Z*-isomers of oximes of 2-acetyl- and 2-formyl-5-methyl-4-nitrofuran [8,9].



The reaction of glyoxals **2a** and **2b** with *o*-phenylenediamine gave 2-(5-methyl-2-furyl)quinoxaline (**9a**) and its 4-nitro derivative **9b**, respectively. Quinoxaline **9b** is also formed by the action of 1.1 molar equivalent of 70% aq. HNO_3 on the denitro analog **9a** in concentrated sulfuric acid. The nitration did not proceed to completion and was accompanied by oxidation of the starting compound to 2-(5-hydroxymethyl-2-furyl)quinoxaline (**10**), apparently after pouring the reaction mixture onto ice, and formation of a polymer from a portion of the precipitate upon filtration of the reaction product.

TABLE 1. Physical Characteristics of Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (solvent)	Yield, % (method)
		C	H	N		
2a	$C_7H_6O_3$	60.49 / 60.87	4.73 / 4.37	—	—	42
2b·H_2O	$C_7H_5NO_5·H_2O$	41.64 / 41.85	3.28 / 3.51	7.08 / 6.96	89-92 (H_2O)	79
4b	$C_6H_5NO_5$	42.08 / 42.11	2.87 / 2.95	8.09 / 8.19	160-161 (H_2O)	85
5b	$C_{13}H_9N_3O_4$	57.18 / 57.57	3.60 / 3.34	15.23 / 15.50	>300 (DMF)	95
6a	$C_9H_{12}N_2O_2$	59.72 / 59.98	6.59 / 6.71	15.71 / 15.55	90-91 (H_2O)	63
6b	$C_9H_{11}N_3O_4$	47.88 / 48.00	4.83 / 4.92	18.57 / 18.66	146-148 (EtOH)	70
7a	$C_8H_9N_3O_3$	49.03 / 49.21	4.53 / 4.65	21.77 / 21.53	208-209 (EtOH)	90
8a	$C_9H_{12}N_6O_3$	42.63 / 42.86	4.68 / 4.80	33.09 / 33.32	227-228 (EtOH)	95
8b	$C_9H_{11}N_7O_5$	36.21 / 36.33	3.67 / 3.76	32.97 / 33.36	>300 (DMF–H_2O)	95
9a	$C_{13}H_{10}N_2O$	74.43 / 74.25	4.75 / 4.81	13.21 / 13.32	80-81 (EtOH)	81
9b	$C_{13}H_9N_3O_3$	61.03 / 61.18	3.47 / 3.53	16.23 / 16.48	203-204 (EtOH–DMF)	95 (A) 31 (B)*

* Relative to **9a** consumed.

Hydroxymethyl derivative **10** could not be separated from the starting compound by preparative chromatography. The structure of this product was demonstrated only by ^{1}H NMR spectroscopy. Nitro derivative **9b** was isolated from the mixture by crystallization from 6:1 ethanol–DMF. The yield of this product calculated using the ^{1}H NMR spectrum of the mixture was 23% relative to starting **9a** and 31% relative to the starting compound consumed.

The success of the nitration is attributed to the strong electron-withdrawing effect of the quinoxaline group, which imparts stability to the furan ring, while complete polymerization is observed upon heating 2-(5-methyl-2-furyl) derivatives of imidazo[1,2-*a*]pyridine [10] and imidazo[1,2-*a*]pyrimidine. Partial polymerization occurs in the nitration of the nitrile of 5-methyl-2-furancarboxylic acid [5].

In the latter case, after separation of the nitro nitrile and polymer, a precipitate of the 2,4-dinitrophenylhydrazone of acetaldehyde formed upon addition of 2,4-dinitrophenylhydrazine to the filtrate and not of the nitrile of 5-formyl-2-furancarboxylic acid as might have been expected by analogy with the nitration of the ethyl ester of 5-methyl-2-furancarboxylic acid but this was not reflected in our previous communication [5].

After separation of quinoxaline **9b** and polymer, 2,4-dinitrophenylhydrazone **12** was also obtained upon addition of the same hydrazine to the filtrate. The structure of **12** was indicated by its melting point, elemental analysis, and ^{1}H NMR spectrum.

TABLE 2. ^{1}H NMR Spectra of Compounds Synthesized

Com-pound	Chemical shifts, δ, ppm., *J* (Hz)*			
	3-H	4-H	5-CH_3	Other protons
2a	7.76	6.50	2.42	9.48 (1H, s, CHO)
2a·H_2O	7.50	6.36	2.42	5.45 (1H, s, CH); 5.6 (2H, br. s, 2OH)
2b	8.10	—	2.77	9.40 (1H, s, CHO)
2b·H_2O	7.90	—	2.75	5.42 (1H, s, CH); 5.6 (2H, br. s, 2OH)
3b	8.06	—	2.76	—
4b	7.66	—	2.75	12.11 (1H, br. s, COOH)
5b	8.15	—	2.90	7.4-7.8 (3H, m, 5-H–7-H); 7.95 (1H, ddd, *J* = 8.4, 1.1, 0.4, 8-H); 12.05 (1H, br. s, NH)
6a*[2]	7.46	6.32	2.36	3.18 (6H, s, NMe_2); 6.93 (1H, s, CH=N)
6b	7.87	—	2.75	3.71 (6H, s, NMe_2), 6.95 (1H, s, CH=N)
7a	7.65	6.40	2.40	6.65 (2H, br. s, NH_2); 7.68 (1H, s, CH=N); 10.94 (1H, br. s, NH)
8a	7.24	6.31	2.30	6.30 (2H, br. s, NH_2); 6.72 (2H, br. s, NH_2); 7.60 (1H, s, CH=N); 9.83 (1H, s, NH); 10.72 (1H, s, NH)
E,Z-**8b**	7.42	—	2.73	6.24 (2H, br. s, NH_2); 6.50 (2H, br. s, NH_2); 7.66 (1H, s, CH=N); 10.02 (1H, s, NH); 10.51 (1H, s, NH)
Z,E-**8b**	7.55	—	2.73	6.50 (2H, br. s, NH_2); 6.90 (2H, br. s, NH_2); 8.01 (1H, s, CH=N); 10.62 (1H, s, NH); 11.21 (1H, s, NH)
9a	7.53	6.46	2.50	7.84 (2H, m, 6-H, 7-H); 8.05 (2H, m, 5-H, 8-H); 9.43 (1H, s, 3-H)
9b	8.18	—	2.85	7.85 (2H, m, 6-H, 7-H); 8.05 (2H, m, 5-H, 8-H); 9.49 (1H, s, 3-H)
10	7.75	6.62	—	4.58 (2H, d, CH_2OH); 4.8 (1H, t, *J* = 4.8, $CH_2O\underline{H}$); 7.8 (2H, m, 6-H, 7-H); 7.95-8.1 (2H, m, 5-H, 8-H); 9.38 (1H, s, 3-H)

* For compounds **2-9a** *J* (3,4-CH_3) = 3.3-3.5, *J* (3,5-CH_3) = 0.4, *J* (4,5-CH_3) = 0.9 Hz; for compounds **2-9b** *J* (3,5-CH_3) = 0.4 Hz.

*[2] In acetone-d_6.

The formation of aldehyde indicates the oxidative cleavage of the 5-methyl-4-nitro-2-furyl group at the $C_{(4)}$–$C_{(5)}$ and $C_{(5)}$–O bonds in contrast to the 5-nitro-2-furyl group, which is attached to the oxidation-resistant heterocycle (imidazo[1,2-*a*]pyridine, imidazo[1,2-*a*]pyrimidine). The 5-nitro-2-furyl group is lost upon nitric acid oxidation only at the $C_{(5)}$–O bonds to give hetarylacrylic acids ($HetCOCH{=}CHCO_2H$) [10, 11].

EXPERIMENTAL

The purity of the products was checked by thin-layer chromatography on Silufol UV-254 plates using 3:1 benzene–ethyl acetate and 25:4:1 benzene–dioxane–acetic acid as the eluents and by ^{1}H NMR spectroscopy. The ^{1}H NMR spectra were taken on a Bruker WH-90/DS spectrometer at 90 MHz in DMSO-d_6 with TMS as the internal standard. The IR spectra were taken on a Perkin–Elmer 580B spectrometer for vaseline mulls. The melting points were taken on a Boetius block.

The physical characteristics of these compounds are given in Tables 1 and 2.

5-Methyl-2-furylglyoxal (2a). A sample of ketone **1a** (62 g, 0.5 mol) was added to a solution of H_2SeO_3 (64.5 g) in dioxane (300 ml) and water (20 ml) prepared at 45-50°C. The mixture was heated at reflux for 4 h with stirring, left stand overnight, and filtered to remove selenium. The solvent was distilled off the filtrate and the residue was distilled in vacuum with a 2-cm-high rod-and-disk type fractionating column, taking the fraction distilling at 100-103°C (20 hPa). Yield of compound **2a** 29 g.

5-Methyl-4-nitro-2-furylglyoxal (2b). A sample of compound **1b** (6.76 g, 40 mmol) was added to a solution of H_2SeO_3 (5.16 g, 40 mmol) in a mixture of water (3 ml) and acetic acid (20 ml) at 50°C, heated at reflux with stirring for 4 h, left stand overnight, and filtered to remove selenium. The filtrate was evaporated in vacuum to give 6.6 g of orange oil. The crude product was heated with water (20 ml) and after maintenance at 2-3°C for 48 h, filtered to yield yellow crystals, which were dried over P_2O_5 to give 5.86 g of a mixture of 80% glyoxal monohydrate, 15% ketone **1b**, and 3% glyoxylic acid **3b** as well as traces of unhydrated glyoxal and carboxylic acid **4b**.

A sample of *o*-phenylenediamine (1 g) was added to the filtrate after removal of the precipitate, warmed for 10 min, and filtered after 24 h to give 0.92 g of 2-(5-methyl-4-nitro-2-furyl)quinoxaline **9b**, which accounts for 0.72 g of glyoxal **2b**·H_2O. The total yield of glyoxal monohydrate was 6.36 g.

Recrystallization of crude glyoxal twice from 10 parts water gave pure product. IR spectrum, ν, cm^{-1}: 1360 and 1542 (NO_2), 1692 (C=O), 3000-3400 (CO_2H).

5-Methyl-4-nitro-2-furancarboxylic Acid (4b). Three samples of 26% aq. H_2O_2 (2 ml) were added to a solution of glyoxal **2b** (0.5 g, 2.5 mmol) in a mixture of water (15 ml) and acetic acid (3 ml). The mixture was maintained for 1 h at room temperature after each of the three additions. The mixture was extracted with ether to give 0.36 g **4b**. IR spectrum, ν, cm^{-1}: 1340 and 1555 (NO_2), 1705 (CO_2H).

3-(5-Methyl-4-nitro-2-furyl)quinoxal-2-one (5b). A sample of ketone **1b** (3.38 g, 20 mmol) was oxidized in a mixture of acetic acid (20 ml) and water (3 ml) upon heating at reflux for 5 h and the reaction products were removed as described above. The product was analyzed by thin-layer chromatography and ^{1}H NMR spectroscopy. A sample of *o*-phenylenediamine (2.16 g, 20 mmol) in water (30 ml) was added to the crude product containing 50-60 mol % 5-methyl-4-nitro-2-furylglyoxylic acid **3b** and heated for several minutes. The precipitate was filtered off and heated at reflux with ethanol (100 ml). The portion which did not dissolve was recrystallized from DMF to give 1.3 g of compound **5b**.

N,N-Dimethylhydrazone of 5-Methyl-2-furylglyoxal (6a). A sample of N,N-dimethylhydrazine (0.30 g, 4.4 mmol) was added to glyoxal **2a** (0.56 g, 4 mmol) in water (4 ml) and maintained for 3 h at room temperature. The solvent was evaporated off to give 0.45 g of hydrazone.

N,N-Dimethylhydrazone of 5-Methyl-4-nitro-2-furylglyoxal (6b) was obtained analogously from compound **2b** (0.4 g, 2 mmol). The precipitate formed was filtered off. Yield of hydrazone 0.32 g.

Semicarbazone 7a and Bissemicarbazones 8a and 8b were obtained by the standard procedures.

2-(5-Methyl-4-nitro-2-furyl)quinoxaline (9a). A mixture of freshly prepared glyoxal **2a** (1.38 g, 10 mmol), *o*-phenylenediamine (1.08 g, 10 mmol), water (10 ml), and ethanol (5 ml) was heated at reflux for several minutes. The initial oily product crystallized and was filtered and washed with dilute ethanol to give 1.71 g of compound **9a**.

2-(5-Methyl-4-nitro-2-furyl)quinoxaline (9b). A. A mixture of glyoxal **2b**·H_2O (1 g, 5 mmol), *o*-phenylenediamine (0.54 g, 5 mmol), ethanol (5 ml), and water (5 ml) was heated for several minutes. The precipitate was filtered off to give 1.08 g of yellow crystals, which sublimate above 150°C.

B. A sample of **9a** (2.1 g, 10 mmol) was added in portions to concentrated sulfuric acid (50 ml) vigorously stirred at from -18 to -15°C. Then, a mixture of 70% HNO_3 (0.70 ml, 11 mmol) and concentrated sulfuric acid (2 ml) was added at the same temperature over 50 min. The mixture was stirred at the same temperature for 1 h and then poured with vigorous stirring onto a mixture of ice and water (500 g). The precipitate was filtered off and washed thoroughly with water to give 0.72 g of product consisting of 15 mol % of compound **9a**, 80 mol % of compound **9b**, and 5 mol % of **2-(hydroxymethyl-2-furyl)quinoxaline (10)** as indicated by ^{1}H NMR spectroscopy. A portion of the product formed a tar upon filtration and hardened over time. A precipitate of 0.21 g of a 1:1 mixture of compounds **9a** and **10** as indicated by ^{1}H NMR spectroscopy was obtained from one-half of the filtrate after neutralization by sodium hydroxide and standing for 24 h.

Crystallization of the first precipitate from 6:1 ethanol–DMF gave pure nitro compound **9b**. The yield calculated by means of ^{1}H NMR spectroscopy was 0.60 g.

A solution of 2,4-dinitrophenylhydrazine (0.5 g) in concentrated sulfuric acid was added to the second half of the filtrate after removal of crude quinoxaline **9b**. The 2,4-dinitrophenylhydrazone of acetaldehyde **12** was filtered off and washed with hot ethanol to give 0.08 g of compound **12**; mp 144-146°C [12]. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 2.03 (3H, d, *J* = 5, CH_3); 7.75 (1H, d, *J* = 9.7, 6-H); 8.03 (1H, q, *J* = 5, CH=N); 8.31 (1H, ddd, *J* = 9.7, 2.6, 0.4, 5-H); 8.83 (1H, d, *J* = 2.6, 3-H); 11.39 (1H, s, NH). Found, %: C 42.58; H 3.72; N 25.23. $C_8H_8N_4O_8$. Calculated, %: C 42.85; H 3.60; N 24.98.

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