

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.

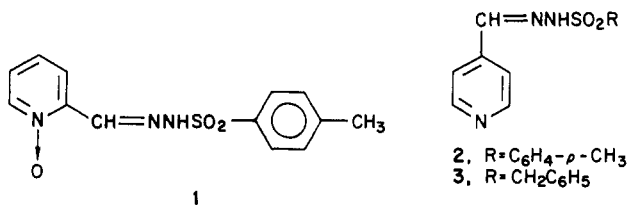
## Relationship between Structure and Antineoplastic Activity of (Arylsulfonyl)hydrazones of 4-Pyridinecarboxaldehyde

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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  $\alpha$  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.<sup>1-5</sup> 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.<sup>1</sup>



Two compounds of this type were synthesized earlier<sup>1</sup> (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  $\alpha$  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.<sup>6-9</sup> 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<sup>1</sup> 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-oxido-pyridine-2-carboxaldehyde,<sup>2</sup> 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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**Table I.** Physical Constants for Aldehyde and Ketone (Arylsulfonyl)hydrazones

| <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <chem>Cl[N+]1=CC=C(R)C=C1</chem><br/>A         </div> <div style="text-align: center;"> <chem>[O-][N+]1=CC=C(R)C=C1</chem><br/>B         </div> <div style="text-align: center;"> <chem>c1ccncc1R</chem><br/>C         </div> </div> |   |          |                      |   |                |
|---|---|----------|----------------------|---|----------------|
| compd   | R   | yield, % | mp, °C<br>dec        | formula   | anal.          |
| Group A (Pyridine Hydrochlorides)   |   |          |                      |   |                |
| 4   | CHNNHSO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>  | 71       | 139–140              | C <sub>12</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>2</sub> S               | C, H, N, S     |
| 5   | CHNNHSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-CH <sub>3</sub>                                       | 77       | 151–152              | C <sub>13</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>2</sub> S               | C, H, N        |
| 6   | CHNNHSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-OCH <sub>3</sub>                                      | 73       | 134–135              | C <sub>13</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>3</sub> S               | C, H, N, Cl, S |
| 7   | CHNNHSO <sub>2</sub> C <sub>6</sub> H <sub>2</sub> -2,4,6-(CH <sub>3</sub> ) <sub>3</sub>                   | 68       | 117–118              | C <sub>15</sub> H <sub>18</sub> ClN <sub>3</sub> O <sub>2</sub> S               | C, H, N        |
| 8   | CHNNHSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-Cl  | 64       | 132–133              | C <sub>12</sub> H <sub>11</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub> S | C, H, N        |
| 9   | CHNNHSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-NHCOCH <sub>3</sub>                                   | 77       | 115–117              | C <sub>14</sub> H <sub>15</sub> ClN <sub>3</sub> O <sub>3</sub> S               | C, H, N, S     |
| 10  | CHNNHSO <sub>2</sub> C <sub>6</sub> H <sub>3</sub> -3,4-(OCH <sub>3</sub> ) <sub>2</sub>                    | 73       | 134–135              | C <sub>14</sub> H <sub>16</sub> ClN <sub>3</sub> O <sub>4</sub> S               | C, H, N, Cl, S |
| 11  | CHNNHSO <sub>2</sub> C <sub>6</sub> H <sub>2</sub> -2,4,6-[CH(CH <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub> | 54       | 110–112              | C <sub>21</sub> H <sub>30</sub> ClN <sub>3</sub> O <sub>2</sub> S               | C, H, N, Cl, S |
| 12  | CHNNHSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-NO <sub>2</sub>                                       | 58       | 125–127              | C <sub>12</sub> H <sub>11</sub> ClN <sub>3</sub> O <sub>4</sub> S               | C, H, N        |
| 13  | CHNN(CH <sub>3</sub> )SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-Cl                                   | 74       | 233–235              | C <sub>13</sub> H <sub>13</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub> S | C, H, N        |
| Group B (4-Nitrobenzenes)   |   |          |                      |   |                |
| 14  | CHNNHSO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>  | 79       | 164–166 <sup>a</sup> | C <sub>13</sub> H <sub>11</sub> N <sub>3</sub> O <sub>4</sub> S                 | C, H, N, S     |
| 15  | CHNNHSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-CH <sub>3</sub>                                       | 75       | 157–158              | C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> O <sub>4</sub> S                 | C, H, N, S     |
| 16  | CHNNHSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-OCH <sub>3</sub>                                      | 81       | 146–148              | C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> O <sub>5</sub> S                 | C, H, N, S     |
| 17  | CHNNHSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-Cl  | 70       | 168–169              | C <sub>13</sub> H <sub>10</sub> ClN <sub>3</sub> O <sub>4</sub> S               | C, H, N, S     |
| 18  | CHNNHSO <sub>2</sub> C <sub>6</sub> H <sub>2</sub> -2,4,6-(CH <sub>3</sub> ) <sub>3</sub>                   | 67       | 158–159 <sup>b</sup> | C <sub>16</sub> H <sub>17</sub> N <sub>3</sub> O <sub>4</sub> S                 | C, H, N, S     |
| Group C (Pyridine)  |   |          |                      |   |                |
| 19  | C(CH <sub>3</sub> )NNHSO <sub>2</sub> C <sub>6</sub> H <sub>2</sub> -2,4,6-(CH <sub>3</sub> ) <sub>3</sub>  | 76       | 153–154              | C <sub>16</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> S                 | C, H, N        |

<sup>a</sup> Lit. mp 167 °C.<sup>14</sup> <sup>b</sup> Lit. mp 153 °C (fast heating); 170 °C (slow heating).<sup>15</sup>**Table II.** Effects of (Arylsulfonyl)hydrazones on the Survival Time of Mice Bearing Sarcoma 180 Ascites Cells

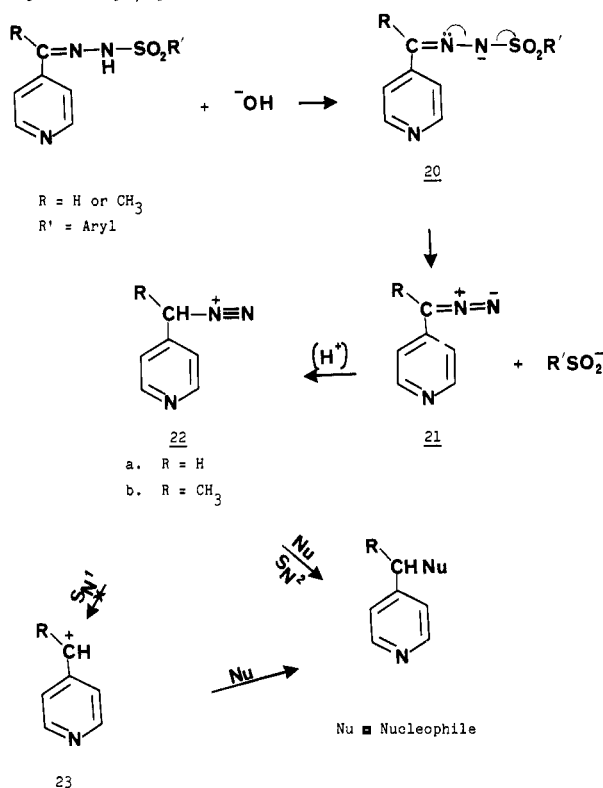
| compd | max effective<br>daily dose, <sup>a</sup><br>mg/kg | av Δ<br>wt, <sup>b</sup> % | av survival<br>time of<br>treated animals,<br>days ± SE | av survival<br>time of<br>control animals,<br>days ± SE | % T/C <sup>c</sup> |
|-------|--|----------------------------|---|---|--------------------|
| 2     | 100  | -16.7                      | 32.4 ± 2.3  | 14.6 ± 3.1  | 222                |
| 4     | 100  | -8.6                       | 32.0 ± 1.7  | 14.2 ± 1.5  | 225                |
| 5     | 100  | -14.5                      | 36.4 ± 1.0  | 14.6 ± 3.1  | 249                |
| 6     | 100  | -10.7                      | 31.0 ± 1.7  | 14.2 ± 1.5  | 218                |
| 7     | 50   | -8.4                       | 34.0 ± 3.2  | 14.2 ± 1.5  | 239                |
| 8     | 150  | -5.4                       | 28.6 ± 1.3  | 11.8 ± 0.5  | 242                |
| 9     | 150  | -5.2                       | 34.0 ± 4.3  | 11.8 ± 0.5  | 288                |
| 10    | 200  | -9.1                       | 32.8 ± 2.6  | 11.8 ± 0.5  | 278                |
| 11    | 200  | -3.1                       | 31.0 ± 1.4  | 11.8 ± 0.5  | 262                |
| 12    | 75   | -8.1                       | 37.4 ± 2.8  | 11.4 ± 0.7  | 328                |
| 13    | 100  | -4.2                       | 16.0 ± 1.3  | 14.6 ± 3.1  | 110                |
| 14    | 150  | -12.1                      | 20.8 ± 1.4  | 11.4 ± 0.7  | 182                |
| 15    | 100  | -17.4                      | 29.6 ± 5.0  | 15.0 ± 1.6  | 197                |
| 16    | 100  | -19.0                      | 23.8 ± 4.3  | 15.0 ± 1.6  | 159                |
| 17    | 100  | -16.0                      | 28.4 ± 2.2  | 15.0 ± 1.6  | 189                |
| 18    | 100  | -10.2                      | 26.4 ± 1.3  | 11.4 ± 0.7  | 231                |
| 19    | 100  | +3.2                       | 20.6 ± 2.6  | 16.8 ± 2.4  | 123                |

<sup>a</sup> Administered once daily for six consecutive days, beginning 24 h after tumor transplantation. <sup>b</sup> Average change in body weight from onset to termination of drug therapy. <sup>c</sup> % T/C = average survival time of treated/control animals × 100.**Table III.** Effects of (Arylsulfonyl)hydrazones on the Survival Time of Mice Bearing the P388 Leukemia

| compd | max effective<br>daily dose, <sup>a</sup><br>mg/kg | av Δ<br>wt, <sup>b</sup> % | av survival<br>time of<br>treated animals,<br>days ± SE | av survival<br>time of<br>control animals,<br>days ± SE | % T/C <sup>c</sup> |
|-------|--|----------------------------|---|---|--------------------|
| 4     | 150  | -3.1                       | 18.0 ± 1.1  | 14.6 ± 0.4  | 123                |
| 5     | 150  | -7.6                       | 17.2 ± 0.9  | 14.6 ± 0.4  | 118                |
| 6     | 150  | +0.7                       | 18.0 ± 1.2  | 14.6 ± 0.4  | 123                |
| 7     | 100  | -2.2                       | 18.8 ± 0.7  | 14.6 ± 0.4  | 129                |
| 8     | 200  | -5.4                       | 16.6 ± 0.6  | 14.8 ± 0.4  | 112                |
| 9     | 150  | -3.1                       | 17.6 ± 1.4  | 14.6 ± 0.4  | 121                |
| 10    | 100  | -3.0                       | 17.6 ± 0.7  | 14.8 ± 0.4  | 119                |
| 11    | 200  | -0.9                       | 17.0 ± 0.3  | 13.8 ± 0.5  | 123                |
| 12    | 200  | -7.5                       | 17.6 ± 0.5  | 13.8 ± 0.5  | 128                |
| 14    | 150  | -0.1                       | 14.8 ± 0.5  | 14.2 ± 0.5  | 104                |
| 15    | 200  | -3.0                       | 15.2 ± 0.2  | 14.2 ± 0.5  | 107                |
| 16    | 200  | -5.7                       | 14.6 ± 0.2  | 14.8 ± 0.4  | 99                 |
| 17    | 200  | -2.4                       | 15.2 ± 0.2  | 14.2 ± 0.5  | 107                |
| 18    | 150  | -3.5                       | 17.2 ± 0.5  | 14.2 ± 0.5  | 121                |

<sup>a</sup> Administered once daily for six consecutive days, beginning 24 h after tumor transplantation. <sup>b</sup> Average change in body weight from onset to termination of drug therapy. <sup>c</sup> % T/C = average survival time of treated/control animals × 100.

Scheme I. Proposed Mechanism of Alkylation by (Arylsulfonyl)hydrazones of 4-Pyridinecarboxaldehyde



$\sigma$  or the Hansch  $\pi$  values of the aryl substituents.<sup>10</sup> Thus, the most active member of the series was compound 12 [4-NO<sub>2</sub>], followed by 9 [4-NHCOCH<sub>3</sub>] and 10 [3,4-(OC<sub>2</sub>H<sub>5</sub>)<sub>2</sub>]. The (arylsulfonyl)hydrazone of 4-acetylpyridine (19) and the methyl[(4-chlorophenyl)sulfonyl]hydrazone of 4-pyridinecarboxaldehyde hydrochloride (13) were much less active than the corresponding desmethyl analogues (7 and 8, respectively).

If an alkylation mechanism similar to the one proposed<sup>11</sup> for the (arylsulfonyl)hydrazones of 1-oxido-2-pyridinecarboxaldehyde is responsible for the activity of (arylsulfonyl)hydrazones of 4-pyridinecarboxaldehyde, the presence or in vivo generation of a hydrazone proton  $\alpha$  to the sulfonyl group would be a precondition for antineoplastic activity. Hence, the lack of formation of an alkylating species could be responsible for the inactivity of compound 13. The low level of activity displayed by 19, on the other hand, could be due to the mechanism of the final alkylation step (Scheme I). Thus, compound 22, once formed, could react with a nucleophile by either an S<sub>N</sub>1 or S<sub>N</sub>2 mechanism. An S<sub>N</sub>1 mechanism would involve the formation of the highly unstable  $\gamma$ -picolyl carbocation (23) and, therefore, is quite unlikely. An S<sub>N</sub>2 mechanism, on the other hand, would involve a secondary substrate (22b) in the case of 13 and a primary substrate in the case of the corresponding desmethyl analogue (22a). Since branching at the  $\alpha$ -carbon decreases the rate of S<sub>N</sub>2 reaction,<sup>12</sup> one would expect 22b to be much less reactive toward nucleophiles than 22a. The results of experiments done to confirm these hypotheses and to elucidate other aspects

of the mechanism of action of this series of compounds will be published elsewhere.

The compounds synthesized displayed much lower levels of activity against the P388 leukemia than against Sarcoma 180. This finding may be the result of the relatively rapid host dissemination of leukemic cells coupled with the relatively great reactivity of compounds of this class. Thus, (arylsulfonyl)hydrazones of these classes might well be useful clinically against neoplastic cells confined to the pleural and/or peritoneal cavities. The most active compounds of this class tested to date against the P388 leukemia are 7 and 12; the nitrobenzene analogues were essentially inactive against this tumor.

## Experimental Section

Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were determined with a Varian T-60A spectrometer with Me<sub>4</sub>Si as an internal standard. The spectral data were as expected; therefore, routine data are not included. Elemental analyses were performed by the Baron Consulting Co. (Orange, CT). Where analyses are indicated by symbols of elements, the analytical results for those elements were within  $\pm 0.4\%$  of the theoretical values. Pertinent physical data for the compounds synthesized are listed in Table I.

**Antitumor Activity.** The ascites cell forms of Sarcoma 180 and P388 leukemia were grown in CDF-1 mice. Transplantation was carried out with donor animals bearing 7-day tumor growths; experimental details have been described earlier.<sup>13</sup> Mice were weighed during the course of experiments, and the percentage change in body weight from onset to termination of therapy was used as an indication of host toxicity. Dosage levels of each compound were administered over a range of 50–200 mg/kg per day for six consecutive days beginning 24 h after tumor implantation. Where a hydrochloride salt was used, the pH of the drug solution was adjusted to 6.5–7.0 prior to administration. 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 (Arylsulfonyl)hydrazones of 4-Pyridinecarboxaldehyde Hydrochloride.** To a solution of 4-pyridinecarboxaldehyde hydrochloride (1.43 g, 0.01 mol) in methanol (5 mL) was added the appropriate (arylsulfonyl)hydrazide (0.011 mol) in tetrahydrofuran (5 mL). The reaction mixture was filtered immediately and cooled. The (arylsulfonyl)hydrazone that precipitated was filtered, washed with cold methanol, and dried. Recrystallization from methanol-ether afforded the analytically pure product.

**General Procedure for Preparation of (Arylsulfonyl)hydrazones of 4-Nitrobenzaldehyde.** These compounds were prepared by using a method analogous to one previously employed by this laboratory<sup>1</sup> for the synthesis of 2-nitrobenzaldehyde (*p*-tolylsulfonyl)hydrazone.

**4-Acetylpyridine [(2,4,6-Trimethylphenyl)sulfonyl]hydrazone (19).** To a solution of 4-acetylpyridine (1.21 g, 0.01 mol) in methanol (5 mL) was added [(2,4,6-trimethylphenyl)sulfonyl]hydrazide (2.35 g, 0.011 mol), and the mixture was heated on a boiling water bath. When crystallization began, the heating was stopped and the reaction mixture cooled slowly to 0 °C. The (arylsulfonyl)hydrazone was filtered, washed with cold methanol, and dried.

**N-Methyl-N-[(4-chlorophenyl)sulfonyl]hydrazide.** To an ice-cold solution of 4-chlorobenzenesulfonyl chloride (4.22 g, 0.02 mol) in tetrahydrofuran (15 mL) was added methylhydrazine (2.2 mL, 0.04 mol) at a rate that maintained the temperature between 0 and 5 °C. Stirring was continued for 1 h after addition was complete. The reaction mixture was diluted with 250 mL of cold

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water, and the desired compound separated as a white solid (3.9 g, 88%): mp 109–110 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.76 and 7.42 (2 d, 4 H, aromatic), 3.60 (br, 2 H,  $\text{NH}_2$ ), 2.90 (s, 3 H,  $\text{CH}_3$ ).

**Acknowledgment.** This research was supported in part by U.S. Public Health Service Grant CA-02817 from the National Cancer Institute.

**Registry No.** 4, 70027-02-0; 4·HCl, 93061-74-6; 5, 18708-54-8; 5·HCl, 58414-95-2; 6, 93061-87-1; 6·HCl, 93061-75-7; 7, 93061-88-2; 7·HCl, 93061-76-8; 8, 93061-89-3; 8·HCl, 93061-77-9; 9, 93061-90-6; 9·HCl, 93061-78-0; 10, 93061-91-7; 10·HCl, 93061-79-1; 11, 82222-59-1; 11·HCl, 93061-80-4; 12, 93061-92-8; 12·HCl, 93061-81-5;

13, 93061-93-9; 13·HCl, 93061-82-6; 14, 50626-29-4; 15, 1747-50-8; 16, 93061-83-7; 17, 93061-84-8; 18, 16286-94-5; 19, 93061-85-9; 4-pyridinecarboxaldehyde hydrochloride, 93061-73-5; 4-acetylpyridine, 1122-54-9; 4-chlorophenylsulfonyl chloride, 98-60-2; *N*-methyl-*N*-[(4-chlorophenyl)sulfonyl]hydrazide, 93061-86-0; methylhydrazine, 60-34-4; phenylsulfonyl hydrazide, 80-17-1; [(4-methylphenyl)sulfonyl]hydrazide, 1576-35-8; [(4-methoxyphenyl)sulfonyl]hydrazide, 1950-68-1; [(2,4,6-trimethylphenyl)sulfonyl]hydrazide, 16182-15-3; [(4-chlorophenyl)sulfonyl]hydrazide, 2751-25-9; [(4-acetylamino)phenyl)sulfonyl]hydrazide, 3989-50-2; [(3,4-dimethoxyphenyl)sulfonyl]hydrazide, 23095-32-1; [(2,4,6-triisopropylphenyl)sulfonyl]hydrazide, 39085-59-1; [(4-nitrophenyl)sulfonyl]hydrazide, 2937-05-5.