Relationship between Structure and Antineoplastic Activity of Arylsulfonylhydrazones of 2-Formylpyridine *N*-Oxide[1]

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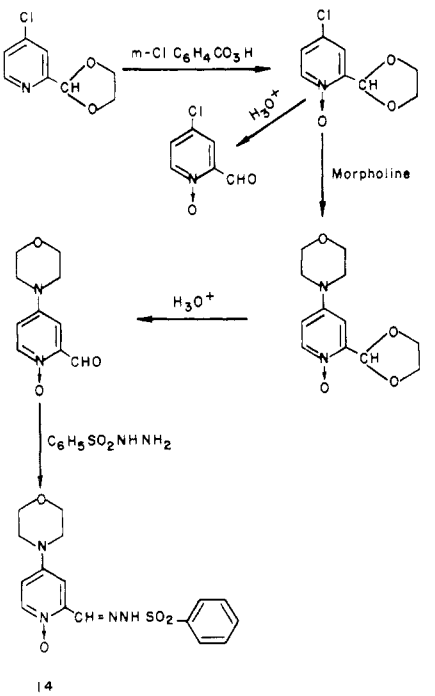
The effects of various structural modifications on the antineoplastic activity of the benzenesulfonylhydrazone of 2-formylpyridine *N*-oxide have been ascertained in mice bearing either Sarcoma 180 or leukemia L1210. To accomplish this a variety of derivatives substituted at the aldehyde proton, the aryl ring, and the 4 position of the pyridine nucleus were synthesized. Antineoplastic activity was retained when nitro, amino, chloro, bromo, fluoro, and methoxy groups were introduced into either the meta or para positions of the phenyl ring of the parent compound. In addition, substitution of the terminal phenyl group by a pyridine ring or by a bulky aromatic ring such as α-naphthyl, β-naphthyl, or fluorenyl did not abolish the marked antitumor activity expressed by this class of agents. Insertion of a nitro function or a morpholino group in the 4 position of the pyridine nucleus of the benzenesulfonylhydrazone of 2-formylpyridine *N*-oxide resulted in two potent anticancer agents, while the introduction of a chloro function in the 4 position led to a pronounced decrease in biological activity. Furthermore, the essentiality of the aldehydic proton for tumor-inhibitory activity was demonstrated by the inactivity of two derivatives in which the aldehydic proton was replaced by a methyl group or by an oxygen atom.

Arylsulfonylhydrazones of 2-formylpyridine *N*-oxide have been shown by our laboratory to possess potent activity against several transplanted murine neoplasms.[3] A representative member of this group, demonstrated to be one of the most active agents of the series, is the *p*-toluenesulfonylhydrazone of 2-formylpyridine *N*-oxide (**2**) which exhibited antineoplastic activity against a broad spectrum of transplanted tumors, including Sarcoma 180, Hepatoma 129, Ehrlich carcinoma, leukemia L1210, and a subline of Sarcoma 180 resistant to α-(*N*)-heterocyclic carboxaldehyde thiosemicarbazones.[3] Although the precise biochemical basis for the growth inhibitory activity of this class of agents in neoplastic cells is not yet known, compound **2** has been shown to cause moderate inhibition of [^{3}H]thymidine and [^{3}H]uridine incorporation into DNA and RNA, respectively, of Sarcoma 180 ascites cells; protein biosynthesis was found to be relatively insensitive to the action of this agent.[3] Since these sulfonylhydrazones appear to constitute a new class of compounds with potent antineoplastic properties, it was of interest to evaluate the effects of various structural modifications on biological activity. To this end, the present investigation reports (a) the synthesis of a series of derivatives substituted at the aldehyde proton, the aryl ring, and the 4 position of the pyridine nucleus and (b) the antineoplastic potency and host toxicity of these agents in mice bearing either Sarcoma 180 or leukemia L1210 ascites cells. A preliminary report of this study has appeared.[4]

Chemistry. Arylsulfonylhydrazones of 2-formylpyridine *N*-oxide were synthesized by reacting 2-formylpyridine *N*-oxide with various substituted arylsulfonylhydrazides, utilizing methodology described earlier.[3] 2-Formylpyridine *N*-oxide was obtained by SeO_2 oxidation of 2-picoline *N*-oxide. The para-substituted analogues of benzenesulfonylhydrazide (i.e., *p*-NO_2, Cl, Br, F, or OCH_3) were synthesized according to published procedures.[5] The *p*-amino-substituted benzenesulfonylhydrazide was readily fabricated by catalytic reduction (Pd/C) of the corresponding *p*-nitro analogue; reduction of arylsulfonylhydrazines with activated Raney nickel has been shown to result in N–N bond scission yielding arylsulfonamides.[6] *m*-Nitrobenzenesulfonylhydrazide was synthesized according to the procedure of Cremlyn[7] and was then reduced by catalytic hydrogenation to yield the corresponding amino derivative. 3-Pyridylsulfonylhydrazine was fabricated by chlorination of 3-pyridinesulfonic acid with PCl_5 and then by reaction with hydrazine hydrate.[8] Naphthyl-[6] and fluorenylsulfonylhydrazides were similarly obtained (see Tables I and II).

Scheme I



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The 4-substituted analogues of 2-formylpyridine *N*-oxide were synthesized by the reactions shown in Scheme I. 4-Chloro-2-formylpyridine ethylene ketal was initially formed by a procedure described earlier by this laboratory.[9] The ketal was converted to the corresponding *N*-oxide by treatment with *m*-chloroperbenzoic acid and the *N*-oxide was then either hydrolyzed to produce the respective carboxaldehyde or treated with morpholine to obtain the 4-substituted morpholine derivative. The latter compound was then hydrolyzed to the corresponding aldehyde and reacted with benzenesulfonylhydrazine to yield the desired material **14**. 4-Nitro-2-formylpyridine *N*-oxide (not shown in Scheme I) was obtained by direct oxidation of 4-nitro-2-picoline *N*-oxide by SeO_2. Although this oxidative reaction was still incomplete after 64 h, the aldehyde was readily separated from the parent compound by silica gel column chromatography. Increasing the reaction temperature by utilization of solvents such as chlorobenzene and dimethylformamide did not improve yields.

Synthesis of 2-picolinoylbenzenesulfonylhydrazide *N*-oxide (**16**) was accomplished by first reacting ethyl 2-picolinate with *m*-chloroperoxybenzoic acid to form the

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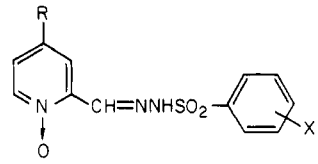
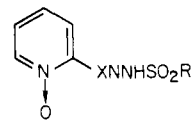
Table I. Physical Constants of Substituted Arylsulfonylhydrazones of Pyridine *N*-Oxide



Compd	X	R	Mp, °C dec	Yield, %	Formula	Analyses
1[a]	H	H				
2[a]	*p*-CH_3	H				
3	*o*-CH_3	H	132	78	$C_{13}H_{13}N_3O_3S$	C, H, N
4	*m*-NO_2	H	112	67	$C_{12}H_{10}N_4O_5S$	C, H, N
5	*p*-NO_2	H	125	73	$C_{12}H_{10}N_4O_5S$	C, H, N
6	*m*-NH_2	H	128	64	$C_{12}H_{12}N_4O_3S$	C, H, N
7	*p*-NH_2	H	135-136	58	$C_{12}H_{12}N_4O_3S \cdot H_2O$	C, H, N
8	*p*-Cl	H	126	78	$C_{12}H_{10}ClN_3O_3S$	C, H, N
9	*p*-Br	H	134	80	$C_{12}H_{10}BrN_3O_3S$	C, H, N
10	*p*-F	H	125	72	$C_{12}H_{10}FN_3O_3S$	C, H, N
11	*p*-OCH_3	H	124-125	82	$C_{13}H_{13}N_3O_4S \cdot H_2O$	C, H, N
12	H	Cl	131	74	$C_{12}H_{10}ClN_3O_3S$	C, H, N
13	H	NO_2	133	78	$C_{12}H_{10}N_4O_5S$	C, H, N
14	H	c-$N(CH_2CH_2)_2O$	124-125	64	$C_{16}H_{18}N_4O_4S$	C, H, N

[a] See ref 3.

Table II. Physical Constants of Substituted Arylsulfonylhydrazones of Pyridine *N*-Oxide



Compd	X	R	Mp, °C dec	Yield, %	Formula	Analyses
15	-$C(CH_3)$=	Phenyl	173	82	$C_{13}H_{13}N_3O_3S$	C, H, N
16	-C(=O)-	Phenyl	210-212	89	$C_{12}H_{11}N_3O_4S$	C, H, N
17	-CH=	3-Pyridyl	103	76	$C_{11}H_{10}N_4O_3S$	C, H, N
18	-CH=	1-Naphthyl	110-111	78	$C_{16}H_{13}N_3O_3S$	C, H, N
19	-CH=	2-Naphthyl	125	74	$C_{16}H_{13}N_3O_3S$	C, H, N
20	-CH=	2-Fluorenyl	135	84	$C_{19}H_{15}N_3O_3S$	C, H, N

Table III. Effects of Arylsulfonylhydrazones of Pyridine *N*-Oxide on the Survival Time of Mice Bearing Sarcoma 180 Ascites Cells

Compd	Max effective daily dose, mg/kg[a]	Av Δ wt, %[b]	Av survival time, days[c] ± SE	% T/C[d]	% 50-day survivors
Control		+30.2	11.4 ± 0.3	100	0
1	40	-5.2	38.6 ± 1.6	339	20
2	60	-8.0	35.0 ± 1.8	307	0
3	60	-1.9	32.5 ± 1.0	285	0
4	60	-7.5	44.5 ± 3.1	390	60
5	80	-7.1	39.3 ± 2.9	345	10
6	80	-10.3	41.5 ± 2.2	364	40
7	60	+2.4	31.5 ± 1.8	276	0
8	40	-0.6	29.6 ± 1.4	260	0
9	40	-3.5	27.4 ± 2.4	240	0
10	60	-5.7	38.4 ± 2.0	337	20
11	80	-11.6	40.6 ± 2.1	356	40
12	20	+10.8	17.8 ± 2.1	156	0
13	60	-5.4	33.4 ± 2.9	293	0
14	20	+1.4	27.6 ± 1.8	242	0
15	60	+23.5	14.8 ± 0.5	130	0
16	40	+20.7	12.2 ± 0.7	107	0
17	60	0.0	31.5 ± 1.6	276	0
18	60	-3.4	29.8 ± 1.8	261	0
19	60	-1.2	35.1 ± 2.2	308	0
20	40	-4.7	31.5 ± 2.4	276	0

[a] Administered once daily for six consecutive days, beginning 24 h after tumor transplantation. The survival time of control tumor-bearing animals was averaged from several experiments and represents 30 animals; treated groups represent 5-15 animals each. [b] Average change in body weight from onset to termination of drug therapy. [c] Mice that survived more than 50 days were calculated as 50-day survivors in the determination of the average survival time. [d] % T/C = average survival time (treated/control) × 100.

corresponding *N*-oxide which was then treated with hydrazine hydrate to yield the hydrazide. Reaction of this material with benzenesulfonyl chloride produced the desired compound. The direct reaction of ethyl 2-picolinate *N*-oxide with benzenesulfonylhydrazide resulted in **16** in poor yield.

Biological Results and Discussion. The tumor-inhibitory properties of various substituted arylsulfonyl-

hydrazones were determined primarily by measuring their effects on the survival time of mice bearing Sarcoma 180 ascites cells; the results obtained are shown in Table III. A range of daily dosage levels of each compound from 10 to 80 mg/kg was tested; however, only the results produced by the maximum effective daily dose of each compound are listed. Meta and para substitution of the phenyl ring with potent electron-withdrawing groups such as NO_2 or with electron-donating groups such as NH_2 did not appear to significantly affect biological activity, since compounds 1 and 4–7 all exhibited potent antineoplastic activity in this test system, increasing the average survival time of tumor-bearing mice from 11.4 days for untreated control animals to between 31.5 and 44.5 days. It is quite probable that the potential impact of the electronic effects of meta and para substituents in the aryl ring on the entire molecule is lessened due to the presence of the SO_2NH bridge between the aryl and heterocyclic ring systems or that the inherent biological effectiveness of these agents is not altered by the electronic effects of such substitution.

In a similar manner, the introduction of a methyl group in the parent compound either at the para (2) or the ortho (3) positions of the phenyl ring did not significantly alter antineoplastic activity. Substitution of the phenyl nucleus with either a *p*-Cl, Br, F, or OCH_3 group also resulted in compounds possessing biological activity in this tumor system; the *p*-Cl (8) and *p*-Br (9) derivatives, however, were significantly less potent than the *p*-F (10) or *p*-OCH_3 (11) substituted derivatives.

Insertion of a chloro function at the 4 position of the pyridine nucleus (12) led to a dramatic lowering of biological activity. This decrease in antineoplastic potency did not appear to be the result of low bulk tolerance in this portion of the molecule or to electronic effects, since the insertion of a NO_2 function (13) or a morpholino group (14) in the 4 position resulted in active agents which produced a maximum increase in the average survival time of tumor-bearing mice of 33.4 and 27.6 days, respectively.

The essentiality of the aldehydic proton for tumor-inhibitory potency is shown by compounds 15 and 16; these two agents which were inactive have the aldehydic proton replaced by a methyl group or an oxygen atom, respectively.

The substitution of the terminal phenyl group of the side chain of 1 by the heterocyclic pyridine ring (17) or by bulky aromatic rings such as α-naphthyl (18), β-naphthyl (19), or fluorenyl (20) did not abolish the potent antineoplastic activity by this class of agents, indicating the lack of a requirement for the phenyl nucleus for biological activity.

Since most of the substituted arylsulfonylhydrazones of pyridine *N*-oxide which were tested possessed similar and potent antineoplastic activity against mice bearing Sarcoma 180 ascites cells, some of the most effective derivatives of this series were also examined in mice bearing leukemia L1210 to determine whether this test system might effectively distinguish between these agents. The results obtained are shown in Table IV; they demonstrate that compounds 3 and 11, which possess an ortho CH_3 group and a para OCH_3 function, respectively, were the most potent agents of this series tested against the L1210 leukemia, increasing the life span of animals bearing this tumor from 8.4 days for untreated tumor-bearing mice to 19.9 and 19.7 days, respectively, at maximum effective daily dosage levels. In comparison, the parent compound 1 at its optimum dose of 80 mg/kg per day prolonged life to only 10.6 days. These results suggest that compounds 3 and 11 are the agents of this series with the most potential, since they possess potent antineoplastic activity against both Sarcoma 180 and the L1210 leukemia.

Table IV. Effects of Arylsulfonylhydrazones of Pyridine *N*-Oxide on the Survival Time of Mice Bearing the L1210 Leukemia[a]

Compd	Max effective daily dose, mg/kg	Av Δ wt, %	Av survival time, days ± SE	% T/C
Control		+14.8	8.4 ± 0.4	100
1	80	−8.0	10.6 ± 1.2	126
2	80	−7.4	14.3 ± 0.9	170
3	100	−11.1	19.9 ± 1.9	237
4	80	−5.4	12.4 ± 1.3	147
10	60	+1.6	11.8 ± 0.8	140
11	80	−4.9	19.7 ± 1.6	234

[a] Experiments were conducted as described in Table III. No 50-day survivors were produced in these experiments.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The IR absorption spectra were obtained with a Perkin-Elmer Model 257 spectrophotometer, with thin films of liquids and KBr pellets of solids. NMR spectra were determined with a Varian T-60A spectrometer with Me_4Si as an internal standard. Elemental analyses were performed by the Baron Consulting Company, Orange, Conn. Where analyses are indicated only by symbols of the elements, the analytical results for those elements were within ±0.4% of theoretical values.

Antitumor Activity. The ascites cell forms of Sarcoma 180, propagated in female CD-1 mice, and leukemia L1210, grown in male BDF1 mice, were employed. Transplantation was carried out using donor mice bearing 7-day tumor growths; experimental details have been described earlier.[10] 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 10–80 mg/kg per day for six 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.

***m*-Aminobenzenesulfonylhydrazide.** To 1.09 g (0.005 mol) of *m*-nitrobenzenesulfonylhydrazide in 100 mL of ethanol was added 250 mg of 10% Pd/C. The mixture was hydrogenated at 30 psi for 30 min, following which it was filtered through Celite, and the solvent was removed under vacuum. The resulting residue was recrystallized from ethanol to yield 0.6 g (64%), mp 134–136 °C. Anal. ($C_6H_9N_3O_2S$) C, H, N.

p-Aminobenzenesulfonylhydrazide was synthesized utilizing a similar procedure with *p*-nitrobenzenesulfonylhydrazide[5] to yield 0.68 g (73%), mp 135–136 °C (lit.[11] mp 130–131 °C).

2-Fluorenesulfonylhydrazide. To a solution of 3 mL of hydrazine hydrate in 15 mL of ethanol at 0 °C was added slowly 2.64 g (0.01 mol) of 2-fluorenesulfonyl chloride. The mixture was stirred for 30 min at room temperature and the resulting precipitate was filtered and recrystallized from ethanol to yield 1.4 g (54%), mp 160–162 °C. Anal. ($C_{13}H_{12}N_2O_2S$) C, H, N.

4-Chloro-2-formylpyridine Ethylene Acetal *N*-Oxide. To 1.85 g (0.01 mol) of 4-chloro-2-formylpyridine ethylene acetal[9] in 100 mL of chloroform was added 1.98 g (0.01 mol) of *m*-chloroperoxybenzoic acid (85%). The solution was stirred at room temperature for 20 h and then treated with K_2CO_3 and water to form a paste. The mixture was triturated, decanted, dried (K_2CO_3), and filtered. Evaporation of the filtrate under vacuum yielded an oil which crystallized upon addition of 20 mL of anhydrous Et_2O and cooling. The white crystals were filtered to yield 1.2 g (60%), mp 108–110 °C. Recrystallization from Et_2O raised the mp to 111–112 °C. Anal. ($C_8H_8ClNO_3$) C, H, N.

4-Morpholino-2-formylpyridine Ethylene Acetal *N*-Oxide. A solution of 1.0 g (0.005 mol) of 4-chloro-2-formylpyridine ethylene acetal *N*-oxide and 5 mL of morpholine was heated at 100 °C for 3 h. Excess morpholine was removed under vacuum, the residue was made alkaline with K_2CO_3 solution, extracted with

$CHCl_3$, and dried (K_2CO_3), and solvent was removed under vacuum. The residue was crystallized from acetone and ether to yield 0.7 g (55%), mp 58–59 °C. Anal. ($C_{12}H_{16}N_2O_4 \cdot H_2O$) C, H, N.

4-Morpholino-2-formylpyridine *N*-Oxide. A solution of 0.506 g (2 mmol) of 4-morpholino-2-formylpyridine ethylene acetal *N*-oxide in 15 mL of 20% HCl was refluxed for 1.5 h. The solution was then made alkaline with Na_2CO_3 and water was removed under vacuum. The residue was extracted with $CHCl_3$, solvent was removed, and the residue was crystallized from acetone to yield 0.3 g (72%) of orange crystals, mp 180–182 °C. Anal. ($C_{10}H_{12}N_2O_3 \cdot H_2O$) C, H, N.

4-Nitro-2-formylpyridine *N*-Oxide. To a solution of 4.62 g (0.03 mol) of 4-nitro-2-picoline *N*-oxide in 100 mL of dioxane was added 3.68 g (0.033 mol) of freshly sublimed SeO_2 and the mixture was refluxed for 64 h. The precipitated selenium was removed by filtration and the filtrate was evaporated under vacuum. The residue was dissolved in 50 mL of water, neutralized with $NaHCO_3$ solution, and evaporated under vacuum to dryness. The remaining solids were extracted with $CHCl_3$ and the solvent was removed to leave a gummy residue which was subjected to silica gel column chromatography using $CHCl_3$ as the eluent. Initial fractions contained unreacted 4-nitro-2-picoline *N*-oxide which was then followed by the desired compound. The fractions containing the aldehyde were collected, the solvent was removed, and the residue was crystallized from benzene to yield 1.2 g (24%), mp 110–112 °C. Anal. ($C_6H_4N_2O_4$) C, H, N.

2-Picolinoylbenzenesulfonylhydrazide *N*-Oxide (16). Ethyl picolinate (4.53 g, 0.03 mol) was initially converted to its *N*-oxide with a molar equivalent of *m*-chloroperoxybenzoic acid, utilizing the procedure outlined for the synthesis of 4-chloro-2-formylpyridine ethylene acetal *N*-oxide. The *N*-oxide was obtained as an oil (3.02 g) that was dissolved in 15 mL of ethanol and directly reacted with 7.5 mL of hydrazine hydrate; this procedure immediately produced a white precipitate. The mixture was stirred for 1 h at room temperature and was filtered to yield 2.5 g (54%) of 2-picolinoylhydrazide *N*-oxide, mp 146–147 °C.

To a solution of 1.53 g (0.01 mol) of 2-picolinoylhydrazide *N*-oxide in 20 mL of pyridine was added slowly at 4 °C a solution of a molar equivalent of benzenesulfonyl chloride in 5 mL of pyridine. The solution was stirred for 1.5 h at room temperature and then the pyridine was removed under vacuum. The residue was washed with water and ethanol to yield 2.6 g (89%) of **16**, mp 210–212 °C.

References and Notes

(1) Presented in part before the fall meeting of American Society for Pharmacology and Experimental Therapeutics, New Orleans, La., Aug 1976; this work was supported by U.S. Public Health Service Grants CA-02817 and CA-16359 from the National Cancer Institute.
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Notes

Chemical Modification of 1,4-Diamino-1,4-dideoxy-3-*O*-(4-deoxy-4-propionamido-α-D-glucopyranosyl)-D-glucitol

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Chemical modification of the 4′-N position of 1,4-diamino-1,4-dideoxy-3-*O*-(4-deoxy-4-propionamido-α-D-glucopyranosyl)-D-glucitol (GlA_1) in the form of 4′-*N*-acyl analogues, e.g., **3**, led to no significant potency enhancement. The *n*-propylamino analogue **4** was more active against gram-positive bacteria but was less active vs. gram-negative bacteria. The intrinsic activity of the 6′-chloro analogue **15** like the antibiotic GlA_1 was not high, but the antibacterial spectrum was broad with moderate activity against most resistant organisms.

Antibiotic 1,4-diamino-1,4-dideoxy-3-*O*-(4-deoxy-4-propionamido-α-D-glucopyranosyl)-D-glucitol (GlA_1) is a component of a new complex of amino glycosides elaborated in fermentation broths by *Streptomycete*[1] and *Pseudomonas*[2] species. It has broad-spectrum activity[1,2] against bacteria including *Pseudomonas aeruginosa* and strains carrying amino glycoside resistance episomes.[1] The antibiotic is composed of 4-deoxy-4-propionamido-D-glucopyranose and 1,4-diamino-1,4-dideoxy-D-glucitol which were synthesized in our laboratories.[3] The structure has been established[3] as **1**, which is identical with the recently described Sorbistin antibiotics (Bristol),[4a] the LL-AM 31 antibiotic complex (Lederle),[4b] and antibiotic P2568 (Takeda).[2c] Recent publications[2c,5] on the preparation of many *N*-acyl derivatives of the natural product **6** prompted us to report on the chemical modification of **1**.

The potency of GlA_2 (**2**) is about 50% of **1**, whereas GlA_0 (depropionyl-GlA_1) (**6**) is totally inactive. The difference in activities of these natural products indicates that the acyl side chain on the 4-aminoglucose moiety is essential for bioactivity. Thus, the approach to enhance the antibiotic activity by introducing a new acyl group on the 4′-amino function would appear attractive. This line of approach has also been investigated independently by other workers.[2c,5]

The natural product **6**, obtained from the antibiotic complex by hydrazinolysis, was selectively reacted with

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