(24 mL, 240 mmol), and formalin (18 mL, 230 mmol) were refluxed in 240 mL of EtOH under nitrogen for 3 h. The solvent was removed under reduced pressure, a small amount of EtOH was added, and the product was allowed to crystallize overnight. The product was collected and rinsed with ice-cold EtOH to yield 7.2 g (19 mmol, 24%) of **2c**, mp 133–134 °C. A small portion of the product was recrystallized from EtOH, mp 135–135.5 °C. Anal. ($C_{24}H_{40}N_2O_2$) C, H, N.

1,4-Dihydroxy-2,3-naphthalenedicarboxaldehyde (3b). Naphthoquinone (7 g, 44 mmol) was hydrogenated at 30 psi in 300 mL of EtOH in the presence of 1 g of 10% Pd/C as catalyst. The catalyst was removed by filtration, and to the filtrate was added formalin (15 mL, 190 mmol) and piperidine (18 mL, 180 mmol). The mixture was heated to 60 °C for 1 h under N_2. After the mixture cooled, the precipitate was collected and washed with ligroin to give 3.8 g (11 mmol, 25%) of **2b**, mp 166–168 °C dec (lit.,[16] ~160 °C dec). This material was oxidized without further purification. To the piperidine derivative (2 g, 5.6 mmol) in 20 mL of warm AcOH was added CrO_3 (1 g, 0.01 mol) in 20 mL of warm 50% aqueous AcOH. The solution was heated for approximately 10 min until an exothermic reaction occurred. The reaction mixture was poured into ice–water to yield a brown precipitate, which was collected, washed with H_2O, dried, and purified by preparative TLC ($CHCl_3$/silica gel). Recrystallization from EtOH gave 0.2 g (0.93 mmol, 16% from **2a**) of yellow crystals, mp 186–187 °C. Anal. ($C_{12}H_8O_4$) C, H.

3,6-Dihydroxy-4,5-dipropylphthalaldehyde (3c). 2,3-Dipropyl-5,6-bis(piperidinomethyl)-1,4-dihydroquinone (**2c**; 2.58 g, 6.6 mmol) in 10 mL of AcOH was heated to 80 °C and CrO_3 (1.11 g, 0.011 mol) in 10 mL of warm 50% aqueous AcOH was added at a rate that maintained the reaction temperature between 80 and 85 °C. Following this addition and completion of the resulting exothermic reaction, the mixture was poured onto ice. After the ice had melted, the resulting precipitate was collected, rinsed with ice-cold MeOH, and subjected to column chromatography on silica gel using toluene as the eluent. The toluene was evaporated under reduced pressure, taking care to not sublime the product, and the resulting bright yellow residue was crystallized from MeOH to give 0.885 g (3.5 mmol, 53%) of **3c**, mp 106.5–107.5 °C. Anal. ($C_{14}H_{18}O_4$) C, H.

4,5-Dimethyl-3-hydroxy-6-methoxyphthalaldehyde (4). A solution of **3a** (0.20 g, 1.0 mmol) in 25 mL of dry acetone in which K_2CO_3 (0.6 g, 4 mmol) had been suspended was refluxed under argon with stirring. Me_2SO_4 (0.11 mL, 1.2 mmol) was added and the mixture was refluxed for 1.5 h. Acetone-insoluble material was removed by filtration and the solvent was evaporated under reduced pressure. The residue was eluted from a column of silica gel with toluene. Material in the second peak (the first peak was unreacted **3a**) was further purified by preparative silica gel TLC developed with $CHCl_3$. The major band was extracted with acetone, the solvent was removed under reduced pressure, and the residue was stored over P_2O_5 under high vacuum. After 6 h, the product was sublimed under high vacuum at approximately 70 °C to yield 0.023 g (0.11 mmol, 11%) of **4**, mp 71–73 °C. Anal. ($C_{11}H_{12}O_4$) C, H.

3,6-Dimethoxy-4,5-dimethylphthalaldehyde (5). Compound **3a** (0.20 g, 1.0 mmol) was refluxed in 25 mL of dry acetone in which 0.6 g of K_2CO_3 had been suspended as described above for the synthesis of **4**. Me_2SO_4 (0.22 mL, 2.3 mmol) was added and the mixture was refluxed for 1 h. Additional Me_2SO_4 (0.22 mL, 2.3 mmol) was added and the reaction was continued for 2 h. The reaction mixture was cooled, filtered, and evaporated under reduced pressure. The residue was suspended in 2 to 3 mL of ice-cold acetone and filtered to give 80 mg (0.35 mmol, 35%) of **5**, mp 130 °C dec. The sample for elemental analysis was obtained by high vacuum sublimation at approximately 100 °C. Anal. ($C_{12}H_{14}O_4$) C, H.

3,6-Dihydroxy-4,5-dimethylphthalaldehyde Hemialdal Tetraacetate (6). A solution of **3a** (0.37 g, 1.9 mmol) in 10 mL of dry pyridine and 5 mL of Ac_2O (53 mmol) was stirred at room temperature overnight. The solvent and excess Ac_2O were evaporated under reduced pressure. EtOH was added and evaporated three times to remove traces of pyridine. The crystalline product was suspended in cold MeOH (5 mL), collected by vacuum filtration, and rinsed twice with cold MeOH to yield 0.6 g (1.6 mmol, 83%) of **6**, which melted over a wide range beginning at approximately 140 °C. Although the product was probably a mixture of isomers, it gave a single spot on silica gel TLC developed in either $CHCl_3$ or toluene. A sample was recrystallized from EtOH. The NMR spectrum and melting point of this product were identical with those of the nonrecrystallized product. Anal. ($C_{18}H_{20}O_9$) C, H.

Hydrolysis of **6** yielded the parent dialdehyde, **3a**. A 10^{-2} M solution of **6** in Me_2SO was immediately diluted to a concentration of 10^{-3} M with PBS, pH 7.3. At each of several time points from 0.75 to 45 min, an aliquot of the solution was diluted 10-fold in EtOH, and the absorption of the ethanolic solution at 400 nm was measured using a Gilford 2443-A rapid sampler attached to a Beckman DU spectrophotometer to monitor the appearance of **3a**.

Acknowledgment. This work was supported in part by U.S. Public Health Service Grants CA-02817 and CA-16359 from the National Cancer Institute. The authors are grateful to Dr. William Loh for assistance in obtaining some of the analytical data.

Synthesis and Antineoplastic Activity of Phenyl-Substituted Benzenesulfonylhydrazones of 2-Pyridinecarboxaldehyde 1-Oxide[1]

William Loh, Lucille A. Cosby, and Alan C. Sartorelli*

Department of Pharmacology and Developmental Therapeutics Program, Comprehensive Cancer Center, Yale University School of Medicine, New Haven, Connecticut 06510. *Received January 7, 1980*

A variety of derivatives of 2-pyridinecarboxaldehyde 1-oxide benzenesulfonylhydrazone, containing substituents on the benzene or pyridine rings as well as on the nitrogen atom which is bonded directly to the sulfonyl group, have been synthesized. The antineoplastic activity of these compounds has been assessed in mice bearing either leukemia L1210 or P388. The most potent agents in this series were 2,4-dimethoxy-, 3,4-dimethoxy-, and 2,4,6-trimethylbenzenesulfonylhydrazone of 2-pyridinecarboxaldehyde 1-oxide, all causing disappearance of tumors in 20–80% of leukemia-bearing mice.

Phenylsulfonylhydrazones of 2-pyridinecarboxaldehyde 1-oxide have been demonstrated by our laboratory[2-5] to possess significant antineoplastic activity against a variety of transplanted murine neoplasms. It was previously ob-

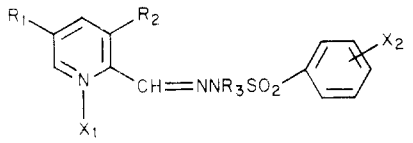
(1) Presented in part before the Division of Medicinal Chemistry at the 178th National Meeting of the American Chemical Society, Washington D.C., Sept 1979. This work was supported by U.S. Public Health Service Grants CA-02817 and CA-16359 from the National Cancer Institute.

(2) A. C. Sartorelli, K. C. Agrawal, B. A. Booth, J. Pittman, D. G. Bartholomew, and A. D. Broom, *J. Med. Chem.*, **19**, 830 (1976).

(3) K. C. Agrawal and A. C. Sartorelli, *J. Med. Chem.*, **21**, 218 (1978).

0022-2623/80/1823-0631$01.00/0

Table I. Physical Constants of Phenylsulfonylhydrazones of 2-Pyridinecarboxaldehyde 1-Oxide



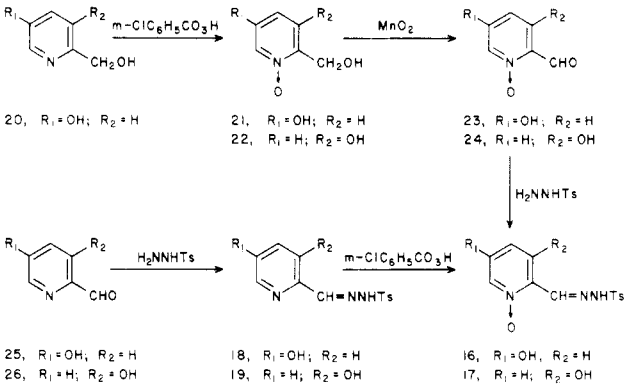
no.	R_1	R_2	R_3	X_1	X_2	mp, °C	recrystn solvent	yield, %	formula[a]
1	H	H	H	O	3-CO_2H	158[b]	EtOH-H_2O	67	$C_{13}H_{11}N_3O_6S$
2	H	H	H	O	4-CO_2H	182[b]	EtOH-H_2O	70	$C_{13}H_{11}N_3O_5S$
3	H	H	H	O	4-CH_2CO_2H	142-143[b]	EtOH-H_2O	71	$C_{14}H_{13}N_3O_5S$
4	H	H	H	O	4-NHAc	158[b]	EtOH-H_2O	73	$C_{14}H_{14}N_4O_4S$
5	H	H	H	O	4-OH	144[b]	EtOH-H_2O	77	$C_{12}H_{11}N_3O_4S$
6	H	H	H	O	4-NMe_2	158[b]	EtOH-H_2O	76	$C_{14}H_{16}N_4O_3S$
7	H	H	H	O	3-CO_2H, 4-OH	167[b]	EtOH-H_2O	87	$C_{13}H_{11}N_3O_6S$
8	H	H	H	O	3-CO_2H, 4-Me	158[b]	EtOH-H_2O	75	$C_{14}H_{13}N_3O_5S$
9	H	H	H	O	2-Me, 5-CO_2H	147[b]	EtOH-H_2O	68	$C_{14}H_{13}N_3O_5S$
10	H	H	H	O	2-OMe, 5-CO_2H	161[b]	EtOH-H_2O	73	$C_{14}H_{13}N_3O_6S$
11	H	H	H	O	3,4-$(OMe)_2$	148[b]	c	74	$C_{14}H_{15}N_3O_5S$
12	H	H	H	O	2,4-$(OMe)_2$	146[b]	EtOH	90	$C_{14}H_{15}N_3O_5S$
13	H	H	H	O	2,4,6-Me_3	137[b]	EtOH-H_2O	63	$C_{15}H_{17}N_3O_3S$
14	H	H	Me	O	4-Me	189-191	EtOH-H_2O	74	$C_{14}H_{15}N_3O_3S$
15	H	H	$CH_2C_6H_5$	O	4-Me	171-173	EtOAc	72	$C_{20}H_{19}N_3O_3S$
16	OH	H	H	O	4-Me	196[b]	EtOH-H_2O	83[d]	$C_{13}H_{13}N_3O_4S$
17	H	OH	H	O	4-Me	185[b]	EtOH	58[e]	$C_{13}H_{13}N_3O_4S$
18	OH	H	H		4-Me	140[b]	c	91	$C_{13}H_{13}N_3O_3S$
19	H	OH	H		4-Me	152[b]	MeOH	41	$C_{13}H_{13}N_3O_3S$

[a] All compounds were analyzed for C, H, N, and S. Analytical results were within ±0.4% of theoretical values. [b] Decomposition at indicated temperature. [c] Obtained analytically pure from reaction mixture. [d] The yield was based on the reaction of aldehyde 23 with 4-toluenesulfonylhydrazide; oxidation of hydrazide 18 afforded 16 in 77% yield. [e] The yield was based on 22 by oxidation of 3-hydroxy-2-pyridinemethanol with subsequent reaction with 4-toluenesulfonylhydrazide; oxidation of hydrazide 19 gave 17 in 83% yield.

served[2-4] that substitutions at the terminal phenyl ring or at the 4 position of the pyridine ring of 2-pyridinecarboxaldehyde 1-oxide benzenesulfonylhydrazone led to excellent antineoplastic activity against Sarcoma 180. Activity was retained when the pyridine *N*-oxide moiety was replaced by pyridazine *N*-oxide or when the terminal phenyl ring was replaced by a pyridine, naphthalene, or fluorene ring system. However, replacement of the pyridine *N*-oxide moiety by benzene, quinoline *N*-oxide, isoquinoline *N*-oxide, or pyrimidine *N*-oxide led to complete loss of carcinostatic potency against Sarcoma 180. Furthermore, the *N*-oxide function, the olefinic hydrogen, and the sulfonyl group appeared to be essential for activity. 2-Pyridinecarboxaldehyde 1-oxide 4-toluenesulfonylhydrazone has been shown to cause single strand breaks in DNA, which appeared to be resistant to repair.[5] In addition, this agent did not markedly affect the synthesis of DNA, RNA, and protein at cytotoxic levels. Thus, this class of agents may have a unique biochemical mechanism of action.

To further evaluate the effects of various structural modifications on biological activity, with the ultimate purpose being a characterization of the parameters necessary for anticancer activity, as well as the development of compounds with more advantageous therapeutic indices and with hydrophilic groups which allow formulation as water-soluble agents, a series of derivatives was prepared substituted at various positions of the phenyl and pyridine rings of 2-pyridinecarboxaldehyde 1-oxide benzenesulfonylhydrazone. In some cases, the nitrogen atom bonded directly to the sulfonyl moiety was also substituted by either a methyl or benzyl group. The antineoplastic activity and host toxicity of these agents have been assessed in mice bearing either the L1210 or P388 leukemias. The findings demonstrated that di- and trisubstitution of the terminal phenyl ring with Me and MeO groups significantly increased antineoplastic activity against both leukemias. Hydroxylation of either the 3 or 5 position of the pyridine ring, however, resulted in complete loss of activity. Furthermore, the hydrogen atom bonded to nitrogen appeared to be essential for activity.

Scheme I



Chemistry. Phenylsulfonylhydrazones of 2-pyridinecarboxaldehyde 1-oxide were synthesized by reacting 2-pyridinecarboxaldehyde 1-oxide with appropriate phenylsulfonylhydrazides (see Table I for physical data). Most of the phenylsulfonylhydrazides, including *N*-benzyl- and *N*-methyl-substituted hyrazides,[6,7] were synthesized according to published procedures.[8-12] 4-(Dimethyl-

(4) J. A. May, Jr., and A. C. Sartorelli, *J. Med. Chem.*, **21**, 1333 (1978).
(5) S. H. Lee and A. C. Sartorelli, *Cancer Res.*, **39**, 2625 (1979).
(6) C. S. Rooney, E. J. Cragoe, Jr., C. C. Porter, and J. M. Sprague, *J. Med. Pharm. Chem.*, **5**, 155 (1962).
(7) A. Nurrenbach and H. Pommer, *Justus Liebigs Ann. Chem.*, **721**, 34 (1969).
(8) K. A. Jensen and O. R. Hansen, *Acta Chem. Scand.*, **6**, 195 (1952).

Table II. Effects of Phenylsulfonylhydrazones of 2-Pyridinecarboxaldehyde 1-Oxide on the Survival Time of Mice Bearing the L1210 Leukemia

compd	max effective daily dose, mg/kg[a]	av Δ wt, %[b]	av survival time, days[c] ± SE	50-day survivors, %	% T/C[c,d]
control		+16.6	9.0 ± 0.3	0	100
1	120	−2.4	12.4 ± 1.5	0	138
2	60	+3.4	10.8 ± 0.6	0	120
3	120	+7.3	10.4 ± 0.2	0	116
4	120	0	15.2 ± 4.2	0	169
5	100	−0.8	12.2 ± 0.7	0	136
6	100	−3.2	16.8 ± 5.0	0	187
7	80	0	14.0 ± 2.5	0	156
8	100	−5.0	11.8 ± 0.9	0	131
9	100	+4.1	12.0 ± 1.0	0	133
10	100	+8.1	11.6 ± 1.1	0	129
11	100	−8.7	19.0 (43.8 ± 6.2)[e]	80	210 (487)[e]
12	80	−2.5	11.7 ± 1.1 (19.4 ± 7.7)[e]	20	130 (216)[e]
13	120	−1.0	11.3 ± 1.9 (26.8 ± 9.5)[e]	40	126 (298)[e]

[a] Administered once daily for 6 consecutive days, beginning 24 h after tumor transplantation. The survival times of control tumor-bearing animals receiving no drug treatment were averaged from several experiments and represents 35 animals; treated groups represent 5–10 animals each. [b] Average change in body weight from onset to termination of drug therapy. [c] Mice that survived more than 50 days were not included in the determination of either the average survival time or the % T/C. [d] % T/C = average survival time (treated/control) × 100. [e] Mice that survived more than 50 days were calculated as 50-day survivors in the determination of the average survival time and the % T/C, which is given in parentheses.

Table III. Effects of Phenylsulfonylhydrazones of 2-Pyridinecarboxaldehyde 1-Oxide on the Survival Time of Mice Bearing the P388 Leukemia[a]

compd	max effective daily dose, mg/kg	av Δ wt, %[b]	av survival time, days[c] ± SE	50-day survivors, %	% T/C[c,d]
control		+15.7	9.4 ± 0.3	0	100
1	80	−6.5	13.8 ± 0.4	0	147
2	100	−4.1	13.8 ± 0.2	0	147
3	100	−5.2	13.6 ± 0.2	0	145
4	80	−4.4	14.8 ± 0.4	0	157
5	100	−15.4	16.0 ± 0.5	0	170
6	100	−4.4	16.4 ± 0.5	0	174
7	100	−9.8	13.8 ± 0.4	0	147
8	100	−5.9	9.3 ± 2.2 (25.6 ± 10.0)[e]	40	99 (272)[e]
9	100	0	17.0 ± 2.7 (23.6 ± 6.9)[e]	20	180 (251)[e]
10	80	−3.1	15.0 ± 2.0 (22.0 ± 7.2)[e]	20	160 (234)[e]
11	120	−18.8	11.5 ± 5.5 (34.6 ± 9.6)[e]	60	122 (368)[e]
12	100	−10.3	21.2 ± 2.8 (27.0 ± 6.0)[e]	20	226 (287)[e]
13	100	−9.3	17.0 ± 1.7 (30.2 ± 8.1)[e]	40	180 (321)[e]

[a] Experiments were conducted as described in Table II. [b] Average change in body weight from onset to termination of drug therapy. [c] Mice that survived more than 50 days were not included in the determination of either the average survival time or the % T/C. [d] % T/C = average survival time (treated/control) × 100. [e] Mice that survived more than 50 days were calculated as 50-day survivors in the determination of the average survival time and the % T/C, which is given in parentheses.

amino)benzenesulfonylhydrazide was prepared by reacting the corresponding sulfonyl chloride[13] with hydrazine hydrate. 4-Toluenesulfonylhydrazones of 3- and 5-hydroxy-2-pyridinecarboxaldehyde were synthesized by two different methods as shown in Scheme I. Either substituted 2-pyridinecarboxaldehyde 1-oxides **23** and **24** were reacted with 4-toluenesulfonylhydrazide or substituted 2-pyridinecarboxaldehydes[14,15] **25** and **26** were first reacted with 4-toluenesulfonylhydrazide followed by N-oxidation with *m*-chloroperoxybenzoic acid. N-Oxidation of 3- and 5-hydroxy-2-pyridinemethanol[15,16] afforded the respective 1-oxides **21** and **22**, which were further oxidized to the corresponding 2-pyridinecarboxaldehydes with activated MnO_2.[17]

Biological Results and Discussion. The antitumor activity of the substituted phenylsulfonylhydrazones of 2-pyridinecarboxaldehyde that were synthesized was determined by measuring their ability to prolong the survival time of mice bearing either leukemia L1210 or P388; the results of these studies are shown in Tables II and III. A range of daily dosage levels from 20 to 120 mg/kg was tested for each compound; however, only the results produced by the maximum effective daily dose of each hydrazone are reported. For hydrazones of 3- and 5-hydroxy-2-pyridinecarboxaldehyde, the phenyl ring substituted with 4-Me was chosen because of the moderate level of activity of 2-pyridinecarboxaldehyde 1-oxide 4-

(9) N. V. Savitskaya and M. N. Shchukina, *Zh. Obshch. Khim.*, 24, 2052 (1954).
(10) R. J. W. Cremlyn, *J. Chem. Soc. C*, 11 (1968).
(11) R. J. W. Cremlyn and R. Hornby, *J. Chem. Soc. C*, 1341 (1969).
(12) N. J. Cusack, C. B. Reese, A. C. Risius, and B. Roozpeikar, *Tetrahedron*, 32, 2157 (1976).
(13) C. N. Sukenik, J. A. P. Bonapace, N. S. Mandel, P.-Y. Lau, G. Wood, and R. G. Bergman, *J. Am. Chem. Soc.*, 99, 851 (1977).
(14) D. Heinert and A. E. Martell, *Tetrahedron*, 3, 49 (1958).
(15) E. J. Blanz, Jr., F. A. French, J. R. DoAmaral, and D. A. French, *J. Med. Chem.*, 13, 1124 (1970).
(16) N. Elming, *Acta Chem. Scand.*, 11, 1496 (1957).
(17) E. P. Papadopoulos, A. Jarrar, and C. H. Issidorides, *J. Org. Chem.*, 31, 615 (1966).

toluenesulfonylhydrazone against leukemia L1210.[3,4]

Substitution of the phenyl ring with a polar substituent such as 3-CO_2H, 4-CO_2H, or 4-CH_2CO_2H (**1–3**) resulted in agents with only marginal activity against leukemias L1210 (T/C = 116–138) and P388 (T/C = 145–147). Disubstitution with CO_2H and Me (**8** and **9**) or CO_2H and MeO (**10**) also resulted in compounds possessing weak activity (T/C = 129–133) in the L1210 tumor system but somewhat better activity against the P388 leukemia where 20–40% 50-day survivors were obtained. Insertion of a 4-NHAc (**4**), 4-OH (**5**), or 4-NMe_2 (**6**) function and disubstitution with 3-CO_2H, 4-OH (**7**) led to compounds displaying somewhat better anticancer activity (T/C = 136–187). Disubstitution of the phenyl ring with electron-donating groups such as 3,4-$(OMe)_2$ (**11**) and 2,4-$(OMe)_2$ (**12**) and trisubstitution with 2,4,6-Me_3 (**13**) yielded compounds with the most potent antineoplastic activity in this series against both leukemias L1210 and P388 (T/C = 216–487 and 287–368, respectively, when mice that survived more than 50 days were included as 50-day survivors in the calculation of average survival times and % T/C, and disappearance of tumors in 20–80% of leukemia bearing mice).

The hydrogen atom attached to nitrogen which is bonded directly to the sulfonyl group appeared to be essential for tumor-inhibitory potency, since compounds **14** and **15**, in which the hydrogen atom of the hydrazone was replaced by either a methyl or a benzyl group, respectively, were inactive against both of the transplanted test leukemias.

4-Toluenesulfonylhydrazones with a hydroxyl substitution at the 3 or 5 position of the pyridine nucleus were synthesized and tested, since such hydroxylation in the case of α-(N)-heterocyclic carboxaldehyde thiosemicarbazones increased the therapeutic index.[18] However, compounds **16** and **17** proved to be inactive against both leukemia cell lines. These findings, in addition to previous observations,[3,4] indicate that the pyridine nucleus of the phenylsulfonylhydrazones is exceedingly sensitive to alteration and suggest that the pyridine ring requires specific and as yet undefined electronic and/or stereochemical factors for antineoplastic activity. Compounds **18** and **19**, which do not possess the *N*-oxide function, were also found to be inactive.

The toxicity of these compounds was estimated in tumor-bearing animals by lethality and by measurement of drug-induced loss in body weight measured from onset to termination of therapy. Mice bearing the L1210 leukemia receiving injections of these agents at dosage levels up to 120 mg/kg per day did not experience more than 10% loss in body weight. However, significantly more toxicity was produced by agents of this class in mice bearing the P388 leukemia; thus, a daily dose of 100 mg/kg of **5** and **12** and 120 mg/kg of **11** caused a 15.4, 10.3, and 18.8% loss in body weight, respectively, of treated animals.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Baron Consulting Co., Orange, Conn. The spectral data were as expected and are not included. Pertinent data for synthesized compounds are listed in Table I.

Antitumor Activity. Leukemias L1210 and P388, grown in female CDF-1 mice, were employed. Transplantation was carried out using donor mice bearing 7-day tumor growths, with experimental details as described earlier.[19] Mice were weighed during the course of the experiments, and the percentage change in body weight from onset to termination of therapy was used as an indication of drug toxicity. Dosage levels of each compound were administered in the range of 20–120 mg/kg per day for 6 consecutive days beginning 24 h after tumor implantation. Determination of the sensitivity of ascitic neoplasms to these agents was based upon the prolongation of survival time afforded by drug treatments.

General Procedure for Preparation of Phenylsulfonylhydrazones. The appropriate hydrazide (5 mmol) was dissolved in EtOH (10–25 mL) by warming on a steam bath. To this solution was added the appropriate aldehyde (5 mmol) dissolved in EtOH (5 mL). In cases where the hydrazide was not very soluble, the mixture of the hydrazide and aldehyde was heated in EtOH (10–50 mL) until the reaction was complete as monitored by TLC. After refrigeration overnight, the hydrazone was filtered, washed with EtOH, and recrystallized from an appropriate solvent. A catalytic amount of concentrated H_2SO_4 (3 drops) was required for the preparation of hydrazone **19**.

4-(Dimethylamino)benzenesulfonylhydrazide. 4-(Dimethylamino)benzenesulfonyl chloride[13] (10.98 g, 0.05 mol) was added slowly to hydrazide hydrate (10 mL, 85%) in EtOH (100 mL) and stirred for 2 h at 0 °C. The hydrazide was filtered, washed with cold EtOH, and recrystallized from H_2O to afford 10.26 g (95% yield), mp 153–154 °C dec.

5-Hydroxy-2-pyridinemethanol 1-Oxide (21). 5-Hydroxy-2-pyridinemethanol[15] (**20**; 6.26 g, 0.05 mol) was dissolved in MeOH (25 mL) and $CHCl_3$ (50 mL) was added. To this solution was added *m*-chloroperoxybenzoic acid (12.5 g, 6.5–7.3 mmol) dissolved in $CHCl_3$ (150 mL), and the mixture was refrigerated overnight. The product was obtained by filtration and washed with $CHCl_3$ to yield 5.61 g (88%), mp 183–184 °C.

Oxidation of 3- and 5-Hydroxy-2-pyridinemethanol 1-Oxide. A suspension of freshly prepared MnO_2[17] (15 g) in a solution of **21** (2.82 g, 0.02 mol) in *p*-dioxane (250 mL) was heated at 90 °C for 1 h. The hot mixture was filtered through Celite, and the oxide was washed successively with hot *p*-dioxane (200 mL) and hot EtOH (200 mL). The combined filtrate and washings were evaporated under reduced pressure, and the residue was recrystallized from EtOH–ether to yield 1.47 g (53%) of **23**, mp 206 °C dec.

3-Hydroxy-2-pyridinecarboxaldehyde 1-oxide (**24**) was prepared from **22**[16] (2.12 g, 15 mmol) in a similar manner and was not isolated but was treated immediately with 4-toluenesulfonylhydrazide (2.79 g, 15 mmol) dissolved in EtOH (20 mL), to afford the hydrazone in 58% yield (based on **22**).

N-Oxidation of 4-Toluenesulfonylhydrazones of 3- and 5-Hydroxy-2-pyridinecarboxaldehyde. Hydrazones **18** and **19** were prepared from the respective 3- and 5-hydroxy-2-pyridinecarboxaldehydes[14,15] (**25** and **26**) as described. *m*-Chloroperoxybenzoic acid (1.40 g, 6.5–7.3 mmol) was added to a stirred solution of hydrazone **18** (1.46 g, 5 mmol) in ether–MeOH (5:1, v/v; 40 mL) and stirred overnight. The solid was filtered and washed with ether. Recrystallization from EtOH–H_2O afforded pure **16** (77% yield), the melting point being undepressed upon admixture with the sample prepared from aldehyde **23** and 4-toluenesulfonylhydrazide. Hydrazone **19** was similarly oxidized to **17** in 83% yield.

Acknowledgment. The authors thank Florence Dunmore for her excellent assistance.

(18) K. C. Agrawal and A. C. Sartorelli, *Prog. Med. Chem.*, **15**, 321 (1978).

(19) K. C. Agrawal, B. A. Booth, and A. C. Sartorelli, *J. Med. Chem.*, **11**, 700 (1968).