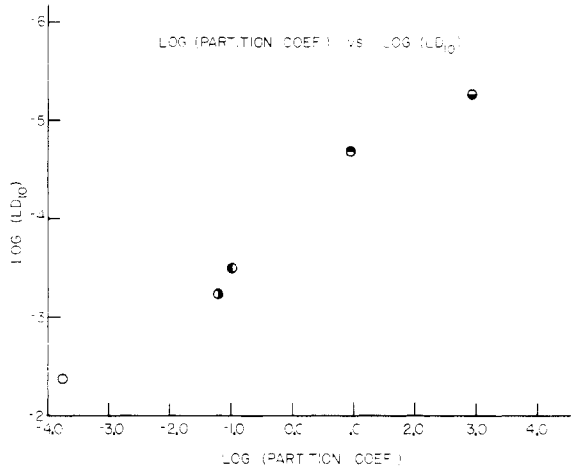


**Figure 2.** Correlation between the 1-octanol–saline partition coefficients and the $LD_{10}$ of rhodium(II) carboxylates: ○, rhodium(II) chloride; ◑, rhodium(II) methoxyacetate; ◐, rhodium(II) acetate; ◓, rhodium(II) propionate; ◒, rhodium(II) butyrate.

pounds would have greater ability to dissolve into proteins, such as enzymes, and exert a biological effect.[13]

The amount of rhodium absorbed by tumor cells increases as the partition coefficient increased. The antitumor activity and therapeutic indices also increased through rhodium(II) pentanoate. The observed decrease in antitumor activity, toxicity, and therapeutic efficacy of the hexanoate complex suggests that either steric problems are beginning to be seen or rhodium(II) compounds must exhibit some intermediate degree of water solubility to be effective.

This study shows that rhodium(II) carboxylates present promise as antitumor drugs in the treatment of neoplasias. However, the simple extension of the carboxylate R chain beyond the butyrate or pentanoate is not effective in altering the therapeutic possibilities of the drug. Because of the lipid solubility of rhodium(II) complexes the study of their effect against CNS neoplasias would be merited. Also, the synthesis of other rhodium(II) carboxylates with functional R groups may prove to be advantageous.

## References and Notes

(1) This research was supported by Grants CA-12327 and CA-13817 from the National Cancer Institute, National Institutes of Health.
(2) A. Erck, L. Rainen, J. Whileyman, I.-M. Chang, A. P. Kimball, and J. Bear, *Proc. Soc. Exp. Biol. Med.*, **147**, 1278 (1974).
(3) J. L. Bear, H. B. Gray, L. Rainen, I.-M. Chang, R. Howard, G. Serio, and A. P. Kimball, *Cancer Chemother. Rep.*, **59**, 611 (1975).
(4) Abbreviations used: ILS, increase in life span; TI, therapeutic index; $a$, molar absorptivity; ip, intraperitoneal; $LD_{10}$, that dose that kills 10% of an animal population from drug toxicity; Cl, chloride; MAc, methoxyacetate; Ac, acetate; Prop, propionate; But, butyrate; Pent, pentanoate; Hex, hexanoate; rhodium(II) acetate, tetra-$\mu$-acetato-dirhodium(II); rhodium(II) propionate, tetra-$\mu$-propionato-dirhodium(II); rhodium(II) butyrate, tetra-$\mu$-butyrato-dirhodium(II); rhodium(II) pentanoate, tetra-$\mu$-pentanoato-dirhodium(II); rhodium(II) hexanoate, tetra-$\mu$-hexanoato-dirhodium(II); rhodium(II) methoxyacetate, tetrakis-$\mu$-methoxyacetato-dirhodium(II).
(5) R. G. Hughes, Jr., J. L. Bear, and A. P. Kimball, *Proc. Am. Assoc. Cancer Res.*, **13**, 120 (1972).
(6) J. Kitchens and J. L. Bear, *Thermochim. Acta*, 1, 537 (1970).
(7) S. A. Johnson, H. R. Hunt, and H. M. Neuman, *Inorg. Chem.*, **2**, 960 (1963).
(8) H. E. Skipper and L. H. Schmidt, *Cancer Chemother. Rep.*, **17**, 1 (1962).
(9) H. E. Haley, G. A. Fischier, and A. D. Weldr, *Cancer Res.*, **21**, 532 (1961).
(10) C. J. Dawes, "Biological Techniques in Electron Microscopy", Barnes and Noble, New York, N.Y., 1971.
(11) K. Das and J. L. Bear, *Inorg. Chem.*, in press.
(12) R. A. Howard, A. M. Wynne, J. L. Bear, and W. W. Wendlandt, *J. Inorg. Nucl. Chem.*, **38**, 1015 (1976).
(13) R. A. Howard, T. G. Spring, and J. L. Bear, *Cancer Res.*, **36**, 4402 (1976).

# Antiprotozoal Thiazoles. 2. 2-(5-Nitro-2-furyl-, thiazolyl-, and 1-methylimidazolyl-)thiazoles

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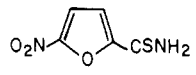
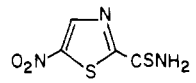
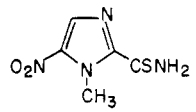
Ten 2-substituted 4-thiazolecarboxaldehyde hydrazones bearing 5-nitro-2-furyl, 5-nitro-2-thiazolyl, and 1-methyl-5-nitro-2-imidazolyl functions have been prepared and screened for activity against *Trypanosoma cruzi* infections in mice. The results permitted the ranking of these substituents in decreasing order of activity: 1-methyl-5-nitro-2-imidazolyl > 5-nitro-2-furyl > 5-nitro-2-thiazolyl, the last being inactive. Some structural features of the side chain necessary for optimum activity are discussed. The most active compound, 4-[[[2-(1-methyl-5-nitro-2-imidazolyl)-4-thiazolyl]methylene]amino]thiomorpholine 1,1-dioxide, compared favorably with the standard Nifurtimox against three recent clinical isolates of *T. cruzi*, including one with a high myocardial tissue infiltration.

A recent report[1] from these laboratories has described the synthesis and antitrypanosomal activity of a series of 2-(5-nitro-2-thienyl)-4-thiazolecarboxaldehyde hydrazones. The purpose of this second paper is to report the extension of this work to three other nitro heterocyclic nuclei, i.e., furan, thiazole, and 1-methylimidazole together with a comparison of their activity.

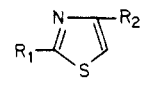
**Chemistry.** The syntheses of these compounds required the corresponding 5-nitro-2-cyano heterocycles as intermediates. 5-Nitro-2-furancarbonitrile[2] and 5-nitro-2-thiazolecarbonitrile[3] were prepared by published procedures. 1-Methyl-5-nitro-2-imidazolecarbonitrile[4] was readily prepared in high yield from the carboxaldehyde by treatment with *O,N*-bis(trifluoroacetyl)hydroxylamine.[5] The conversion of these nitriles to the thiocarboxamides **1–3** proceeded smoothly by the Taylor–Zoltewicz method[1,6] in good yield (Table I). Subsequent Hantzsch cyclization with 1,3-dichloroacetone was carried out as described previously to give the 4-chloromethylthiazoles **4–6** (Table II). Compounds **5** and **6** were converted to the 4-

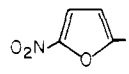
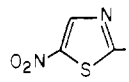
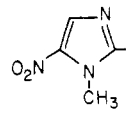
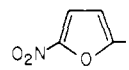
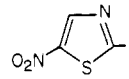
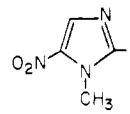
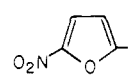
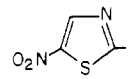
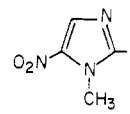
Table I. 5-Nitro-2-thiocarbamyl Heterocycles

| Compd | Structure | Recrystn solvent | Yield,[a] % | Mp, °C | Formula | Analyses |
|---|---|---|---|---|---|---|
| 1 |  | EtOAc-pe[b] | 80 | 189[c] | $C_5H_4N_2O_3S$ | |
| 2 |  | $CHCl_3$-$Et_2O$ | 93 | 204-207 | $C_4H_3N_3O_2S_2$ | C, H, N |
| 3 |  | EtOH-pe | 93.5 | 148-150 | $C_5H_6N_4O_2S$ | C, H, N, S |

[a] Pure material. [b] pe = petroleum ether, bp 60-80 °C. [c] Lit.[2] mp 185-187 °C.

Table II. 2,4-Disubstituted Thiazole Derivatives



| Compd | $R_1$ | $R_2$ | Recrystn solvent | Yield,[a] % | Mp, °C | Formula | Analyses |
|---|---|---|---|---|---|---|---|
| 4 |  | $-CH_2Cl$ | $C_6H_6$-pe[b] | 77 | 132-133[c] | $C_8H_5ClN_2O_3S$ | C, H, N, Cl, S |
| 5 |  | $-CH_2Cl$ | $CHCl_3$-pe | 76 | 128-130 | $C_7H_4ClN_3O_2S_2$ | C, H, N, S |
| 6 |  | $-CH_2Cl$ | EtOH | 82 | 160-162 | $C_8H_7ClN_4O_2S$ | C, H, N, Cl, S |
| 7 |  | $-CH_2OCOCH_3$ | *i*-PrOH | 85 | 143 | $C_{10}H_8N_2O_5S$ | C, H, N, S |
| 8 | | $-CH_2OH$ | EtOAc-pe | 95 | 152 | $C_8H_6N_2O_4S$ | C, H, N, S |
| 9 | | -CHO | $C_6H_6$ | 12[d] 76[e] | 178 | $C_8H_4N_2O_4S$ | C, H, N, S |
| 10 |  | -CHO | Dioxane-pe | 49[d] | 185-187 | $C_7H_3N_3O_3S_2$ | C, H, N |
| 11 |  | -CHO | EtOH | 88[f] | 180-182 | $C_8H_6N_4O_3S$ | C, H, N |
| 12 |  | -CH=N-c-$NC_5H_{10}$ | $C_6H_6$-pe | 82 | 175 | $C_{13}H_{14}N_4O_3S$ | C, H, N, S |
| 13 | | -CH=N-c-$NC_6H_{12}$ | $C_6H_6$-pe | 82 | 170-171 | $C_{14}H_{16}N_4O_3S$ | C, H, N, S |
| 14 | | -CH=N-c-$N(CH_2CH_2)_2O$ | $C_6H_6$ | 65 | 178-180 | $C_{12}H_{12}N_4O_4S$ | C, H, N, S |
| 15 | | -CH=N-c-$N(CH_2CH_2)_2S$ | $C_6H_6$ | 56 | 190 | $C_{12}H_{12}N_4O_3S_2$ | C, H, N, S |
| 16 | | -CH=N-c-$N(CH_2CH_2)_2SO_2$ | Dioxane-pe | 64.5 | 232 | $C_{12}H_{12}N_4O_5S_2$ | C, H, N, S |
| 17 |  | -CH=N-c-$NC_5H_{10}$ | $CHCl_3$-pe | 80 | 165-167 | $C_{12}H_{13}N_5O_2S_2$ | C, H, N, S |
| 18 | | -CH=N-c-$N(CH_2CH_2)_2O$ | $CHCl_3$ | 87 | 214 | $C_{11}H_{11}N_5O_3S_2$ | C, H, N, S |
| 19 | | -CH=N-c-$N(CH_2CH_2)_2S$ | Dioxane-pe | 79 | 184-187 | $C_{11}H_{11}N_5O_2S_3$ | C, H, N, S |
| 20 |  | -CH=N-c-$N(CH_2CH_2)_2O$ | EtOH-$H_2O$ | 85 | 204-205 | $C_{12}H_{14}N_6O_3S$ | C, H, N, S |
| 21 | | -CH=N-c-$N(CH_2CH_2)_2SO_2$ | DMF-EtOH | 87 | 236-237 | $C_{12}H_{14}N_6O_4S_2$ | C, H, N, S |

[a] Pure material. [b] pe = petroleum ether, bp 60-80 °C. [c] Lit.[8] mp 131-132 °C. [d] Sommelet reaction. See ref 1. [e] See Experimental Section. [f] Kröhnke reaction. See ref 1.

carboxaldehydes **10** and **11** by the Sommelet or Kröhnke reactions via the appropriate hexaminium or pyridinium salts. The furan compound **4** gave only 12% of the required aldehyde **9** in the Sommelet reaction, the remainder of the product being polymeric material. In another approach to **9**, various attempts to react **4** with pyridine in the first step of the Kröhnke reaction resulted in intractable tars. The reaction of **4** with anhydrous sodium acetate in DMF gave the acetoxymethyl compound **7** and, after acid hydrolysis, the thiazolemethanol **8**. Oxidation of the latter with sodium dichromate in glacial acetic acid provided the aldehyde **9** in a yield of 76%.

The acid-catalyzed condensation of the aldehydes **9–11** with various cyclic hydrazines formed the required hydrazones **12–21** in satisfactory yields.

An examination of the NMR spectra of the hydrazones **12–21**, both in the presence and absence of the NMR "shift" reagents $Eu(fod)_3$ and $Eu(thd)_3$, has provided evidence of a single geometrical isomer of the hydrazone -CH=N- double bond. However, lack of suitable model compounds has precluded the assignment of the exact structure of these compounds.

Table III. IMST[a] of Mice Treated with 2-(5-Nitro-2-heterocyclic)thiazoles

| Compd | $LD_{50}$ in mice, mg/kg ip | $LD_{50}$ in mice, mg/kg po | *Trypanosoma cruzi* (BH) Dose, mg/kg × 5 ip[b] 100 | 50 | 25 | 10 | 5 | Dose, mg/kg × 5 po[b] 200 | 100 | 50 | 25 | 10 | 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **12** | >800 | >1600 | S[c] | S | 42 | 3 | 0 | 32 | 39 | 8 | 0 | | |
| **13** | >800 | >1600 | 39 | 7 | 4 | | | 2 | 0 | | | | |
| **14** | >800 | >1600 | S | S | S | 27 | 0 | S | S | 41 | 19.5 | 0 | 0 |
| **15** | >800 | >1600 | S | S | 18 | 0 | 0 | 18 | 4 | 0 | | | |
| **16** | >800 | >1600 | S | 44 | 18.5 | 5 | 0 | 5 | 3 | 7 | 6 | 0 | |
| **17** | >800 | >1600 | 0 | | | | | 0 | | | | | |
| **18** | >800 | >1600 | 4 | | | | | 0 | | | | | |
| **19** | >800 | >1600 | 4 | 3 | 0 | | | 1 | 0 | | | | |
| **20** | >800 | >1600 | S | 7 | 4 | 0 | | | | 0 | 0 | | |
| **21** | >800 | >1600 | S | S | S | S | 18.5 | S | S | S | S | 14 | 15 |
| **22**[d] | >800 | >1600 | S | 27 | 12 | 0 | 0 | S | 0 | 0 | 0 | 0 | 0 |
| Nifurtimox[e] | >800 | >1600 | S | S | S | S | 2.5 | S | S | S | S | 4 | 0 |

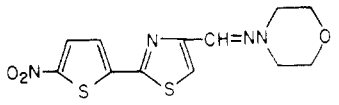
[a] Increase in mean survival time in days. Mean survival time of untreated mice infected with *T. cruzi* (BH) = 14 (±1) days. [b] See Experimental Section in ref 1. [c] S denotes that all the mice in the group survived a minimum of 60 days postinfection with negative parasitaemia. [d] Compound 22 = 4-[[[2-(5-nitro-2-thienyl)-4-thiazolyl]methylene]amino]-morpholine. See ref 1 and Discussion. [e] Nifurtimox = 3-methyl-4-(5-nitro-2-furfurylideneamino)thiomorpholine 1,1-dioxide. See ref 9.

Table IV. Pathology of Recent *Trypanosoma cruzi* Isolates

| Isolate designation | Rel trypanosome count: Blood | Rel trypanosome count: Cardiac muscle | Survival time (days) of untreated mice |
|---|---|---|---|
| "Y" | High | Low | 10-12 |
| "Peru" | Medium/low | Medium | 12-13 |
| BHC/10 | Low | High | 19 |

**Biological Results and Discussion.** The results of screening in mice infected with *Trypanosoma cruzi* (BH strain) and acute toxicity are shown in Table III.

Details of the methods used were given in our earlier paper,[1] in which we described the antitrypanosomal activity of a series of 5-nitro-2-thienyl-4-thiazolecarboxaldehyde hydrazones and, in particular, that of compound **22**.




**22**

A comparison of the nitrofuran analogue **14** with the thiophene **22** showed an increase in activity, **14** being curative at doses down to 25 mg/kg ip and 100 mg/kg po. The modification of the side-chain ring from morpholine to piperidine (**12**) produced a fall in activity. Increasing the ring size to seven atoms in the azepine **13** caused further loss. The replacement of oxygen in the side chain with sulfur (**15**) caused only a slight decrease in ip activity but led to a considerable fall orally. The oxidation of the thiomorpholine side chain to the dioxide **16** resulted in a similar small loss of ip activity and a major loss orally. This loss of oral activity in compounds **15** and **16** may be explained by their relative insolubility, leading to poor oral absorption.

The nitrothiazole compounds **17**–**19** were virtually devoid of activity both ip and po.

The 1-methyl-5-nitroimidazoles **20** and **21** demonstrated an interesting reversal of the order of activity compared to their furan analogues **14** and **16**. Compound **21** was clearly more potent than the most active furan **14** and, indeed, proved to be the most potent compound we have yet found against *T. cruzi*. Compound **21** cured mice infected with the BH strain at levels of 10 mg/kg ip and 25 mg/kg po, comparing well with the standard Nifurtimox.

Table V. IMST[a] of Mice Infected with New Isolates of *Trypanosoma cruzi* and Treated with 21 or Nifurtimox[b]

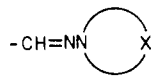
| Isolate | Drug | Dose × 10, mg/kg po: 25 | 10 | 5 |
|---|---|---|---|---|
| "Y" | **21** | S | S | 37 |
| | Nif[b] | 40 | 8 | 0 |
| "Peru" | **21** | S | S | 35 |
| | Nif | S | S | 0 |
| BHC/10 | **21** | 22 | 12 | 4 |
| | Nif | 6.5 | 5.5 | 3 |

[a] See footnote *a* in Table III. [b] See ref 9.

The BH strain of *T. cruzi* has been carried in the laboratory for many years and now has a somewhat modified virulence compared with recent clinical isolates of this parasite. In order to investigate the activity of **21** more realistically, a study of its effect on more recent clinical isolates was undertaken. The three strains selected had the differing pathological characteristics shown in Table IV. The results of a comparison of **21** with the standard drug Nifurtimox after ten daily doses of 25, 10, and 5 mg/kg are given in Table V. It will be seen that **21** compares favorably with the standard against these more virulent strains. However, both **21** and the standard showed considerably less activity against the BHC/10 strain, which involves a high degree of infiltration of the myocardial tissue with "leishmanial" forms of the protozoan. In this form the trypanosome is relatively isolated from the action of chemotherapeutic agents.

In this work and our previous publication, we have demonstrated the antitrypanosomal action of some 4-thiazolecarboxaldehyde hydrazones bearing one of four different nitroheterocyclic rings in the 2 position of the thiazole ring. From these data it is possible to rank these ring systems in their order of antitrypanosomal activity; thus, 1-methyl-5-nitroimidazolyl > 5-nitro-2-furyl > 5-nitro-2-thienyl > 5-nitro-2-thiazolyl. In addition, our findings suggest some further structural features that are

necessary for high activity, namely that of the hydrazone side-chain configuration. This should be of the type



where the ring is six-membered and X is a heteroatom, O, S, or $SO_2$. However, it should be acknowledged that these side-chain variations may simply modify physicochemical parameters affecting absorption, such as solubility or partition coefficient, and not be significant at the binding site.

## Experimental Section

Melting points were obtained by means of a Kofler hot-stage microscope and are uncorrected. All compounds described have IR, UV, and NMR spectra that were fully in accord with their proposed structures. Where microanalyses are indicated by the symbols of the elements only, the results observed were within ±0.4% of the theoretical values. All compounds were recrystallized using decolorizing charcoal and dried to constant weight in a vacuum oven. Evaporations were performed under vacuum using a Büchi Model R rotary evaporator.

**1-Methyl-5-nitroimidazole-2-carbonitrile.**[4] 1-Methyl-5-nitroimidazole-2-carboxaldehyde[7] (75 g, 0.484 mol) was dissolved in a mixture of pyridine (75.5 g, 0.956 mol) and dry $C_6H_6$ (750 mL). *O,N*-Bis(trifluoroacetyl)hydroxylamine[5] (108.9 g, 0.484 mol) was added and the mixture boiled under reflux for 6 h. The solvent was removed under vacuum, and the remaining red oil was taken up in EtOAc, washed with $H_2O$, and dried ($MgSO_4$). The oil remaining after evaporation crystallized on scratching and weighed 65.3 g (89%): mp 80–85 °C (lit.[4] mp 85 °C).

**1-Methyl-5-nitroimidazole-2-thiocarboxamide (3).** The above nitrile (31.0 g, 0.204 mol) was dissolved in molten DMF–HCl complex[1,6] (200 mL) at 40–45 °C and thioacetamide (19.9 g, 0.306 mol) added. The stirred solution was held at 45–50 °C for 6 h and poured into ice–water, giving a bright yellow precipitate, weighing when dry 31 g: mp 145–150 °C. Extraction of the filtrate with $CHCl_3$ and work-up gave a further crop of product (4.45 g): total yield 35.45 g (93.5%). A sample recrystallized from EtOH–petroleum ether (bp 60–80 °C) had mp 148–150 °C. Anal. ($C_5H_6N_4O_2S$) C, H, N, S.

Compounds **1** and **2** were prepared in a similar manner. The cyclizations[1] of these thiocarboxamides **1–3** with 1,3-dichloroacetone can be performed readily in various solvents, e.g., DMF, dioxane, or sulfolane, to give the 4-chloromethylthiazoles **4–6**. *Caution: compounds* **4–6** *are powerful vesicants and should be handled with care!*

**2-(5-Nitro-2-furyl)-4-acetoxymethylthiazole (7).** A mixture of 2-(5-nitro-2-furyl)-4-chloromethylthiazole (**4**) (17.1 g, 0.07 mol) and anhydrous NaOAc (20.5 g, 0.25 mol) in DMF (70 mL) was stirred and heated to 95 °C on a steam bath for 3.5 h. The resulting suspension was diluted with ice–water (250 mL), and the precipitate was washed with $H_2O$ and dried. The solid was extracted with boiling $C_6H_6$ (120 mL), and the extracts were treated with decolorizing charcoal and concentrated to give 15.7 g (85%) of yellow-orange crystals of **7**, mp 140 °C. A sample recrystallized from *i*-PrOH had mp 143 °C. Anal. ($C_{10}H_8N_2O_5S$) C, H, N, S.

**2-(5-Nitro-2-furyl)-4-thiazolemethanol (8).** Compound **7** (15.0 g, 0.056 mol) was boiled with a solution of concentrated HCl (10 mL) and $H_2O$ (10 mL) in dioxane (70 mL) for 45 min. The solution was concentrated to approximately $^1/_3$ volume and $H_2O$ (100 mL) added. The yellow precipitate was washed with $H_2O$ and dried to yield 12.0 g (95%) of **8**. A sample recrystallized from EtOAc–petroleum ether (bp 60–80 °C) melted at 152 °C. Anal. ($C_8H_6N_2O_4S$) C, H, N, S.

**2-(5-Nitro-2-furyl)-4-thiazolecarboxaldehyde (9).** A solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (10.4 g, 0.035 mol) in AcOH (25 mL) was added dropwise to a stirred solution of **8** (22.6 g, 0.1 mol) in AcOH (125 mL) maintained at 60 °C. This temperature was held for 45 min after the addition. The green solution was diluted with $H_2O$ (700 mL) and the fine precipitate collected and washed thoroughly with $H_2O$ to remove chromium salts. After drying the product was extracted with boiling $C_6H_6$ (3 × 500 mL) and the combined extracts were treated with decolorizing charcoal. On evaporation a fluffy yellow solid was obtained weighing 17.1 g (76%). A sample recrystallized from $C_6H_6$ melted at 178 °C. Anal. ($C_8H_4N_2O_4S$) C, H, N, S. The 2,4-dinitrophenylhydrazone had mp 256–258 °C.

The aldehydes **10 and 11** were prepared by the Sommelet or Kröhnke syntheses described earlier[1] from the chloromethylthiazoles **5** and **6**.

**Thiazolecarboxaldehyde Hydrazones 12–22** were readily prepared by boiling the aldehydes **9–11** with the appropriate hydrazines in $CHCl_3$ solution containing a trace of AcOH for 30 min. The hydrazines used were obtained from commercial sources or prepared by published procedures.

**Biological Screening.** This was carried out as described in the previous publication.[1]

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## References and Notes

(1) J. P. Verge and P. Roffey, *J. Med. Chem.*, **18**, 794 (1975).
(2) W. R. Sherman and A. Von Esch, *J. Med. Chem.*, **8**, 25 (1965).
(3) D. W. Henry, *J. Med. Chem.*, **12**, 303 (1969).
(4) C. Rufer, H.-J. Kessler, and E. Schroder, *Chim. Ther.*, **6**, 286 (1971).
(5) J. H. Pomeroy and C. A. Craig, *J. Am. Chem. Soc.*, **81**, 6340 (1959).
(6) E. C. Taylor and J. A. Zoltewicz, *J. Am. Chem. Soc.*, **82**, 2526 (1960).
(7) D. W. Henry and D. R. Hoff, Belgian Patent 661 262 (1965); *Chem. Abstr.*, **64**, 2093 (1966).
(8) S. Minami, A. Fujita, and K. Yamamoto, Japanese Patent 16 787 (1966); *Chem. Abstr.*, **66**, 10927 (1967).
(9) M. Bock, A. Haberkorn, H. Herlinger, K. H. Meyer, and S. Petersen, *Arzneim.-Forsch.*, **22**, 1564 (1972).