PREPARATION OF FLUOROHETEROCYCLES I. SYNTHESIS AND REACTIVITY OF 2-FLUOROPYRAZINE 1-OXIDE

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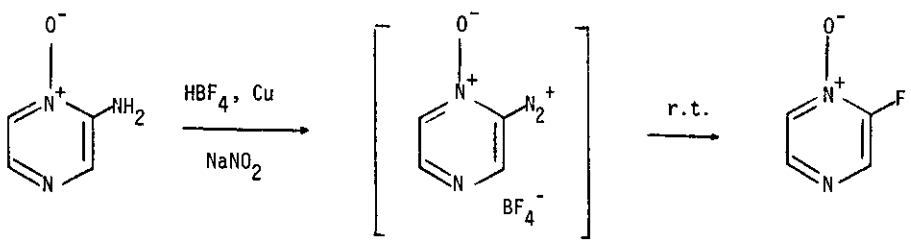
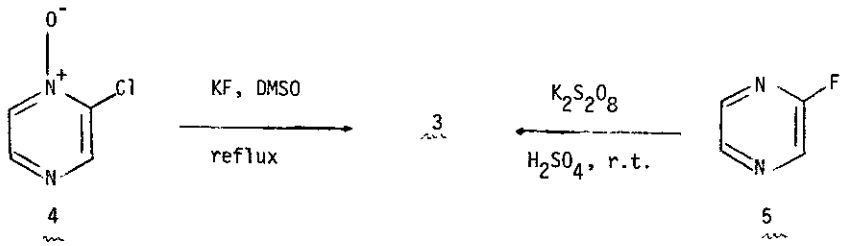
Abstract - The title compound was prepared by three different methods: Balz-Schiemann reaction, halogen exchange, and by direct N-oxidation of 2-fluoropyrazine. The resulting 2-fluoropyrazine 1-oxide was reacted with a variety of nucleophiles to yield the corresponding 2-substituted pyrazine 1-oxides.

Diazotization of 2-aminopyrazine 1-oxide (1) with fluoroboric acid and sodium nitrite in the presence of activated copper powder yielded crystalline diazonium fluoroborate (2) which upon decomposition gave 2-fluoropyrazine 1-oxide (3) in moderate yields (Balz-Schiemann method).[1]



1 2 3

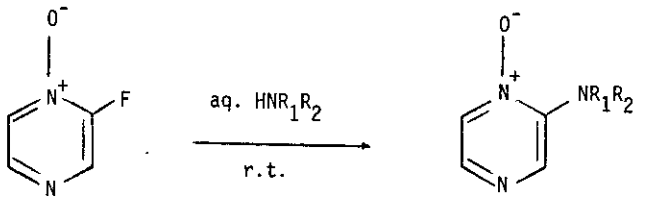
Alternatively, 3 was also prepared by halogen exchange method[2] (potassium fluoride/DMSO) from 2-chloropyrazine 1-oxide (4) and by direct N-oxidation[3] (potassium persulfate/H_2SO_4, v.t.) of 2-fluoropyrazine (5) in the respective yields of 27 and 38%. The selective formation of 3 by the above N-oxidation reaction is in accordance with the results obtained with other weakly basic pyrazines.[3,4]



4 5

2-Fluoropyrazine 1-oxide (3) underwent nucleophilic substitution more rapidly than its 2-chloro analog (4). The facile displacement of fluorine atom from 3 was utilized in the preparation of a number of 2-substituted pyrazine 1-oxides. Several of these compounds have previously been prepared by other methods[5] (i.e., 2-NH_2, 2-OCH_3, 2-OH) and by us from 4[6] which allowed us to assess the relative reactivity of 3 and 4 towards various nucleophiles.

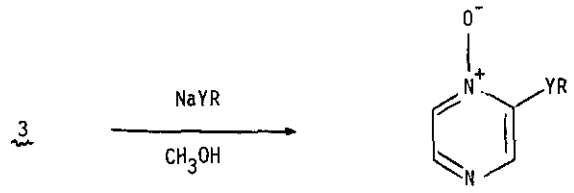
Aminolysis of 3 with ammonium hydroxide, methylamine, dimethylamine, morpholine and piperidine proceeded smoothly at 40-50°C and was completed within 2 h to produce 2-amino- (1), 2-methylamino- (6), 2-dimethylamino- (7), 2-morpholino- (8), and 2-piperidinopyrazine 1-oxide (9), respectively. This compares with refluxing temperatures for 4 required to accomplish the same substitution (ca 100-130°C).[6]



3

1 $R_1 = R_2 = H$
6 $R_1 = CH_3$, $R_2 = H$
7 $R_1 = R_2 = CH_3$
8 $R_1R_2 = C_4H_8O$
9 $R_1R_2 = C_5H_{10}$

The hydrolysis and alcoholysis with anions such as hydroxides, alkoxides, and mercaptides proceeded readily with 3 to produce the appropriate derivatives as compared to reflux temperatures and prolonged heating (up to several h) required for 4. Physical properties of these derivatives and experimental variables are listed in Table I.



10 Y = O, R = H*

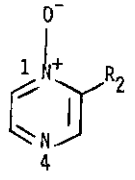
11 Y = O, R = CH_3

12 Y = S, R = H*

13 Y = S, R = CH_2CH_3

(*see the NMR section for further discussion)

TABLE I. Physical Properties and Experimental Variables for Some 2-Substituted Pyrazine 1-Oxides

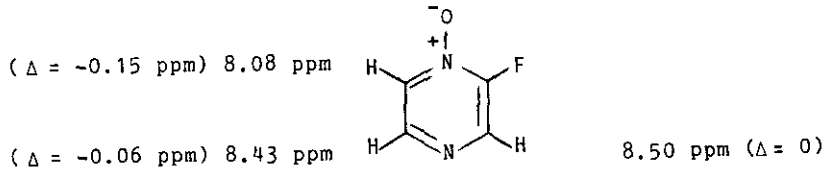


Cmpd No.	Substituent	mp, °C[a]	Reaction Time[b] (Temperature)	Yield, %	Elemental Analyses[c] %C	%H	%N
1	NH_2[d]	187-188	3, 20 min (100)[e] 4, 45 min (110)[e]	75 80	37.82 (37.70)	4.54 (4.31)	37.82 (37.70)
6	$NHCH_3$	117.5-119	3, 15 min (45) 4, 45 min (100)	90 95	48.17 (48.21)	5.63 (5.78)	33.46 (33.33)
7	$N(CH_3)_2$	142-143.5	3, 15 min (45) 4, 45 min (100)	97 92	51.96 (51.85)	6.51 (6.60)	30.08 (30.14)
8	NC_4H_8O	183-185	3, 20 min (40) 4, 60 min (80)	90 98	53.02 (53.03)	6.13 (6.42)	23.19 (23.19)
9	NC_5H_{10}	84-85.5	3, 20 min (40) 4, 60 min (80)	92 95	60.50 (60.30)	7.29 (7.31)	23.34 (23.19)
10	OH	230-232	3, 20 min (50) 4, 120 min (100)	80 60	mp 225-230[9]		
11	OCH_3	143-144	3, 10 min (25) 4, 45 min (65)	91 85	47.84 (48.03)	4.78 (4.84)	22.12 (21.75)
12	SH 0.5 H_2O	71-74	3, 24 h (25)[f]	21	35.02 (34.97)	3.68 (3.73)	20.43 (20.11)
13	SCH_2CH_3	106-108	3, 30 min (25) 4, 10 h (25)	89 83	46.37 (46.25)	5.15 (5.20)	17.87 (17.84)

[a]Melting points were taken on a Thomas-Hoover melting point apparatus and were uncorrected. [b]In °C. [c]Calc. (Found). [d]Previously prepared by hydrolysis of 2-acetamido derivative (mp 186-187°C)[5]. [e]In a steel bomb and increased pressure. [f]Isolated from the reaction with Na_2S (see Experimental).

^1H NMR DATA

At this point, it is appropriate to address the nmr assignments of compound 3. The ^1H nmr spectrum of 3 appears as a complex multiplet at about δ8.3 ppm, due to the additional H-F coupling. In order to simplify its interpretation we treated 0.1 mM of 2-fluoropyrazine 1-oxide (3) in 0.4 ml of $CDCl_3$ with 0.10 ml portions of 100 mg/1.0 ml (~0.1 mM) Profod solution. This nmr shift reagent successfully resolved two sets of peaks and after the 6th addition further separated the more shielded group of signals into two other distinct sets of peaks. In this manner, resonances at δ8.50 ppm, δ8.43 ppm, and δ8.08 ppm were assigned to H_3, H_5, and H_6, respectively.

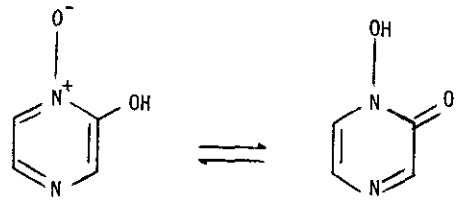


$$\Delta = \delta H_{\text{fluoropyrazine}} - \delta H_{\text{1-oxide}}$$ (negative sign indicates shielding)

It is apparent from Table II that moderate shielding occurs at H_6 and is of the same magnitude as observed for 2-chloropyrazine 1-oxide (4).[3]

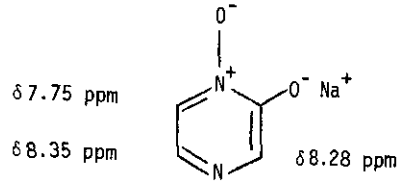
The coupling constants of 3 were determined by the homonuclear decoupling technique. When the lowest resonance attributed to H_6 was irradiated at that frequency, the signal at the lower field (H_5) collapsed into a doublet of doublets and the two coupling constants were unambiguously assigned to J_{H_5F} (4.7 Hz) and $J_{H_3H_5}$ (0.5 Hz).[7] The other doublet of doublets yielded J_{H_3F} (8.5 Hz). Similarly, irradiation of H_5 yielded $J_{H_3H_6}$ (1.3 Hz) and J_{H_6F} (1.8 Hz) and decoupling of H_3 determined $J_{H_5H_6}$ (4.0 Hz).

Difficulty in choosing the correct representations for compounds 10 and 12 was also addressed. Compound 10 could conceivably exist as 2-hydroxypyrazine 1-oxide (10a) or as its tautomeric isomer 1-hydroxy-1,2-dihydro-2-pyrazinone (10b) or as a mixture of both. The complexity of the problem is augmented by questioning the validity of methods used for collecting evidence to support and show the predominance of one structure over the other. The naturally occurring antibiotics, aspergillic acids, exist in the stable "one" form. Their infrared spectra show a carbonyl absorption at 1640 cm^{-1}.[8] Similar ir band at 1652 cm^{-1} for 10 as well as its



10a 10b

^{1}H nmr comparison with that of 2-methoxy compound (11) would seem to indicate that it, too, exists mainly in the hydroxypyrazinone form (10b) (see Table II). However, the ^{1}H nmr of 10 in d_6-DMSO and that of its sodium salt (14) favor 10a. It may be that in the solid state and in the relatively non-polar solvents ($CDCl_3$) the cyclic hydroxamic acid 10b is favored over 10a and that in polar solvents (d_6-DMSO) the reverse is true. The positive phenol test, 10, gave an intense wine-red color in aqueous or alcoholic $FeCl_3$, may be indicative of either structure.[9,10]



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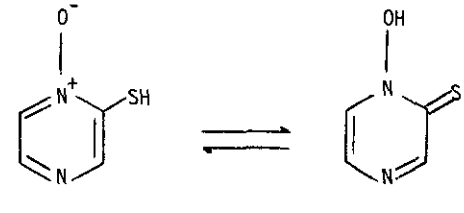
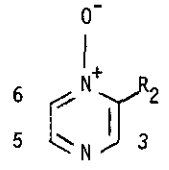
Similarly, derivative 12 can exist either as 2-mercaptopyrazine 1-oxide (12a) or as 1-hydroxy-1,2-dihydro-2-pyrazinethione (12b). It was difficult to assign the



12a 12b

C=S stretching frequency in the infrared spectrum of 12, and most of our "proof" centered on the ^{1}H nmr spectral comparison of 12 with that of 2-ethylthiopyrazine 1-oxide (13) (Table II). On this basis, we have tentatively assigned 12b as the major tautomer. This assessment has precedence from the literature[5] where the α- and γ-thiones are usually more favored than their corresponding α- and γ-oxo

TABLE II. ^{1}H NMR Data of Some 2-Substituted Pyrazine 1-Oxides



Cmpd No.	Molecular Formula	Substituent (R)	Chemical Shifts[a,b] R_2	R_3	R_5	R_6	Coupling Constants (Hz) $J_{3,5}$	$J_{3,6}$	$J_{5,6}$
1	$C_4H_5N_3O$	NH_2	7.35[c] 6.80[d]	8.55 8.25	8.51 7.99	8.12 7.73	- -	- -	4.0 4.0
3	$C_4H_3FN_2O$	F[e]	-	8.50	8.43	8.08	0.5	1.3	4.0
4	$C_4H_3ClN_2O$	Cl	-[c] -	8.62 8.90	8.36 8.58	8.22 8.51	- -	1.5 -	4.0 -
5	$C_4H_3FN_2$	F(non-oxide)[f]	-	8.51	8.49	8.23	0.5	1.3	2.7
6	$C_5H_7N_3O$	$NHCH_3$	3.08	8.02	8.03	7.78	-	-	4.0
7	$C_6H_9N_3O$	$N(CH_3)_2$	3.09	8.15	8.00	7.97	-	-	-
8	$C_8H_{11}N_3O_2$	NC_4H_8O	3.41 3.90	8.10	8.00	8.00	-	-	-
9	$C_9H_{13}N_3O$	NC_5H_{10}	3.36 1.75	8.13	8.00	8.00	-	-	-
10	$C_4H_4N_2O_2$	OH[g]	6.35[c] -	8.50 8.70	8.36 8.46	7.71 8.33	- -	1.0 -	4.5 4.5
11	$C_5H_6N_2O_2$	OCH_3	4.22 4.45[c]	8.31 8.50	8.22 8.36	8.22 8.18	- -	- 1.8	4.1 4.2
12	$C_4H_4N_2OS$	SH[g]	-	8.48	8.44	8.44	-	-	-
13	$C_6H_8N_2OS$	SCH_2CH_3	3.10 1.46	8.42	8.27	8.18	-	1.0	4.0
14	$C_4H_3N_2O_2Na$	ONa	-[c]	8.28	8.35	7.75	-	-	4.0
15	$C_8H_6N_4O_2S$	$SC_4H_3N_2O$[b]	-	8.86	8.86	8.74	-	-	-

[a] All spectra were recorded as dilute solutions in $CDCl_3$ except where otherwise indicated. [b] δ(ppm) downfield from TMS. [c] d_6-DMSO. [d] $CDCl_3$ and d_6-DMSO. [e] The assignments were made as discussed in the text; $J(H_3F)$=8.5 Hz; $J(H_5F)$=4.7 Hz; $J(H_6F)$=1.8 Hz. [f] This compound was commercially available; $J(H_3F)$=8.2 Hz; $J(H_5F)$=4.7 Hz; $J(H_6F)$=1.4 Hz. [g] This compound may exist in the "one" form. [h] Compound 15 was isolated from the synthesis of 12 (see Experimental) and was identified as bis-2,2'-pyrazylsulfide 1,1'-dioxide.

N-oxide derivatives. It should be, however, kept in mind that these tautomeric equilibria are summations of the opposing influence of the greater acidity of -SH over -OH versus the greater bond strength of C=O vs C=S which favors the 1,2-dihydro compounds.

EXPERIMENTAL

Preparation of 2-Fluoropyrazine 1-Oxide (3).

Method A (Balz-Schiemann reaction). A mixture of 220 mg (2.0 mmol) of 2-amino-pyrazine 1-oxide (1) and 38.5 mg of activated copper powder were added to 1.5 ml of 40% fluoroboric acid. Once the amine dissolved, the whole was cooled to -5°C in an efficient salt-ice bath. To this clear yellow solution was added in small portions, over a period of 10 min, 1.0 ml of water containing 172.5 mg (2.5 mmol) of sodium nitrite. Almost immediately the diazonium fluoroborate salt starts to form and as this semi-crystalline suspension begins to thicken mechanical stirring is required to allow the efficient mixing in of the remaining $NaNO_2$ solution. The addition of 5.0 ml of CH_2Cl_2 considerably helped in thinning out the suspension. The resulting brown slurry was slowly brought up to 15°C and kept there for 20 min to allow the decomposition of the diazonium salt (2).

The reaction mixture was partially neutralized with saturated sodium carbonate (pH=5), utilizing the ice bath to maintain the temperature at about 10-15°C during the neutralization. The resulting bilayered solution was placed in a separatory funnel, bottom layer separated and the remaining aqueous solution extracted with additional 5 x 15 ml portions of CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and solvent evaporated to dryness under reduced pressure (70 Torr) to yield a yellow oil. This material was eluted through a short alumina column (5 cm, o.d. 1 cm) and the remaining liquid vacuum distilled to yield 38.8 mg (17%) of pure 3 (bp 72°C/0.05 Torr). Anal. Calcd. for $C_4H_3N_2OF$: C, 42.11; H, 2.64; N, 24.56. Found: C, 42.17; H, 2.59; 24.40.

Method B (Halogen exchange via 2-chloropyrazine 1-oxide (4)). To 10 ml of dimethyl sulfoxide was added 200 mg (2.1 mmol) of finely ground potassium fluoride dihydrate and whole refluxed for 48 h. Solution was then dehydrated by distilling off 5 ml of the solvent (vapor pressure became constant) through a short condenser. The resulting suspension was cooled to 100°C and 248 mg (1.9 mmol) of 4 was added and this mixture refluxed for another 70 min. Short-path vacuum distillation and another microdistillation of the first fraction (60-80°C/50 Torr) through the small

Vigreux column yielded 36.5 mg (32%) of the material which was identical in all respects with compound 3 isolated from Method A.

Method C (By direct oxidation of 2-fluoropyrazine (5)). To a stirred solution of 100 mg (1.0 mmol) of 5 in 1.5 ml of concentrated sulfuric acid cooled to 10°C was slowly added 300 mg (1.1 mmol) of potassium persulfate. The reaction is exothermic and it is imperative that the temperature be maintained at about 25°C. After 24h the thick solution was diluted with 5 ml of ice water and whole extracted with 5 x 10-ml portions of $CHCl_3$. The combined organic extracts were successively washed with saturated sodium bicarbonate (3 x 10 ml) and twice with saturated sodium carbonate, aqueous layer discarded and organic layer dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent afforded 42 mg (37.7%) of 3, which was identical to the product obtained from the other two methods.

Aminolysis of 3 and 4. A mixture of 1.00 g (7.4 mmol) of 2-chloropyrazine 1-oxide (4) and 4.8 ml of concentrated ammonium hydroxide was heated in a 50-ml stainless-steel bomb at 110°C for 45 min. The cooled reaction mixture was evaporated to dryness and the air-dried residue was mixed with activated charcoal, and extracted in a Soxhlet apparatus with 250 ml of chloroform for 10 h. The extract, upon removal of the solvent and crystallization of the crude residue from absolute ethanol, afforded 600 mg (75%) of the amino compound (1).

The same reaction was carried out with 2-fluoropyrazine 1-oxide (3) and methanolic ammonia for 20 min to produce compound 1 in 80% yield (see Table I).

Preparation of 2-Mono- (6) and 2-Dimethylaminopyrazine 1-Oxide (7). In a typical experiment, an excess of 40% aqueous methylamine (8.0 ml) was added dropwise to 1.31 g (10.0 mmol) of 2-chloropyrazine 1-oxide (4) in 50 ml of CH_2Cl_2 cooled in an ice bath. After the addition was completed, the ice bath was removed and the whole was refluxed at 100°C for 45 min. The reaction mixture was cooled, placed in a separatory funnel, and the organic layer, washed with a 10-ml (5.0 mmol) solution of potassium carbonate. The CH_2Cl_2 layer was separated and additional CH_2Cl_2 (5 x 60 ml) extractions were made of the aqueous layer. The combined CH_2Cl_2 extracts were dried over anhydrous Na_2CO_3, filtered, and evaporated in vacuo at room temperature. The remaining oily residue was chromatographed on a short column of neutral alumina (grade III) and eluted with $CHCl_3$ to yield 1.19 g (95%) of 2-monomethylaminopyrazine 1-oxide (6). An analytical sample was prepared by sublimation at 60-70°C/0.05 Torr. The same procedure furnished 2-dimethylaminopyrazine 1-oxide (7) in 92% yield (see Table I).

Compounds 6 and 7 were also prepared from 2-fluoropyrazine N-oxide (3) at 45°C/15 min in 90% and 97% yield, respectively.

Preparation of 2-Morpholinopyrazine 1-Oxide (8). To a solution of 149 mg (1.14 mmol) of 2-chloropyrazine 1-oxide (4) in 50 ml of tetrahydrofuran was added 189 mg (2.3 mmol) of morpholine as a solution in 10 ml of water. The mixture was refluxed for 85 min at 70°C, during which time solution turned orange. It was cooled, filtered, concentrated, and extracted with CH_2Cl_2 to give a pale yellow solid which was recrystallized from petroleum ether to furnish 202.2 mg (98%) of compound 8. This white, fluffy material was sublimed at 60°C/0.05 Torr for analysis (Table I). Compound 8 was also made from 3 in 90% yield except that milder reaction conditions were required (Table I).

Preparation of 2-Piperidinopyrazine 1-Oxide (9). The reaction procedure was the same as described for the formation of compound 8, except that piperidine was used instead of morpholine to produce a white solid. This product was further purified by sublimation to give 194 mg (95%) of pure 9. Compound 9 was also made from 3 in 92% yield (see Table I).

Hydrolysis of 3 and 4. (Synthesis of 10). 2-Fluoropyrazine 1-oxide (3) was hydrolyzed readily at 50°C with 1 M NaOH instead of the more rigorous conditions used for the hydrolysis of 4 (reflux with 2N NaOH for 2 h).[9] Namely, treatment of 114.1 mg (1.0 mmol) of 3 with 3.9 mmol of 1 N NaOH after 20 min and acidification yielded 89.7 mg (80%) of 10, mp 230-232°C (lit. 225-230°C).[9]

Preparation of 2-Methoxypyrazine 1-Oxide (11). To a warm solution of sodium methoxide, prepared from 1.38 g (60 gram-atoms) of sodium and 30 ml of dry methanol, was added in several portions a solution of 3.93 g (30.0 mmol) of 2-chloropyrazine 1-oxide (4) dissolved in 30 ml of dry methanol. The resulting suspension was refluxed for 30 min at which time the tlc (alumina, benzene) showed the absence of the starting material. The heating was continued for additional 15 min, the milky suspension was filtered, and the combined filtrate and hot dry methanol washings (3 x 40 ml) were concentrated to about 30 ml. This residue was diluted with an equal volume of water and extracted with CH_2Cl_2 (5 x 50 ml). The combined extracts were dried (Na_2SO_4), filtered, and solvent removed *in vacuo*, leaving 3.5 g (85%) of a pale yellow oil which solidified on standing. This solid was recrystallized from distilled hexane and sublimed (60°C/0.05 Torr) to produce pure 11. 2-Methoxypyrazine 1-oxide (11) was also obtained from 2-fluoro derivative (3) within 10 min (room temperature) in 91% yield (see Table I).

Preparation of 2-Ethylthiopyrazine 1-Oxide (13). Care was taken to prevent dealkylation of 13 by employing lower temperatures and longer reaction times. Consequently, to a solution of 917 mg (7.0 mmol) of 2-chloropyrazine 1-oxide (4) in 250 ml of dry tetrahydrofuran was added an excess (2.0 ml) of ethyl mercaptan. To this mixture was added 405 mg (7.5 mg atoms) of sodium and the mixture stirred overnight (10 h). This solution was then filtered, filtrate was evaporated to dryness (25°C) and the remaining, clear residue triturated with 50 ml of hexane. The resulting suspension was filtered, filtrate evaporated, and the remaining material sublimed at 50°C/0.05 Torr to yield 895 mg (83%) of pure low-melting solid (13), also prepared from 3 in 89% yield (see Table I for additional information). Synthesis of Thione 12. This compound could not be made via *thiouranium salts*. Alternatively, 1.0 mmol of 4 was placed in large volume of dioxane (800 ml) and treated slowly with Na_2S. Workup and elution of the organic residue with hexane through a short alumina column yielded 21% of 12 and 33% of 2,2'-bispyrazylsulfide 1,1'-dioxide (15), mp 69-71°C. Anal. Calcd. for $C_8H_6N_4O_2S$: C, 43.23; H, 2.73; N, 25.22. Found: C, 42.91; H, 2.89; N, 24.88.

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