EtOAc to give **27** (12.8 g, 64%).

3-*tert*-Butyl-5-(4-chlorobenzoyl)-6-methylsalicylic Acid (31). $AlCl_3$ (7.8 g, 58.9 mmol) and 4-chlorobenzoyl chloride (10.8 g, 61.5 mmol) were added to $ClCH_2CH_2Cl$ (60 mL) at room temperature. When solution occurred, the stirred mixture was cooled to −5 °C and 3-*tert*-butyl-6-methylsalicylic acid (6.3 g, 29 mmol) suspended in $ClCH_2CH_2Cl$ (15 mL) added. After 40 min at −5 °C the mixture was poured on to ice and acidified with 2 N HCl. Extraction with $CHCl_3$ and evaporation gave an oil. Extraction of the oil with boiling petrol gave on evaporation **31** (3.0 g, 29%).

5-(4-Bromo-α-hydroxybenzyl)-2′-chloro-3-methyl-4′-nitrosalicylanilide (34). $NaBH_4$ (1.0 g, 26.3 mmol) and **11** (1.0 g, 2.0 mmol) were added to EtOH (100 mL), and the mixture was stirred for 18 h. The mixture was acidified with 2 N HCl and the solid precipitate collected. The solid was washed with H_2O and dried to give **34** (800 mg, 80%), mp 193–195 °C. Anal. ($C_{21}H_{16}BrClN_2O_5$) C, H, N.

Fasciolicidal Activity. Activity in vitro was detected by incubating two adult fluke (from rats) in Hedon-Fleig solution (10 mL). Test compounds (5 ppm) were administered in Me_2SO (50 μL or less), and if the fluke did not move, the compounds were active. Compounds in Tables I and II were tested by a single sc injection in lissapol in rats at the doses indicated. Rats were previously infected with 20 metacercariae and dosed at 12 weeks postinfection. The rats were examined 5 days later and compounds that removed 90% of the fluke from the bile duct were considered active. Sheep infected with 250–300 metacercariae were kept until they were passing fluke eggs. The sheep were dosed with compound (10 mg/kg) by oral gavage and egg counts made on midday fecal samples on days 0, 7, and 14 after dosing. Compounds completely suppressing fluke egg production on day 14 were taken to be active against adult liver fluke in sheep. Details of the tests have been reported.[14]

Registry No. **4**, 92524-64-6; **5**, 92524-65-7; **6**, 92524-66-8; **7**, 92524-67-9; **8**, 92524-68-0; **9**, 92524-69-1; **10**, 92524-70-4; **11**, 92524-71-5; **12**, 92524-72-6; **13**, 92524-73-7; **14**, 92524-74-8; **15**, 92524-75-9; **16**, 92524-76-0; **17**, 92524-77-1; **18**, 92524-78-2; **19**, 92524-79-3; **20**, 92524-80-6; **21**, 92524-81-7; **22**, 92524-82-8; **23**, 92524-83-9; **24**, 92524-84-0; **25**, 92524-85-1; **26**, 92524-86-2; **27**, 92524-87-3; **28**, 92524-88-4; **29**, 92524-89-5; **30**, 92524-90-8; **31**, 92524-91-9; **32**, 92524-92-0; **33**, 92524-93-1; **34**, 92524-94-2; 2-Cl, 4-$NO_2C_6H_3NH_2$, 121-87-9; 2-CH_3, 4-$NO_2C_6H_3NH_2$, 121-01-7; 2-Br, 4-$NO_2C_6H_3NH_2$, 13296-94-1; 2-CF_3, 4-$BrC_6H_3NH_2$, 445-02-3; 3,5-$Cl_2C_6H_3NH_2$, 626-43-7; 3,4-$Cl_2C_6H_3NH_2$, 95-76-1; 4-$CNC_6H_4NH_2$, 873-74-5; 4-$NO_2C_6H_4COCl$, 122-04-3; 4-CNC_6H_4COCl, 6068-72-0; 4-ClC_6H_4COCl, 122-01-0; 4-BrC_6H_4COCl, 586-75-4; 4-IC_6H_4COCl, 1711-02-0; 3,4-$Cl_2C_6H_3COCl$, 3024-72-4; 2,4-$Cl_2C_6H_3COCl$, 89-75-8; 3-methylsalicylic acid, 83-40-9; salicylic acid, 69-72-7; 3,6-dimethylsalicylic acid, 3921-12-8; 3-*tert*-butyl-6-methylsalicylic acid, 6934-03-8.

(14) G. C. Coles, *J. Parasitol.*, 61, 54 (1975).
(15) G. C. Coles, K. G. Simpkin, and J. Barrett, *Exp. Parasitol.*, 49, 122 (1980).

Reactivators of Organophosphorus-Inhibited Acetylcholinesterase. 1. Imidazole Oxime Derivatives

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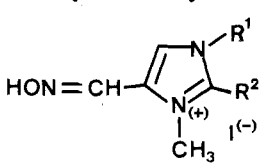
Received July 25, 1983

4-[(Hydroxyimino)methyl]-3-methylimidazolium iodides were prepared and tested for their reactivating potency on acetylcholinesterase inhibited by tetraethyl pyrophosphate (TEPP). The in vitro testing revealed that the new compounds are weak reactivators of the phosphorylated electrophorus acetylcholinesterase.

Since the discovery of oximes[1] as potent reactivators of organophosphorus-inhibited acetylcholinesterase (acetylcholine hydrolase, EC 3.1.1.7, AcChE), 2-pyridine aldoxime methiodide (2-PAM)[2] has been found to be particularly effective, and most oximes assayed as potential reactivators have been modeled after this aldoxime. Many *N*-pyridinium derivatives of 2-PAM have thus been investigated[3-6]. Derivatives where the pyridine ring has been substituted by other N-heterocycles are also described as AcChE reactivators[5,7-10].

The aim of this work was the synthesis and biological screening of 1-aryl(alkyl)-4-[(hydroxyimino)methyl]-3-methylimidazolium iodides (**1a–f**) and 1-aryl(alkyl)-4-[(hydroxyimino)methyl]-3-methyl-2-(methylthio)-imidazolium iodides (**2a–f**) in order to collect experimental data for QSAR analysis of this group of compounds.



R^2= H (Series 1)
R^2= MeS (Series 2)

a R^1= 4-EtOPh
b R^1= 4-MeOPh
c R^1= 4-MePh
d R^1= Ph
e R^1= Et
f R^1= Allyl

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Chemistry. The synthesis of the compounds **1a–f** and **2e–f** was accomplished by methylation of 4-formylimidazole derivatives[11] with methyl iodide and subsequent condensation with hydroxylamine. In this reaction a single product, the *Z* isomer, was usually isolated. Only in the case of **2f** did the oximation reaction give geometrical isomers which separated by fractional recrystallization.

(1) Childs, A. F.; Davies, D. R.; Green, A. L.; Rutland, J. P. *Br. J. Pharmacol. Chemother.* **1955**, *10*, 462.
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(3) Schneckenburger, J. *Arch. Pharm. (Weinheim, Ger.)* **1960**, *302*, 815; **1969**, *302*, 494.
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(6) Wilson, I. B. *Biochim. Biophys. Acta* **1958**, *27*, 196.
(7) Wilson, I. B. *Biochem. Pharmacol.* **1959**, *1*, 200.
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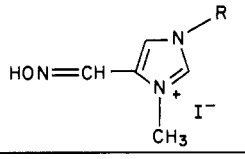
0022-2623/85/1828-0146$01.50/0

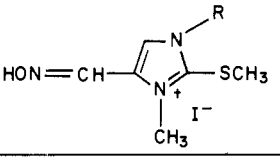
Table I. 1-Aryl(alkyl)-4-[(hydroxyimino)methyl]-3-methylimidazolium Iodides



compd	R	config	yield, %	mp, °C	NMR,[a] δ OH	NMR,[a] δ CH=N	formula[b]
1a	4-EtOPh	*Z*	62	227–229	12.74	7.30	$C_{13}H_{16}N_3O_2I$
1b	4-MeOPh	*Z*	65	228–229	12.72	7.81	$C_{12}H_{14}N_3O_2I$
1c	4-MePh	*Z*	54	234–235	12.68	7.88	$C_{12}H_{14}N_3OI$
1d	Ph	*Z*	80	230	12.75	7.85	$C_{11}H_{12}N_3OI$
1e	Et	*Z*	43	203–205	12.61	7.70	$C_7H_{12}N_3OI$
1f	allyl	*Z*	63	87–88	12.67	7.75	$C_8H_{12}N_3OI$

[a] In Me_2SO-d_6. [b] All compounds were analyzed for C, H, N, and I.

Table II. 1-Aryl(alkyl)-4-[(hydroxyimino)methyl]-3-methyl-2-(methylthio)imidazolium Iodides



compd	R	config	yield, %	mp, °C	NMR,[a] δ OH	NMR,[a] δ CH=N	formula[b]
2a	4-EtOPh	*E*	39	175–177	12.10	8.30	$C_{14}H_{18}N_3O_2SI$
2b	4-MeOPh	*Z*	44	172–175	12.76	7.93	$C_{13}H_{16}N_3O_2SI$
2c	4-MePh	*E*	64	190–193	12.08	8.29	$C_{13}H_{16}N_3OSI$
2d	Ph	*Z*	46	181–182	12.75	7.94	$C_{12}H_{14}N_3OSI$
2e	Et	*Z*	40	169–171	12.60	7.75	$C_8H_{14}N_3OSI$
2f	allyl	*E*	20	132–134	11.91	8.20	$C_9H_{14}N_3OSI$
2f	allyl	*Z*	35	154–156	12.61	7.80	$C_9H_{14}N_3OSI$

[a] In Me_2SO-d_6. [b] All compounds were analyzed for C, H, and N.

The synthesis of these iodides was also accomplished by methylation of (*E*)- and (*Z*)-4-[(hydroxyimino)methyl]-imidazole derivatives[11]. The quaternization of both *E* and Z aldoximes with CH_3I resulted in the corresponding methiodides, having in all cases a *Z* configuration[12].

The compounds **2a–d** could not be prepared by the former methods; it was therefore necessary to use a route involving conversion of 1-aryl-2-(benzylthio)-4-formyl-imidazole to its dimethyl acetal (**3a–d**), methylation and hydrolysis to 1-aryl-4-formyl-3-methyl-2-(methylthio)-imidazolium iodide, followed by reaction with hydroxylamine. In this last reaction a single product was isolated; in the case of **2a** and **2c**, the *E* isomer was isolated and in the case of **2b** and **2d**, the *Z* isomer was isolated.

The methylation of the imidazole ring in the compounds that had a benzylthio group in position 2 of imidazole was accompanied by the substitution of the benzyl group by a methyl group, yielding a 2-(methylthio)imidazole derivative.

The configuration of these compounds was determined by the study of their proton NMR spectra Me_2SO-d_6; $\Delta(\delta(OH) - \delta(CH{=}N))$ is larger in the *Z* isomers[13].

Results and Discussion

The results of the biological testing that are tabulated in Table V indicate that all compounds are weak reactivators of AcChE inhibited by TEPP; the most active of them, **1f** and **2f** (*Z* isomer), are about 2 times less active than 2-PAM.

The introduction of a methylthio group in position 2 of the imidazole ring, **2a–f**, exerts generally a weak negative effect on the reactivating properties, possibly because of steric factors and a partial neutralization of the positive charge on the nitrogen atom by the methylthio group. Therefore, these compounds exhibit a weak affinity for the anionic site of the enzyme.

Reduction of activity in comparison with that of 2-PAM seems to be due to the low acidity of this hydroxyimino group more than to a lack of structural requirements.

Experimental Section

Melting points are uncorrected. Proton NMR spectra were recorded with a Hitachi Perkin-Elmer R-20B spectrometer with Me_4Si as internal standard. Where analyses are indicated only by symbols of the elements, the analytical results obtained for the elements were within 0.4% of the theoretical values.

1-Aryl(alkyl)-4-[(hydroxyimino)methyl]-3-methylimidazolium Iodides 1a–f (Table I). Method A. To 0.01 mol of oxime[11] dissolved in MeOH was added 2.5 mL (0.04 mol) of CH_3I. The solution was heated for 4 days at 60 °C. Evaporation of the solvent gave a residue, which solidified after being washed with Me_2CO. The product was filtered and recrystallized from absolute EtOH.

Method B. To 0.01 mol of 4-formylimidazole derivative[11] dissolved in nitrobenzene was added 0.04 mol of CH_3I. The solution was kept at room temperature for 8–10 days. The quaternary salt that precipitated was filtered and washed with ether.

The 4-formylimidazole methiodide obtained was added in small portions with stirring to a methanolic solution of hydroxylamine. This solution was kept at room temperature for 2 h. The solvent was removed, giving a solid residue, which was washed with ether. The product was filtered and recrystallized from absolute EtOH.

The methanolic solution of hydroxylamine was prepared by dissolving $NH_2OH{\cdot}HCl$ (0.03 mol) in a minimum amount of warm methanol and neutralizing with methanolic KOH. After cooling

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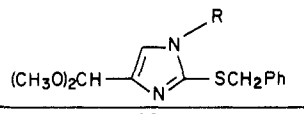
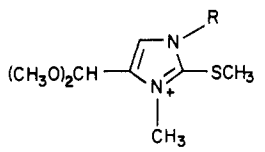
Table III. Dimethyl Acetal of 1-Aryl-2-(benzylthio)-4-formylimidazole



compd[a]	R	yield, %	mp, °C	formula[b]
3a	4-EtOPh	73	*c*	$C_{21}H_{24}N_2O_3S$
3b	4-MeOPh	50	72–74	$C_{20}H_{22}N_2O_3S$
3c	4-MePh	51	76–78	$C_{20}H_{22}N_2O_2S$
3d	Ph	70	*c*	$C_{19}H_{20}N_2O_2S$

[a] The NMR spectra of these compounds in Cl_3CD showed for the protons of the benzylthio group two signals with chemical shifts at δ 7.00 and 4.10. [b] See footnote *b*, Table II. [c] These compounds are oils.

Table IV. 1-Aryl-4-(dimethoxymethyl)-3-methyl-2-(methylthio)imidazolium



compd[a]	R	yield, %	mp, °C	formula[b]
4a	4-EtOPh	51	140–144	$C_{16}H_{23}N_2O_3SI$
4b	4-MeOPh	88	163–165	$C_{15}H_{21}N_2O_3SI$
4c	4-MePh	54	148–150	$C_{15}H_{21}N_2O_2SI$
4d	Ph	40	148–150	$C_{14}H_{19}N_2O_2SI$

[a] The NMR spectra of these compounds in Cl_3CD showed for the protons of the methylthio group one signal with chemical shift at 2.33 ppm and lack of the signals of the benzylthio group; see footnote *a*, Table III. [b] See footnote *b*, Table II.

the KCl was removed by filtration.

1-Alkyl-4-[(hydroxyimino)methyl]-3-methyl-2-(methylthio)imidazolium Iodides 2e–f (Table II). Method A. To 0.01 mol of 1-alkyl-2-(benzylthio)-4-[(hydroxyimino)methyl]-imidazole dissolved in MeOH was added 0.04 mol of CH_3I. The solution was heated for 4 days at 40–70 °C. The solvent was removed, giving an oil which dissolved in absolute EtOH, and was precipitated with ether and recrystallized from absolute EtOH.

Method B. This method is similar to the one we have already described.

Dimethyl Acetal of 1-Aryl-2-(benzylthio)-4-formylimidazoles 3a–d (Table III). The 1-aryl-2-(benzylthio)-4-formylimidazole (0.017 mol) was dissolved in absolute MeOH and left overnight. To this mixture was added 40 mL of a solution of hydrogen chloride in methanol, the final concentration of HCl being 1% with respect to the total amount of methanol. The mixture was kept at room temperature for 30 h. After filtration it was neutralized with methanolic KOH to pH 8–9. It was filtered and the solvent was removed and the residue obtained was extracted with EtOAc. Evaporation of the organic extract left a residue which was chromatographed on a silica gel column with a 1:1 *n*-hexane–ether mixture as eluent for its purification.

1-Aryl-4-(dimethoxymethyl)-3-methyl-2-(methylthio)-imidazolium Iodides 4a–d (Table IV). To 0.01 mol of the dimethyl acetal of 1-aryl-2-(benzylthio)-4-formylimidazole dissolved in nitrobenzene was added 0.04 mol of CH_3I. The mixture was kept at room temperature for 8 days. The product was precipitated with ether, filtered, and washed again with ether. It was recrystallized from absolute EtOH.

1-Aryl-4-[(hydroxyimino)methyl]-3-methyl-2-(methylthio)imidazolium Iodides 2a–d (Table II). The 1-aryl-4-(dimethoxymethyl)-3-methyl-2-(methylthio)imidazolium iodide (0.013 mol) was added to 25 mL of 16% HOAc. The mixture was refluxed for 30 min. Evaporation of the solvent gave an oil, which was washed with absolute EtOH.

The product obtained was added to a methanolic solution of hydroxylamine, which was prepared as previously described, with stirring at room temperature for 2 h.

The yellow salt gradually dissolved and a white precipitate appeared, which was filtered and washed with ether. The filtrate was evaporated under reduced pressure, giving a gummy residue, which dissolved in absolute EtOH was precipitated with ether.

Both solids obtained were the same product. They were recrystallized from absolute EtOH.

Table V. Activities of 4-[(Hydroxyimino)methyl]imidazole Methiodides on TEPP-Inhibited AcChE

compd	pK_a[a]	max reactivation by oxime,[b] 1×10^{-3} M
2-PAM	7.93	100
1a	9.44	none
1b	9.43	none
1c	9.40	45.29 ± 0.03[c]
1d	9.49	33.54 ± 0.05
1e	9.57	30.54 ± 0.06
1f	9.56	57.08 ± 0.04
2a	9.12	23.54 ± 0.02
2b	9.38	none
2c	9.04	23.54 ± 0.06
2d	9.30	none
2e	9.56	17.65 ± 0.02
2f[d]	9.24	none
2f[e]	9.42	46.37 ± 0.02

[a] See Experimental Section. [b] These values are the mean of three experiments. [c] SD. [d] *E* isomer. [e] *Z* isomer.

pK_a Values. These were determined by potentiometric titration with 0.1 N KOH of the oxime (about 10^{-3} M) in aqueous KNO_3 (0.1 M) at 25 °C under a nitrogen a atmosphere. The KNO_3 was used to maintain an approximately constant ionic strength. The pK_a values were calculated by the Bjerrum statistical method[14].

Enzymatic Assays. The in vitro reactivating potency of the new compounds was determined with electrophorus electricus acetylcholinesterase (AcChE, Boehringer Mannhein Co.). The inhibited enzyme samples were prepared by incubation of AcChE (9000 IU/mL of veronal buffer, 0.12 M, pH 7.4) with 10^{-5} M TEPP at 30 °C for 30 min, which was the time of maximum inhibition. At the end of the incubation period, the extracts were dialyzed against the same buffer; the buffer was changed every hour (seven times) in order to remove the excess of inhibitor. The enzyme activity was measured before and after the addition of different reactivators at a concentration 10^{-3} M. Incubations were carried out at 30 °C for a specific length of time (3, 15, 30, and 60 min). Maximum reactivation was always reached at 15 min. Measures of AcCHE activity were carried out according to the method of Ellman et al.[15] The reaction mixture for the enzyme assay consisted of the following: 3.0 mL of buffer (phospate, 0.1 M, pH 8.0), 20.0 μL of substrate (acetylthiocholine iodide, 0.075 M, Sigma Co.)., 100 μL of 3,3′-dithiobis[6-nitrobenzoic acid] (DTNB, 0.01 M, Sigma Co.), and 50.0 μL of enzyme (dilution 1:5000 of the initial solution in both cases, inhibited and reactivated enzyme). The reaction rates were recorded with a Pye Unicam SP1700 ultraviolet spectrophotometer. A blank with DTNB, buffer, and substrate was used for each experiment.

Acknowledgment. We thank Drs. J. Niclos and A. Matilla for the pK_a value determinations.

Registry No. **1a**, 92642-72-3; **1b**, 92642-73-4; **1c**, 92642-74-5; **1d**, 92642-75-6; **1e**, 92642-76-7; **1f**, 92642-77-8; **2a**, 92642-78-9; **2b**, 92642-79-0; **2c**, 92642-80-3; **2d**, 92642-81-4; **2e**, 92642-82-5; (*E*)-**2f**, 92642-83-6; (*Z*)-**2f**, 92642-84-7; **3a**, 92642-85-8; **3b**, 92642-86-9; **3c**, 92642-87-0; **3d**, 92642-88-1; **4a**, 92642-89-2; **4b**, 92642-90-5; **4c**, 92642-91-6; **4d**, 92669-34-6; TEPP, 107-49-3; AChE, 9000-81-1; NH_2OH·HCl, 5470-11-1; 1-(4-ethoxyphenyl)-2-(benzylthio)-4-formylimidazole, 3681-86-5; 1-(4-methoxyphenyl)-2-(benzyl-

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thio)-4-formylimidazole, 3681-84-3; 1-(4-methylphenyl)-2-(benzylthio)-4-formylimidazole, 3681-92-3; 1-phenyl-2-(benzylthio)-4-formylimidazole, 50541-33-8; 1-(4-ethoxyphenyl)-4-formylimidazole, 52046-24-9; 1-(4-methoxyphenyl)-4-formylimidazole, 52046-23-8; 1-phenyl-4-formylimidazole, 88091-36-5; 1-ethyl-4-formylimidazole, 88091-37-6; 1-allyl-4-formylimidazole, 88091-38-7; 1-ethyl-2-(methylthio)-4-formylimidazole, 92642-93-8; 1-allyl-2-(methylthio)-4-formylimidazole, 92642-92-7.

Relationship between Structure and Antineoplastic Activity of (Arylsulfonyl)hydrazones of 4-Pyridinecarboxaldehyde

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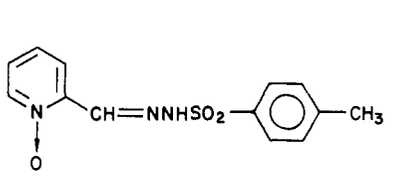
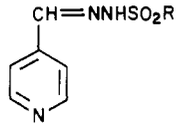
The effects of various structural modifications on the antineoplastic activity of (arylsulfonyl)hydrazones of 4-pyridinecarboxaldehyde were examined in mice bearing either Sarcoma 180 or P388 leukemia. The introduction of different functional groups into the phenyl ring of the benzenesulfonyl moiety did not alter tumor inhibitory activity appreciably, and the pyridine ring could be replaced by 4-nitrobenzene without loss of antineoplastic activity. However, the aldehyde proton and the hydrazone proton α to the sulfonyl group were essential, and their substitution resulted in inactive anticancer agents.

The relatively wide-spectrum antitumor activity displayed by 1-oxidopyridine-2-carboxaldehyde (*p*-tolylsulfonyl)hydrazone (1) has led our laboratory to conduct a relatively extensive study of the structural requirements for activity by this class of agents.[1-5] The *N*-oxide function was found to be essential for tumor-inhibitory activity except in those cases in which the formylhydrazone side chain was in the 4-position of the pyridine ring.[1]



1



2. R = C_6H_4-*p*-CH_3
3. R = $CH_2C_6H_5$

Two compounds of this type were synthesized earlier[1] (2 and 3) and both displayed anticancer activity against Sarcoma 180, but no additional modifications of this type were attempted. Since these compounds appeared to constitute a new group of antineoplastic agents, it was of interest to study the effects of various structural modifications on biological activity. To this end, this paper reports (a) the synthesis of a series of 4-pyridinecarboxaldehyde (arylsulfonyl)hydrazones substituted at the aldehyde carbon, the benzene ring, and the hydrazone nitrogen α to the sulfonyl group, (b) the synthesis of a series of (arylsulfonyl)hydrazones derived from 4-nitrobenzaldehyde, and (c) the antineoplastic activity of these agents in mice bearing the P388 leukemia and/or Sarcoma 180 ascites cells.

Chemistry. (Arylsulfonyl)hydrazones of 4-pyridinecarboxaldehyde hydrochloride, 4-nitrobenzaldehyde, and 4-acetylpyridine (Table I) were prepared by reacting the appropriate aldehyde or ketone with various (arylsulfonyl)hydrazides. Commercially unavailable (arylsulfonyl)hydrazides, including the *N*-methyl-substituted one, were prepared by using or adapting published procedures.[6-9] The preparation of (arylsulfonyl)hydrazones of 4-pyridinecarboxaldehyde hydrochloride was dictated by the observation that these compounds were considerably more stable at room temperature than those derived from 4-pyridinecarboxaldehyde, i.e., the free base.

Biological Results and Discussion. The tumor inhibitory properties of various (arylsulfonyl)hydrazones were determined by measuring their effects on the survival time of mice bearing the P388 leukemia and/or Sarcoma 180 ascites cells; the results are shown in Tables II and III. A range of daily dosage levels was tested for each compound; however, only the results produced by the maximum effective daily dose of each agent are listed.

In general, the (arylsulfonyl)hydrazones of 4-pyridinecarboxaldehyde hydrochloride were found to be potent inhibitors of the growth of Sarcoma 180, increasing the survival time of treated tumor-bearing mice two- to threefold. Replacement of the pyridine ring of the parent compound with 4-nitrophenyl resulted in retention of activity against this tumor. Earlier studies by this laboratory[1] demonstrated a complete loss of activity against Sarcoma 180 when the pyridine *N*-oxide portion of compound 1 was replaced by 2-nitrophenyl.

As observed with (arylsulfonyl)hydrazones of 1-oxidopyridine-2-carboxaldehyde,[2] extensive modification of the aryl group of the sulfonylhydrazone portion of the molecule was possible without appreciable loss of activity against Sarcoma 180. However, no clear-cut correlation could be discerned between the levels of activity and the Hammett

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