

**α -TRICHLOROMETHYLSULFONYL-5-NITRO-2-FURALDEHYDES,
A NEW TYPE OF SH-GROUP UNCOUPLERS AND INTERMEDIATES
IN THE SYNTHESIS OF 5-NITRO-2-FURYLARYLNITRILIMINES***

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Trichloromethylsulfonyl-5-nitro-2-furaldehyde 4-X-phenylhydrazones *I* (X = H, CH₃, Cl, CN, NO₂, COOC₂H₅) were obtained by reacting 4-X-phenyldiazonium salts with 5-nitrofurfuryltrichloromethyl sulfone. These compounds react with diazomethane and trimethylamine to give the corresponding N-methylated derivatives and nitrilimines, respectively, the latter under elimination of trichlorosulfonic acid. The hydrazone-diaziridine tautomerism was studied by ¹H, ¹⁵N, and ¹³C NMR methods; also the IR and UV spectra of the compounds synthesized are discussed. All hydrazones showed a very strong effect on the stimulation of mitochondria respiration and constitute a new type of SH-group uncouplers acting already in a 10⁻⁸ mol l⁻¹ concentration.

5-Nitrofurfurylaryl sulfones, although relatively strong CH-acids (pK_a 9.33–10.34) enter a condensation reaction exclusively with aromatic and heterocyclic aldehydes to form α,β -unsaturated sulfones^{1–3}. A substantially stronger 5-nitrofurfuryltrichloromethyl sulfone (pK_a 6.36) gives with the above-mentioned aldehydes α,β -unsaturated sulfones as well⁴, but, nevertheless, it also reacts with aliphatic aldehydes cyclopropanes^{5,6}, cyclobutenes and butadienes related to 5-nitrofurane being the products⁷.

This paper concerns the synthesis of α -trichloromethylsulfonyl-5-nitro-2-furaldehyde arylhydrazones (*I*), obtained by condensation of 5-nitrofurfuryltrichloromethyl sulfone with arenediazonium salts in ethanolic sodium acetate (Table I). The highest yields of hydrazones were obtained at a 1 : 1.25 ratio of sodium nitrite to concentrated hydrochloric or sulfuric acids (X = NO₂, COOC₂H₅).

Hydrazones *Ia–If* are very strongly polarized systems due to a great electron-accepting effect of 5-nitrofurane ring and trichloromethanesulfonyl group. Treatment of these compounds with diazomethane leads to substitution of hydrogen in the NH group by methyl group under formation of N-methylated derivatives *II*.

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The N-methylated derivatives of hydrazones obtained by methylation with diazo-methane were reported by further authors^{10,11} as well. It is noteworthy that compounds *I* and *II*, as strongly polarized systems, do not enter the 1,3-cycloaddition

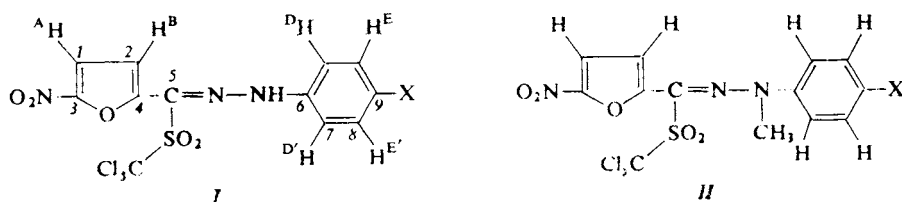
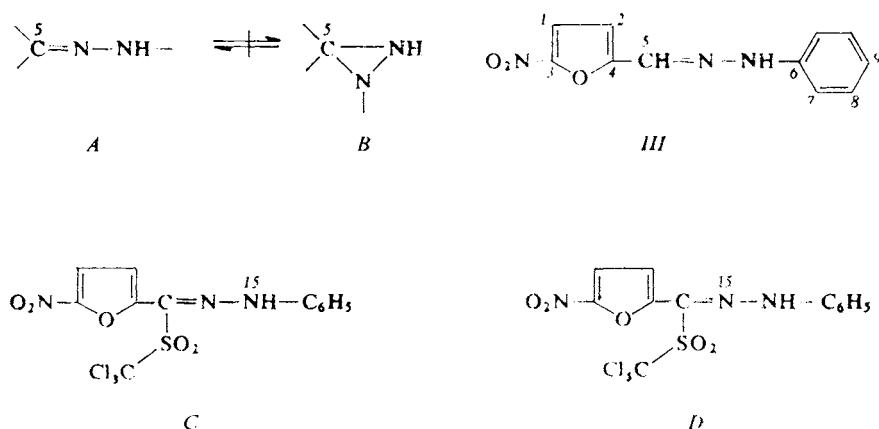


TABLE I
Characteristic data of hydrazones *I* and *II*

Compound X	Formula (M_r)	M.p., °C (yield, %)	Calculated/ /Found		SD ₅₀ mol l ⁻¹ ^a
			% S	% N	
<i>Ia</i> H	C ₁₂ H ₈ Cl ₃ N ₃ O ₅ S (412.6)	170–172 (44)	7.75 7.50	10.20 10.10	1.2 · 10 ⁻⁷
<i>Ib</i> CH ₃	C ₁₃ H ₁₀ Cl ₃ N ₃ O ₅ S (426.6)	173–176 (36)	7.50 7.30	9.85 9.44	1.4 · 10 ⁻⁷
<i>Ic</i> Cl	C ₁₂ H ₇ Cl ₄ N ₃ O ₅ S (447.1)	178–180 (33)	7.17 7.04	9.41 9.11	6.3 · 10 ⁻⁸
<i>Id</i> CN	C ₁₃ H ₇ Cl ₃ N ₄ O ₅ S (436.5)	205 (28)	7.33 7.30	12.83 12.83	5.0 · 10 ⁻⁸
<i>Ie</i> NO ₂	C ₁₂ H ₇ Cl ₃ N ₄ O ₇ S (456.5)	165–168 (23)	7.00 7.05	12.27 12.30	8.9 · 10 ⁻⁸
<i>If</i> COOC ₂ H ₅	C ₁₅ H ₁₂ Cl ₃ N ₃ O ₇ S (484.5)	183–185 (31)	6.62 6.67	8.68 8.79	7.0 · 10 ⁻⁸
<i>IIa</i> H	C ₁₃ H ₁₀ Cl ₃ N ₃ O ₅ S (426.6)	156 (64)	7.54 7.50	9.89 9.60	—
<i>IIc</i> Cl	C ₁₃ H ₉ Cl ₄ N ₃ O ₅ S (461.1)	158–160 (55)	6.95 7.14	9.13 9.18	—
<i>IIId</i> CN	C ₁₄ H ₉ Cl ₃ N ₄ O ₅ S (450.5)	168–170 (50)	7.09 7.18	12.40 12.60	—

^a SD₅₀ concentration of the compound corresponding to 50% respiration stimulation from the measured maximum values of respiration stimulation.

reaction with diazomethane, neither react with it by a stepwise mechanism like analogous carbon analogues^{8,9}. Cycloaddition reaction with diazomethane was also unsuccessful in tetrahydrofuran–dioxane under catalysis of water, *i.e.* when meeting condition for reaction of a $>C=N-$ bond of azomethine to 1,2,3-triazolines¹². This finding indicated the unreactivity of $>C=N-$ bond in hydrazones. On the other hand, the unwillingness to enter the cycloaddition reaction and the mere formation of N-methylated derivatives could be rationalized by accepting the isomeric diaziridine instead of hydrazone structure¹³, or their tautomeric equilibrium, which might affect the reaction with diazomethane (Scheme 1).



SCHEME 1

Since the IR, UV and ^1H NMR spectra could doubtlessly not back this assumption, we got more information from the ^{13}C NMR spectra of hydrazones *Ia*, *IIa* and model 5-nitro-2-furaldehyde phenylhydrazone (*III*). Should the compounds exist as diaziridines, their spectra will show difference at $\text{C}_{(5)}$ when compared with the hydrazone *III*. Chemical shift values of the sp^2 hybridized $\text{C}_{(5)}$ atom of structure A will be over 100 ppm, whilst those of structure B below 100 ppm. Although the measured chemical shifts (Table II) are in the expected range over 100 ppm, they are still insufficient to reject structure B. Therefore, we synthesized ^{15}N -labelled hydrazones *Ia* (C and D) and measured their ^1H and ^{15}N NMR spectra. Coupling constants $^1J(^{15}\text{NH})$ in hydrazones vary within 91–96 Hz and $^2J(\text{NNH})$ within 0–20 Hz *ref.*¹⁴. The singlet at 12.20 ppm of hydrazone *Ia* C was split into a doublet with $^1J(^{15}\text{NH}) = 95.7$ Hz, that of hydrazone D occurred as singlet at δ 12.20 ppm. These data unambiguously evidence the hydrazone structure of the compounds under investigation. Interestingly enough, they do not undergo a cycloaddition reaction with diazomethane. The ^1H NMR spectra of hydrazones *I* and *II* (Table III) show

that the electron accepting substituents considerably influence the adjacent protons (E, E') of the phenyl ring; consequently, splitting of the singlet of *Id*–*If* into doublet took place. The doublet-doublet of phenyl protons of compounds *Ia*–*Ic* appeared as one multiplet. The IR spectra of *Ia*–*If* display absorption bands at $1\,000$ – $1\,040\text{ cm}^{-1}$ and 876 – 878 cm^{-1} characteristic of furan¹⁵, $\nu(\text{SO}_2)_s$ at $1\,150$ – $1\,180\text{ cm}^{-1}$, $\nu(\text{NO}_2)_{as}$ at $1\,515$ – $1\,553\text{ cm}^{-1}$, $\nu(\text{NH})$ at $3\,325$ – $3\,360\text{ cm}^{-1}$, and $\nu(\text{N}-\text{CH}_3)$ at $2\,910\text{ cm}^{-1}$ (*Ila*), $2\,860\text{ cm}^{-1}$ (*Ilc*), $2\,963\text{ cm}^{-1}$ (*Ild*). Absorption bands $\nu(\text{NO}_2)_s$ and $\nu(\text{SO}_2)_{as}$ were overlapped in the $1\,337$ – $1\,360\text{ cm}^{-1}$ region like those of $\nu(\text{C}=\text{N})$ and $(\text{C}=\text{C})$ in the $1\,576$ – $1\,604\text{ cm}^{-1}$. The UV spectra of hydrazones (Table IV) reveal four absorption bands at 202 – 212 nm , 235 – 263 nm , 318 – 333 nm , and 393 – 418 nm . The first three bands could be ascribed to electronic transitions in the phenyl or 5-nitrofuranyl moiety of the molecule, the fourth one is associated

TABLE II
¹³C NMR spectral data (δ , ppm)

Compound	C ₍₁₎	C ₍₂₎	C ₍₃₎	C ₍₄₎	C ₍₅₎	C ₍₆₎	C ₍₇₎	C ₍₈₎	C ₍₉₎	C ₍₁₀₎
<i>Ia</i>	116.0	112.2	151.4	141.1	116.8	144.0	115.6	128.9	124.9	103.8
<i>Ila</i>	119.8	112.8	151.4	143.5	114.4	145.9	118.8	129.2	126.3	103.8
<i>III</i>	115.4	109.9	154.6	150.7	123.6	143.6	112.7	128.9	120.4	—

TABLE III
¹H NMR chemical shift values of hydrazones *I* and *II* (δ , ppm)

Compound ^a	H ^A	H ^B	H ^D , H ^{D'}	H ^E , H ^{E'}
<i>Ia</i>	7.75 d	7.20 d	7.42 m	7.48 m
<i>Ib</i>	7.46 d	7.33 d	7.26 m	7.37 m
<i>Ic</i>	7.74 d	7.20 d	7.42 m	7.42 m
<i>Id</i>	7.78 d	7.29 d	7.45 d	7.78 d
<i>Ie</i>	7.78 d	7.36 d	7.20 d	7.47 d
<i>If</i>	7.50 d	6.95 d	8.14 d	7.39 d
<i>Ila</i>	7.36 d	7.03 d	7.36 m	
<i>Ilc</i>	7.32 d	7.11 d	7.38 m	
<i>Ild</i>	7.70 d	7.33 d	7.80 m	

^a For *Ia*–*If* and *Ila*, *c,d*: $J_{AB} = 4\text{ Hz}$; $J_{ED} = 8\text{ Hz}$ for *Id* and *If*, $J_{ED} = 8.5\text{ Hz}$ for *Ie*; CH_3 (s) 3.60 for *Ila*, 3.58 for *Ilc*, 3.51 for *Ild*.

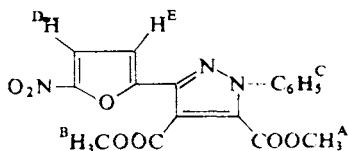
with those of the whole conjugated system (K-band). The latter is hypsochromically shifted by 35–60 nm in relation to that of the planar reference 5-nitro-2-furaldehyde phenylhydrazone¹⁷ (*III*, 453 nm); this is considered an evidence for the nonplanarity of these compounds at the $>C=N-$ bond similarly as with α,β -unsaturated sulfones^{1–7}. This band appears in the same region as that of analogous α -dichloromethylsulfonyl-5-nitro-2-furaldehyde 4-X-phenylhydrazones¹⁶ (395 to 426 nm). As seen, replacement of an SO_2CHCl_2 group for SO_2CCl_3 does not result in enhancement of molecule deplanarization. UV spectra of N-methylated hydrazones *II* (Table IV) almost lack this band, or, it appears in form of a weak, hypsochromically to 380–392 nm shifted inflex only. This fact evidences an enhancement of deplanarization of the molecule due also to distortion of the aryl residue induced by the methyl group attached to nitrogen.

TABLE IV
UV Spectral data

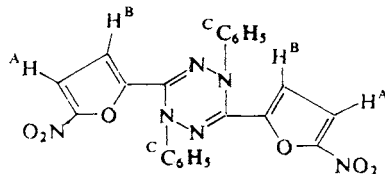
Compound		$\lambda_{\max}, \text{nm}^a$ (log $\epsilon, \text{m}^2 \text{mol}^{-1}$)			
<i>Ia</i>	i	208	238	318	409
		(4.18)	(4.17)	(4.26)	(4.02)
<i>Ib</i>	s	206	241	325	418
		(4.02)	(4.03)	(4.10)	(4.09)
<i>Ic</i>		202	244	320	400
		(4.28)	(4.12)	(4.18)	(4.03)
<i>Id^b</i>	s	209	256	333	393
		(4.12)	(4.05)	(4.20)	(4.10)
<i>Ie^c</i>		203	235	s 333	416
		(4.17)	(4.00)	(3.79)	(4.16)
<i>If^d</i>		212	263	318	411
		(4.99)	(4.76)	(4.02)	(4.80)
<i>IIa</i>		204	234	310	i 3.92
		(4.17)	(4.06)	(4.16)	(3.76)
<i>IIc</i>		207	236	316	i 384
		(4.23)	(4.26)	(4.33)	(4.06)
<i>IId</i>		208	250	330	i 380
		(4.02)	(3.97)	(4.25)	(4.03)

^a i Inflex, s shoulder; ^b shoulder at 524 nm; ^c shoulder at 550 nm; ^d shoulder at 543 nm.

Treatment of hydrazones *I* with triethylamine or pyridine afforded, in contrast with analogous hydrazones containing an SO_2CHCl_2 grouping¹⁶, nitrilimines *in situ* and trichloromethanesulfonic acid. Nitrilimine generated from hydrazone *Ia* was determined after 1,3-cycloaddition to dimethyl butinedioate as 1-phenyl-3-(5-nitro-2-furyl)-4,5-bis(methoxycarbonyl)pyrazol (*IV*) and a small amount of dimeric 1,4-diphenyl-3,6-bis(5-nitro-2-furyl)-1,4-dihydro-1,2,4,5-tetrazine (*V*). Sym-



IV



V

metry of compound *V* was seen in the ^1H NMR spectrum by a doublet integrated intensity of phenyl (singlet) and furan (doublet-doublet) hydrogens. The mass spectrum showed, in addition to the peak of molecular radical ion, fragments originating primarily by cleavage at $>\text{C}=\text{N}-$ and $>\text{N}-\text{N}=-$ bonds.

Hydrazones *I* were tested on stimulation of mitochondria respiration in the presence of succinate, glutamate or malate as substrates. As found, hydrazones *I* constitute a new highly effective type of SH— group uncouplers, *i.e.* strongly polar systems reacting with thiol groups. They have, then, properties close to those of carbonylcyanide phenylhydrazone and its derivatives¹⁸ and can be, therefore, employed for investigation of oxidation–reduction processes taking place in cells^{19,20}. The effective concentration of these substances (SD_{50}) was found to be 10^{-7} to 10^{-8} mol $\cdot$ l^{-1} (Table I). The decoupling effect in a 10^{-7} mol l^{-1} concentration possess also hydrazone with an SO_2CHCl_2 group¹⁶.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage. The ^1H NMR spectra of deuteriochloroform or deuteriodimethyl sulfoxide solutions were measured with a Tesla BS 478 B apparatus operating at 80 MHz. The ^{15}N NMR and ^{13}C NMR spectra of deuterated dimethyl sulfoxide solutions were recorded with a Jeol FX 100 apparatus at 10.04 and 25 MHz, respectively, tetramethylsilane being the internal standard. The IR, UV and mass spectra were taken with UR 20 (Zeiss, Jena, KBr discs), Specord UV VIS (Zeiss, Jena, $5 \cdot 10^{-5}$ mol l^{-1} ethanolic solutions), and AEI MS-902 (70 eV) apparatuses, respectively.

α -Trichloromethylsulfonyl-5-nitro-2-furaldehyde 4-X-Phenylhydrazones *Ia–If*

Sodium acetate (0.54 g, 6 mmol) in water (10 ml) was added to 5-nitrofurfuryltrichloromethyl sulfone⁴ (0.92 g, 3 mmol) dissolved in ethanol (100 ml) at 60°C . To the mixture cooled to 5°C diazonium salt prepared from 6 mmol of the amine was added during 10–15 min. The precipitate was filtered off and crystallized from ethanol or acetic acid.

α -Trichloromethylsulfonyl-5-nitro-2-furaldehyde N-Methyl-4-X-phenylhydrazones *IIa,c,d*

Ethereal solution of diazomethane (15 ml, 5 mmol) was added to 4-X-phenylhydrazone (1 mmol) dissolved in dioxane or tetrahydrofuran (200 ml) at 0–5°C. The mixture was stirred at 10–15°C. for 3 h, concentrated under reduced pressure to 100 ml and separated by chromatography on silica gel using chloroform–benzene 1 : 1 (*IIa*), or alternatively by adding a small amount of n-hexane to the concentrated solution, cooling in refrigerator overnight and filtering the precipitate which was followed by crystallization from ethanol (*IIc,d*).

1-Phenyl-3-(5-nitro-2-furyl)-4,5-bis(methoxycarbonyl)pyrazole (*IV*),
and 1,4-Diphenyl-3,6-bis(5-nitro-2-furyl)-1,4-dihydro-1,2,4,5-tetrazine (*V*)

Triethylamine (0.4 g, 10 mmol) in a small amount of ether was added to a mixture of phenylhydrazone *Ia* (2 g, 5 mmol) either in ethereal or dioxane solution and dimethyl butinedioate (1.4 g, 10 mmol) at room temperature. The reaction course was monitored by chromatography on Silufol sheets. The mixture was concentrated after the reaction was through, the ammonium salt was filtered off, washed with benzene, and the filtrate was chromatographed on silica gel with benzene as eluent. Compound *IV* remaining at the start line was crystallized from ethanol, the benzene solution was concentrated and rechromatographed on silica gel with benzene–ethyl acetate 5 : 1. Yield of *IV* was 25%, m.p. 140°C. For $C_{17}H_{13}N_3O_7$ (371.3) calculated: 54.98% C, 3.50% H, 11.32% N; found: 53.67% C, 4.01% H, 10.02% N. UV spectrum (dioxane), $\lambda_{\max}$, nm ($\log \epsilon$, $m^2 \text{ mol}^{-1}$): 230 (4.96), 346 (4.77). ^1H NMR spectrum: (C^2HCl_3), δ , ppm: 3.85 (s, H^A), 3.94 (s, H^B), 7.50 (s, H^C) 7.34 (d, H^D), 7.25 (d, H^E), $J_{ED} = 4 \text{ Hz}$. Mass spectrum (m/z , for ^{35}Cl): 371 (M^{+}).

Yield of *V* was 15%, m.p. 232°C. For $C_{22}H_{14}N_6O_6$ (458.4) calculated: 57.64% C, 3.05% H, 18.34% N; found: 56.29% C, 3.10% H, 18.20% N. UV spectrum (dioxane), $\lambda_{\max}$, nm ($\log \epsilon$, $m^2 \cdot \text{mol}^{-1}$): 225 (4.42), 256 (4.24), 310 (4.44), 411 (4.00). ^1H NMR spectrum (C^2HCl_3), δ , ppm: 7.10 (d, H^A), 6.15 (d, H^B), 7.37 (s, H^C), $J_{AB} = 4 \text{ Hz}$. IR spectrum (KBr), cm^{-1} : $\nu(\text{C}=\text{N})$ 1710, $\nu(\text{C}-\text{C})$ 1590, $\nu(\text{COC})$ 1013, $\nu(\text{NO}_2)_s$ 1350, $\nu(\text{NO}_2)_{as}$ 1510. Mass spectrum, m/z : 458 (M^{+}).

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