1-[(2-Acetoxy)methyl]-5-iodouracil (9). *N,O*-Bis(trimethylsilyl)acetamide (6 mL, 0.024 mol) was added to a mixture of 5-iodouracil (2.4 g, 0.01 mol) and **6** (4 g, 0.015 mol) in dry CH_2Cl_2 (30 mL). After overnight stirring *in the dark*, the mixture was cooled in an ice bath, $SnCl_4$ (0.6 mL, 0.024 mol) was added, and the temperature was allowed to come to 25 °C overnight. After the usual workup, the crude oily product was passed through a silica gel column (50 g), using 2:1 $CHCl_3$–acetone as the eluent. Appropriate TLC-homogeneous fractions were pooled and evaporated to give the product as a pale pink glass (2.5 g, 75%), which solidified on standing: mp 110–113 °C; TLC (silica gel, 2:1 $CHCl_3$–acetone) R_f 0.53; NMR (Me_2SO-d_6) τ 7.9 (s, CH_3CO), 6.0 (A_2B_2 pattern, $AcOCH_2CH_2O$), 4.9 (s, OCH_2N), 2.3 (s, C_6 H). Anal. ($C_9H_{11}N_2O_5I$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-5-iodouracil (11). Sodium hydroxide (1 N, 15 mL) was added to an ice-cold solution of **9** (2.4 g, 0.0068 mol) in MeOH (50 mL), and the mixture was stirred at room temperature for 2 h. Cooling was resumed, and 1 N HCl was added carefully until the pH came to 4.0. Solvent evaporation under reduced pressure and dry-column chromatography of the residue on silica gel (50 g) with 9:1 $CHCl_3$–EtOH as the eluent afforded the product as a colorless powder (1.6 g, 76% yield): mp 165–175 °C; TLC (siliica gel, 9:1 $CHCl_3$–EtOH) R_f 0.33; UV λ_{max} (95% EtOH) 280 nm; NMR (Me_2SO-d_6) τ 4.5 (s, CH_2CH_2), 4.9 (NCH_2O), 1.7 (s, C_6 H). Anal. ($C_7H_9N_2O_4I$) C, H, N, I.

Acknowledgment. This work was supported in part by Project Grant CA 23151 from the National Cancer Institute (NIH). The authors are indebted to Linda Anderson and Gerda Swedowsky for their technical assistance in obtaining the in vivo antitumor activity data and cell culture data, respectively.

N*-N*-S* Tridentate Ligand System as Potential Antitumor Agents

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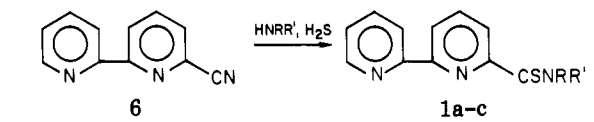
Received January 14, 1981

Compounds containing an N*-N*-S* tridentate ligand were synthesized and tested for antitumor activity against P-388 lymphocytic leukemia in mice. Of these, only 2,2′-bipyridyl-6-carbothioamide (**1a**) showed antitumor activity at relatively high dosage levels. Compound **1a** was also evaluated against L-1210 and S180 cells in culture and found to have significant activity.

Several α-N-heterocyclic carboxaldehyde thiosemicarbazones and their iron and copper complexes have been tested for antitumor activity.[1-6] These agents inhibit ribonucleoside diphosphate reductase, an obligatory enzyme in the pathway of synthesis of precursors of DNA. These thiosemicarbazones coordinate with ferrous and ferric ions through the N*-N*-S* tridentate ligand to give iron complexes. The inhibition occurs because the thiosemicarbazones chelate the iron necessary for the enzyme or because the iron complexes block the enzyme.[7,8]

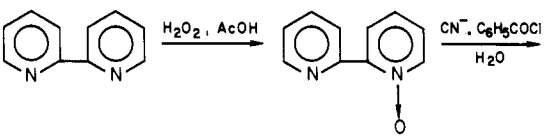
In order to extend the knowledge of the structure–activity relationships of these antitumor agents, a series of new compounds containing the N*-N*-S* tridentate ligand system has been synthesized. These derivatives can be divided into three groups (Chart I). The first group (a) includes thioamides of 2,2′-bipyridyl and of 1,10-phenanthroline. The second group (b) includes iminomethyl derivatives of 6-pyridine-2-carbothioamide. With these compounds only the second one of the two nitrogen atoms of the ligand belongs to a heterocyclic ring. The third group (c) includes imino derivatives of thiosemicarbazones of α,α-dicarbonyl compounds. In this case, none of the two sp^2 hybridized nitrogen atoms of the ligand belongs to any heterocyclic ring.

Scheme I



6 1a-c

Scheme II



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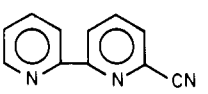

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Chemistry. In the first group, the 1,10-phenanthroline-2-carbothioamide (**2**) is a compound previously described and studied as a tridentate ligand of iron(II).[9] The 2,2′-bipyridyl-6-carbothioamides **1a–c** were synthesized from 2,2′-bipyridyl-6-carbonitrile (**6**) (Scheme I).

The 2,2′-bipyridyl-6-carbonitrile (**6**) was prepared by reacting 2,2′-bipyridyl 1-oxide (**5**) with sodium cyanide and benzoyl chloride in water; **5** was synthesized by oxidizing 2,2′-bipyridyl with H_2O_2 in AcOH (Scheme II). This method gave a higher total yield and used fewer steps than the one described by Case.[10]

In the second group, the compounds **3a–e** and **11** were synthesized from 2-cyano-6-(acetoxymethyl)pyridine (**7**)

(1) E. J. Blanz, Jr., F. A. French, J. R. Doamaral, and D. A. French, *J. Med. Chem.*, **13**, 1124 (1970).
(2) F. A. French, E. J. Blanz, Jr., S. C. Shaddik, and R. W. Brockman, *J. Med. Chem.*, **17**, 172 (1974).
(3) I. Antonini, F. Claudi, G. Cristalli, P. Franchetti, M. Grifantini, and S. Martelli, *Eur. J. Med. Chem.*, **14**, 89 (1979).
(4) W. Antholine and D. H. Petering, *Proc. Am. Assoc. Cancer Res.*, **15**, 63 (1974).
(5) K. C. Agrawal, B. A. Booth, E. C. Moore, and A. C. Sartorelli, *Proc. Am. Assoc. Cancer Res.*, **15**, 289 (1974).
(6) W. E. Antholine, J. M. Knight, and D. H. Petering, *J. Med. Chem.*, **19**, 339 (1976).
(7) A. C. Sartorelli, K. C. Agrawal, and E. C. Moore, *Biochem. Pharmacol.*, **20**, 3119 (1971).
(8) F. A. French, E. J. Blanz, Jr., J. R. Doamaral, and D. A. French, *J. Med. Chem.*, **13**, 1117 (1970).
(9) H. A. Goodwin, F. E. Smith, E. König, and G. Ritter, *Aust. J. Chem.*, **26**, 521 (1973).
(10) F. H. Case, *J. Org. Chem.*, **31**, 2398 (1966).

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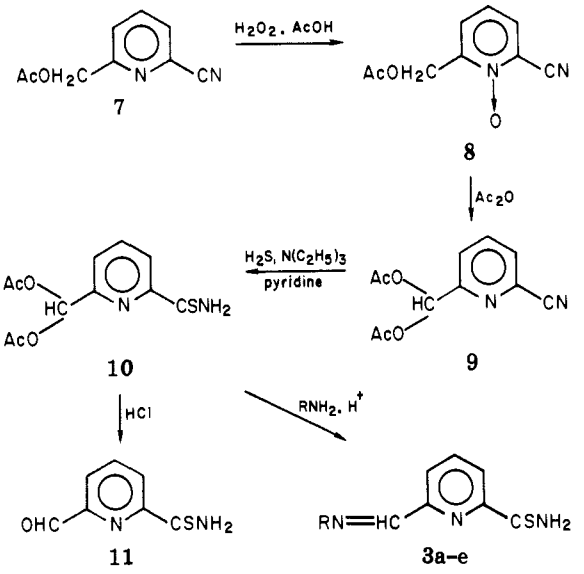
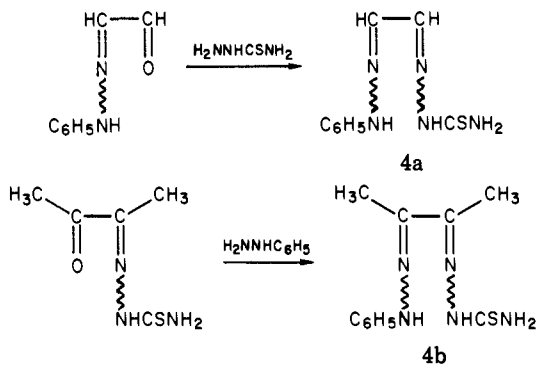
Scheme III



Scheme IV



(Scheme III). Treatment of **7** with hydrogen peroxide and acetic acid gave 2-cyano-6-(acetoxymethyl)pyridine *N*-oxide (**8**), which was then acetylated with Ac_2O to yield **9**. Reaction of **9** with hydrogen sulfide in a mixture of triethylamine and pyridine at room temperature afforded 6-(diacetoxymethyl)pyridine-2-carbothioamide (**10**). Treatment of **10** with various amine derivatives gave compounds **3a–e**. Acidic hydrolysis of **10** yielded **11**.

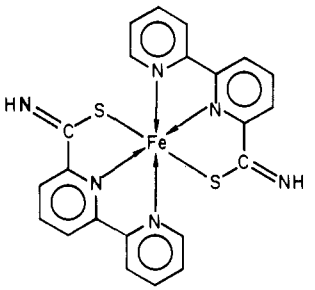
In the third group, the thiosemicarbazones of the phenylhydrazones of glyoxal (**4a**) and of diacetyl (**4b**) were obtained by treatment of glyoxal 2-phenylhydrazone and diacetyl-2-thiosemicarbazone with thiosemicarbazide and phenylhydrazine, respectively (Scheme IV). The thiosemicarbazone of the diacetyl monooxime (**4c**) is a compound previously described in the literature as an N*-N*-S* tridentate ligand.[11] The addition of 2,2′-bipyridyl-6-carbothioamide (**1a**) or of the *N*-phenylamine of 6-formylpyridine-2-carbothioamide (**3e**) to an alcoholic solution of $FeSO_4 \cdot 7H_2O$ gave the dark-blue addition products **12** and **14**. In each case a 1:2 metal to ligand

$$[Fe(HL)_2]SO_4$$
12, L = **1a**
14, L = **3e**

stoichiometry was found by elementary analysis. In aqueous medium, the addition products yielded a blue solution, which is acidic because of the formation of protons according to the reaction:

$$[Fe(HL)_2]^{2+} \rightleftarrows FeL_2 + 2H^+$$

When OH^- ions were added, the equilibrium was displaced to the right and the dark-blue inner complex salts (**13** and **15**) precipitated.



13

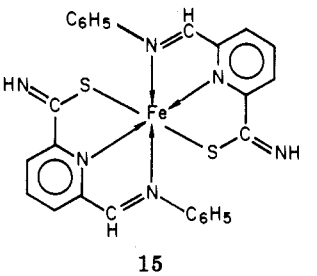


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Table I. Antitumor Activity against P-388 Leukemia in Mice

no.	dose,[a] mg/kg	T/C, %	body wt change (T/C), g
1a	400	143	−0.8/5.0
	200	125	1.5/5.0
	100	112	1.5/5.0
1b	400	toxic	
	200	83	1.0/1.3
	100	91	−0.2/1.3
1c	400	91	0.8/1.3
	200	95	2.1/1.3
	100	95	3.3/1.3
2	400	112	−2.5/5.0
	200	106	1.1/5.0
	100	100	1.5/5.0

[a] Dose was administered on days 1, 5, and 9 to groups of six mice beginning 24 h after tumor transplantation. Compounds 3a–d and 4a–c were inactive at doses of 400 mg/kg, and 3c was inactive at 300 mg/kg.

Table II. Growth Inhibition of Cultured L-1210 and Sarcoma 180 after 48-h Exposure to 2,2′-Bipyridyl-6-carbothioamide (1a)

	L-1210 % inhibn		sarcoma 180 % inhibn	
concn, mol/mL	trial 1	trial 2	trial 1	trial 2
1.6×10^{-8}	95	93	85	60
4×10^{-9}	51	32	35	10

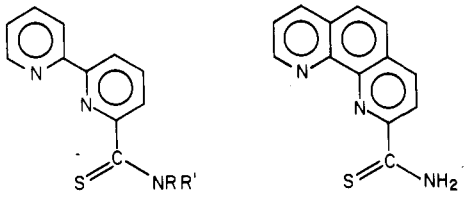
Biological Activity and Discussion

The ligands 1–4 were tested for antitumor activity. The compounds were screened against P-388 lymphocytic leukemia in mice by the Istituto di Ricerche Farmacologiche "Mario Negri", Milan (Italy). CDF_1 mice were injected ip with 10^6 P-388 lymphocytic leukemia cells on day 0 and were treated ip with a suspension in klucel or in saline and Tween 80 of the specific drug dose on days 1, 5, and 9.[14] The results (Table I) indicate that only the 2,2′-bipyridyl-6-carbothioamide (**1a**) showed antitumor activity at relatively high dosage. Compound **1a** was also screened against murine leukemia L-1210 and murine sarcoma S180 cells in culture as described by Lin et al.[15] The solvent

(11) A. V. Ablov, I. B. Bersuker, and V. I. Gol'danskii, *Dokl. Akad. Nauk. SSSR*, **152**(6), 1391 (1963); *Chem. Abstr.*, **60**, 6329*h* (1964).
(12) A. V. Ablov and N. I. Belichuk, *Russ. J. Inorg. Chem.*, 14, 93 (1969).
(13) I. Murase, *Nippon Kagaku Zasshi*, **77**, 682 (1956).
(14) R. I. Geran, N. H. Greenberg, M. M. Macdonald, A. M. Schumacher, and B. J. Abbot, *Cancer Chemother. Rep., Part. 3*, 3(2), 9 (1972).
(15) T. S. Lin, J. P. Neenan, Y. C. Cheng, W. H. Prusoff, and D. C. Ward, *J. Med. Chem.*, **19**, 495 (1976).

Chart I

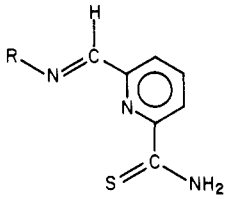
Group a



1a, R = R' = H
b, R = CH_3; R' = H
c, R = CH_3; R' = CH_3

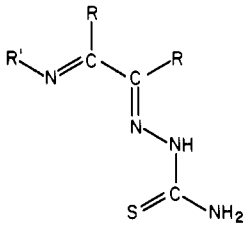
2

Group b



3a, R = OH
b, R = $NHCONH_2$
c, R = $NHCSNH_2$
d, R = NHC_6H_5
e, R = C_6H_5

Group c



4a, R = R = H; R' = NHC_6H_5
b, R = R = CH_3; R' = NHC_6H_5
c, R = R = CH_3; R' = OH

system for **1a** in these test methods was H_2O–Me_2SO (99:1). The percent inhibition in the drug-treated cultures relative to the control is shown in Table II.

The inactivity of **2**, a rigid analogue of **1a**, indicates the necessity of the free rotation between the two nitrogen atoms of the N*-N*-S* systems. The N*-N*-S* tridentate ligands coordinate metals through the thiol form.[9-12,16] Actually the thiol form is possible for **1a**, difficult for **1b** because there is steric interference between CH_3 and SH groups as can be seen using Stuart–Briegleb model studies, and impossible for **1c** without losing their aromaticity. In agreement with this finding, **1b** and **1c** were inactive.

In all the compounds found to be active, the first nitrogen atom of the N*-N*-S* system belongs to a heterocyclic ring. In **3a–e** and **4a–c** the nitrogen atom does not belong to a heterocyclic ring and, therefore, these compounds are not active. These facts suggest that the ribonucleoside diphosphate reductase should have a specific site for the heterocyclic ring to which the first nitrogen atom of the N*-N*-S* tridentate ligand belongs.

Experimental Section

Melting points were determined on a Büchi apparatus and are uncorrected. NMR spectra were obtained with a JEOL JNM C60-HL spectrometer. The IR spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. The UV spectra were recorded on a Perkin-Elmer Model 575 spectrophotometer. The data from NMR, IR, and UV spectroscopy were as expected. TLC was carried out on TLC plates prepared with Merck GF_{254} silica gel. For column chromatography, silica gel 60 from Merck was used. Analyses were performed with a Perkin-Elmer Model 240 CHN analyzer; analyses indicated by elemental symbols where within 0.4% of the theoretical values.

2,2'-Bipyridyl *N*-Oxide (5). Bipyridyl (3 g, 19.2 mmol) was heated with a mixture of 4.5 mL of 36% H_2O_2 and 10 mL of glacial AcOH at 85 °C. After 3 h the solution was evaporated to a thick syrup, dissolved in 100 mL of $CHCl_3$, and treated with K_2CO_3 and a small amount of water to form a paste. The paste was extracted several times with $CHCl_3$, the $CHCl_3$ layer was dried (K_2CO_3), the solvent was evaporated under vacuum, and the residue was chromatographed on a silica gel column, eluting with MeOH–EtOAc (1:4). Evaporation of the eluate gave 1.6 g (48.4%) of a solid: mp 57–58 °C (lit.[13] 58.5–59.5 °C).

6-Cyano-2,2'-bipyridyl (6). Benzoyl chloride (8.47 g, 0.06 mol) was added dropwise in 20 min, with stirring, to a mixture of **5** (5.33 g, 31 mmol) and KCN (7 g, 0.107 mol) in 110 mL of H_2O. The mixture was stirred overnight at room temperature and then it was extracted several times with EtOAc. The EtOAc solution was evaporated and the residue obtained was chromatographed on a silica gel column, eluting with a mixture C_6H_6–EtOAc (4:1). Evaporation of the eluate gave 3.5 g (62.4%) of a solid, mp 129–130 °C (lit.[10] 130–131 °C).

2,2'-Bipyridyl-6-carbothioamide (1a). 6-Cyano-2,2'-bipyridyl (**6**; 1 g, 5.5 mmol) dissolved in 30 mL of anhydrous ethanol was added to 30 mL of anhydrous ethanol through which ammonia gas had been passed for 30 min. Hydrogen sulfide gas was bubbled through the resulting solution until the starting material disappeared [TLC, C_6H_{12}–EtOAc (3:2)]. The solution was then diluted with H_2O (200 mL) and extracted several times with EtOAc. The EtOAc extracts were dried (Na_2SO_4) and evaporated under vacuum to leave a residue which was chromatographed on a silica gel column, eluting with a mixture C_6H_6 and EtOAc (4:1). Evaporation of the first eluate gave a solid, which was recrystallized from EtOH to yield 0.8 g (67.3%) of **1a**: mp 177–178 °C. Anal. ($C_{11}H_9NS$) C, H, N, S.

2,2'-Bipyridyl-6-*N*-methylcarbothioamide (1b). Compounds **6** (1 g, 5.5 mmol) was dissolved in a solution of methylamine in 30 mL of anhydrous ethanol. Hydrogen sulfide gas was bubbled through the resulting solution until the starting material disappeared [TLC, C_6H_{12}–EtOAc (3:2)]. A moderate current of air was then bubbled through the solution for 15 h. The filtered solution was evaporated and the residue was extracted several times with EtOAc and then with CH_3OH. The combined extracts were evaporated and the crude product was chromatographed on a silica gel column eluting with a mixture C_6H_{12}–EtOAc (3:2). Evaporation of the fractions containing **1b** gave 1 g (79%) of product, which was recrystallized from ethanol, mp 93–94 °C. Anal. ($C_{12}H_{11}NS$) C, H, N, S.

2,2'-Bipyridyl-6-*N*,*N*-dimethylcarbothioamide (1c). Compound **1c** was prepared from **6** (1 g, 5.5 mmol) and dimethylamine as above. Evaporation of the ethanol gave a residue which was extracted several times with EtOAc. Evaporation of the filtered extracts yielded a crude product, which was chromatographed on a silica gel column eluting with C_6H_{12}–EtOAc (3:2). Evaporation of the second eluate yielded 0.67 g (50%) of **1c**, mp 78–79 °C. Anal. ($C_{13}H_{13}NS$) C, H, N, S.

2-Cyano-6-(acetoxymethyl)pyridine *N*-Oxide (8). 2-Cyano-6-(acetoxymethyl)pyridine (6 g, 34 mmol) was heated with a mixture of 4 mL of 36% H_2O_2 and 30 mL of glacial AcOH at 80–90 °C. After 3 h, an additional amount (2 mL) of 36% H_2O_2 was added and the heating was continued for 3 h. Evaporation of the solvent gave a residue which was chromatographed on a silica gel column, eluting with a mixture C_6H_6–EtOAc (7:3). Evaporation of the fractions containing **8** afforded 5.4 g (82.5%) of product, mp 113–114 °C (from ethanol). Anal. ($C_9H_8N_2O_3$) C, H, N.

2-Cyano-6-(diacetoxymethyl)pyridine (9). A solution of 5.4 g (28 mmol) of **8** in 25 mL of Ac_2O was refluxed for 6 h. Evaporation of the Ac_2O gave a residue which was chromatographed on a silica gel column, eluting with C_6H_6–EtOAc (9:1). Evaporation of the second eluate yielded 3.8 g (57.7%) of **9**, mp 67–68 °C (from ethanol). Anal. ($C_{11}H_{10}N_2O_4$) C, H, N.

(16) M. Mathew and G. J. Palnik, *J. Am. Chem. Soc.*, 91, 6310 (1969).

6-(Diacetoxymethyl)pyridine-2-carbothioamide (10). Compound **9** (6 g, 25 mmol) was dissolved in a solution of 5.5 mL of $(C_2H_5)_3N$ in 50 mL of anhydrous pyridine. Hydrogen sulfide gas was bubbled through the solution for 1 h. The solution was then diluted with H_2O (200 mL) and extracted several times with EtOAc. The EtOAc extracts were dried (Na_2SO_4) and evaporated under vacuum to leave a residue which was chromatographed on a silica gel column, eluting with a mixture C_6H_6–EtOAc (4:1). Evaporation of the fractions containing **10** gave 5.42 g (79%) of a solid which was recrystallized from a mixture of EtOH and H_2O, mp 100–102 °C. Anal. ($C_{11}H_{12}N_2O_4S$) C, H, N, S.

6-Formylpyridine-2-carbothioamide (11). A solution of **10** (0.9 g, 3.35 mmol) in 38 mL of a mixture EtOH–H_2O (1:1) containing 0.6 mL of concentrated HCl was refluxed for 30 min. The solution was neutralized with 2 N Na_2CO_3 and extracted several times with EtOAc. Evaporation of the solvent afforded a residue which was chromatographed on a short silica gel column, eluting with EtOAc. Evaporation of the fractions containing **11** gave 0.260 g (46.4%) of a solid, mp 147–149 °C. Anal. ($C_7H_6N_2OS$) C, H, N, S.

6-Formylpyridine-2-carbothioamide Oxime (3a). 6-(Diacetoxymethyl)pyridine-2-carbothioamide (1 g, 3.72 mmol) and NH_2OH·HCl (0.5 g, 7.19 mmol) in 50 mL of ethanol were refluxed for 30 min. The cold solution was neutralized with $NaHCO_3$ to pH 5, diluted with H_2O, and extracted several times with $CHCl_3$. Evaporation of the extracts left a residue which was chromatographed on a silica gel column, eluting with a mixture C_6H_6–EtOAc (9:1). Evaporation of the first eluate yielded **3a** (0.51 g, 76%), which was recyrstallized from ethanol, mp 185–186 °C. Anal. ($C_7H_7N_3OS$) C, H, N, S.

6-Formylpyridine-2-carbothioamide Semicarbazone (3b). **10** (1 g, 3.72 mmol) and semicarbazide (0.84 g, 11.1 mmol) in 50 mL of ethanol were refluxed for 5 h. A solid precipitated, which was filtered and recrystallized from ethylene glycol monomethyl ether to give 0.66 g (70%) of **3b**, mp 245–247 °C. Anal. ($C_8H_9N_5OS$) C, H, N, S.

6-Formylpyridine-2-carbothioamide Thiosemicarbazone (3c). **10** (1 g, 3.72 mmol) and thiosemicarbazide (0.48 g, 5.2 mmol) in 50 mL of ethanol and 0.5 mL of concentrated HCl were refluxed for 5 h. A solid precipitated, which was filtered and recrystallized from ethylene glycol monomethyl ether to yield 0.71 g (70%) of **3c**, mp 260–262 °C. Anal. ($C_8H_9N_5S_2$) C, H, N, S.

6-Formylpyridine-2-carbothioamide Phenylhydrazone (3d). **10** (1 g, 3.72 mmol) and phenylhydrazine hydrochloride (1.1 g, 8.8 mmol) in 50 mL of ethanol were refluxed for 8 h. The solution was evaporated to half volume and neutralized to pH 6 with 2 N $NaHCO_3$. A solid precipitated, which was filtered and recrystallized from ethanol to afford 0.71 g (65%) of **3d**, mp 193–194 °C. Anal. ($C_{13}H_{12}N_4S$) C, H, N, S.

6-Formylpyridine-2-carbothioamide *N*-Phenylimine (3e). **10** (1.1 g, 4.1 mmol) and aniline (2.5 g, 26.8 mmol) in 100 mL of anhydrous ethanol were refluxed for 2 h. Evaporation of the solvent gave a residue which was chromatographed on a silica gel column, eluting with C_6H_6–EtOAc (9.5:5). Evaporation of the eluates containing the first fraction yielded an oil, which under vacuum changed into a solid. The solid was washed with Et_2O, filtered, and dried under vacuum to give 0.3 g (30.3%) of **3e**, mp 136–138 °C. Anal. ($C_{13}H_{11}N_3S$) C, H, N, S.

Glyoxal 2-Phenylhydrazone Thiosemicarbazone (4a). Glyoxal 2-phenylhydrazone (1 g, 6.09 mmol) and thiosemicarbazide (0.61 g, 6.69 mmol) in 50 mL of ethanol were refluxed for 2 h. Evaporation of the solvent left a residue which was chromatographed on a silica gel column, eluting with C_6H_6–EtOAc (8:2). Evaporation of the fractions containing **4a** gave 1 g (66.9%) of product, mp 111–113 °C (from EtOAc–C_6H_6). Anal. ($C_9H_{11}N_5S$) C, H, N, S.

Dimethylglyoxal 2-Phenylhydrazone Thiosemicarbazone (4b). Dimethylglyoxal 2-thiosemicarbazone (1 g, 6.1 mmol) and phenylhydrazine (0.73 g, 6.8 mmol) in 50 mL of ethanol were refluxed for 1 h. After the solution was cooled, a solid precipitated, which was filtered and recrystallized from ethanol to yield 1 g (63.8%) of **4b**, mp 220–221 °C. Anal. ($C_{11}H_{15}N_5S$) C, H, N, S.

Bis(2,2′-bipyridyl-6-carbothioamide)iron(II) Sulfate (12). To 1 g (4.6 mmol) of **1a** dissolved in 30 mL of hot ethanol were added 0.645 g (2.3 mmol) of $FeSO_4·7H_2O$ dissolved in 2 mL of water. The addition product immediately precipitated as a dark-blue solid, which was filtered, washed with ethanol, and dried under vacuum: yield 66%; UV λ_{max} (methanol) 265 nm (log ϵ 4.30), 275 (4.71), 313 (4.34), 588 (3.65). Anal. ($C_{22}H_{16}FeN_6S_2·H_2SO_4$) C, H, N, S.

Bis(2,5′-bipyridyl-6-carbothioamide)iron(II) (13). A solution of 1 g of **12** in 10 mL of 0.5 N NaOH was shaken for 10 min. A dark blue solid precipitated, filtered, washed several times with water, and dried under vacuum: yield 99%; UV λ_{max} (methanol) 259 nm (log ϵ 4.50), 308 (4.45), 588 (4.14). This compound is paramagnetic. Anal. ($C_{22}H_{16}FeN_6S_2$) C, H, N, S.

Bis(6-formylpyridine-2-carbothioamide *N*-phenylimine)iron(II) Sulfate (14). To 0.7 g (2.9 mmol) of **3e** dissolved in 40 mL of ethanol was added 0.404 g (1.45 mmol) of $FeSO_4·7H_2O$ in 4 mL of water. The solution was shaken for 10 min and then was evaporated under vacuum. The dark-blue solid obtained was extracted several times with ethyl acetate, and then the product was filtered and dried under vacuum: yield 65%; UV λ_{max} (methanol) 228 nm (log ϵ 4.58), 317 (4.37), 634 (3.69). Anal. ($C_{28}H_{22}FeN_6S_2·H_2SO_4$) C, H, N, S.

Bis(6-formylpyridine-2-carbothioamide *N*-phenylimine)iron(II) (15). A solution of 0.24 g of **14** in 4 mL of 0.5 N NaOH was shaken for 10 min. A dark blue solid precipitated, filtered, and washed with water: yield 98%; UV λ_{max} (methanol) 226 nm (log ϵ 4.60), 318 (4.32), 637 (3.72). Anal. ($C_{26}H_{20}FeN_6S_2$) C, H, N, S.

Acknowledgment. Financial support from the Italian National Research Council is gratefully acknowledged.

Synthesis and Antineoplastic Activity of Mitosene Analogues of the Mitomycins[1a]

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A series of 1-substituted mitosene analogues of the mitomycin antitumor antibiotics was prepared by total synthesis and screened for activity against P388 leukemia in mice. In general, analogues with moderately good leaving groups (mostly esters) at the 1 position were active, whereas analogues without such substituents were inactive or barely active. These results lend support to the idea that mitosenes with leaving groups at position 1 are capable of bifunctional alkylation of DNA in a manner similar to that of mitomycin C. The most active mitosenes were equal in potency (minimum effective dose) to a corresponding aziridinomitosene, but they were less effective in prolonging life span.

Mitomycin C (1) has been shown to cross-link double-helical DNA after reduction to the corresponding hydroquinones **2** (Scheme I).[2] This process, known as bioreductive alkylation,[3] is thought to be the main lethal event

0022-2623/81/1824-1184$01.25/0