Formed by the Sulfation of 2′,3′-Isopropylidene Adenosine with 8-Quinolyl Sulfate and Cu(II). Three reaction mixtures (2 ml each) containing 2′,3′-isopropylidene adenosine (0.1, 0.05, and 0.02 mmol), 8-quinolyl sulfate (0.1 mmol), and $CuCl_2$ (0.06 mmol) in dimethylformamide were allowed to react for 1 hr at 20° with stirring. After the reaction, each reaction mixture was mixed with water (0.1 ml) and warmed for 10 min at 50° to decompose excess 8-quinolyl sulfate. The reaction mixture was diluted with water (2 ml) and centrifuged to separate the Cu(II) complex formed. The supernatant was applied to paper electrophoresis using the buffer solution a. Each paper zone corresponding to 2′,3′-isopropylidene adenosine or its 5′-sulfate was cut off and extracted with water. The absorbance of each extract was measured at 260 nm and the relative amount of 2′,3′-isopropylidene adenosine and its 5′-sulfate was determined.

Determination of Riboflavin Sulfate Formed by the Sulfation of Riboflavin with 8-Quinolyl Sulfate and Cu(II). Three reaction mixtures (2 ml each) containing riboflavin (0.1, 0.05, and 0.02 mmol), 8-quinolyl sulfate (0.1 mmol), and $CuCl_2$ (0.06 mmol) in dimethylformamide were allowed to react for 5 hr at 20° with stirring. After the reaction, each reaction mixture was processed as in the case of 2′,3′-isopropylidene adenosine. Each water extract of the paper zones separated on the paper electrophoresis with the buffer solution b was analyzed by the method described in previous papers.[8]

Preparation of Adenosine 5′-Sulfate. A mixture of 2′,3′-isopropylidene adenosine (307 mg, 1 mmol), 8-quinolyl sulfate (337 mg, 1.5 mmol), and $CuCl_2$ (100 mg, 0.75 mmol) in anhydrous dimethylformamide (15 ml) was allowed to react for 3 hr at 20–22° with stirring. The reaction mixture was mixed with water (0.1 ml) and warmed for 10 min at 50°, followed by dilution with 15 ml of water. After removal of the 8-hydroxyquinoline–Cu(II) complex formed, the filtrate was passed through a column of Dowex 50W (X8, H^+, 20–50 mesh). The acidic effluent was neutralized with saturated $Ba(OH)_2$ solution and the precipitate formed was removed by centrifugation. The clear supernatant was passed through a column of Dowex 50W (X8, H^+, 20–50 mesh) and the acidic effluent was kept in a refrigerator. The needle crystals of 2′,3′-isopropylidene adenosine 5′-sulfate were separated, washed with a small volume of cold water, and dried over P_2O_5 *in vacuo* at room temperature, yield 270 mg (71%), mp 241–245° dec. *Anal.* Calcd for $C_{13}H_{17}N_5O_7S$: C, 40.31; H, 4.43; N, 18.08; S, 8.28. Found: C, 40.52; H, 4.44; N, 18.06; S, 8.35.

Removal of the isopropylidene group from the 2′,3′-isopropylidene adenosine 5′-sulfate prepared as above and isolation of the crystalline calcium salt of adenosine 5′-sulfate were carried out according to the method reported.[8a]

Preparation of Dextran Sulfate. A mixture of dextran (162 mg, 1 mmol glucose unit), 8-quinolyl sulfate (225 mg, 1 mmol), and $CuCl_2$ (67 mg, 0.5 mmol) in anhydrous dimethylformamide (10 ml) was warmed for 5 hr at 40° with stirring. The reaction mixture was diluted with water (50 ml) and the precipitate formed was removed by filtration. The filtrate was passed through a column of Dowex 50W (X8, H^+, 20–50 mesh) and the acidic effluent and washings were combined, neutralized with 2 *N* NaOH, and dialyzed overnight against tap water. The dialyzed solution was concentrated to *ca.* 3 ml *in vacuo* and filtered to remove a small amount of impurities. The clear concentrate was added dropwise into 50 ml of EtOH to precipitate sodium dextran sulfate, which was separated, washed with EtOH, and dried over P_2O_5 *in vacuo* for 3 hr at 80°, yield 220 mg, S, 10.78% (ratio of sulfate group to glucose unit, 0.85).

Preparation of D-Galactose 6-Sulfate. A mixture of 1,2:3,4-di-*O*-isopropylidene-D-galactose (0.52 g, 2 mmol) and 8-quinolyl sulfate (0.67 g, 3 mmol) in anhydrous pyridine was allowed to react in the presence of 8-hydroxyquinoline–Cu(II) (2:1) complex (0.11 g, 0.3 mmol) for 2 hr at 24° with stirring. The reaction mixture was mixed with water (0.1 ml) and warmed for 10 min at 50°. After removal of pyridine, the reaction mixture was diluted with water (20 ml) and the precipitate formed was removed by filtration. The filtrate was passed through a column of Dowex 50W (X8, H^+, 20–50 mesh), and the effluent and washings were combined. The resultant acidic solution (*ca.* 60 ml) was heated for 2 hr at 80° to remove the protecting groups, then neutralized with saturated $Ba(OH)_2$ solution. The precipitate formed was removed by centrifugation and the supernatant was concentrated *in vacuo* to *ca.* 3 ml, followed by precipitation with EtOH (70 ml). The white precipitate (0.54 g) obtained was dissolved in water (5 ml) and passed through a column of Dowex 50W (X8, H^+, 20–50 mesh) to give the free D-galactose 6-sulfate solution, which was mixed with EtOH solution (10 ml) containing brucine base (0.78 g, 1.7 mmol) with stirring. The mixture was evaporated to *ca.* 3 ml *in vacuo* and filtered to remove a small amount of impurities, then mixed with EtOH (50 ml) to separate a crystalline precipitate. The crystals were collected and dried over P_2O_5 *in vacuo* at room temperature, yield 0.93 g (71.0%), mp 170° dec. Satisfactory analytical data for N and S were obtained on the brucinium salt of D-galactose 6-sulfate ($C_6H_{12}O_9S \cdot C_{23}H_{26}O_4N_2$) prepared as above.

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Registry No.—8-Quinolyl sulfate, 2149-36-2; *N,N*-dimethylaniline, 121-69-7; 8-hydroxyquinoline, 148-24-3; 8-hydroxyquinoline–Cu(II) complex, 10380-28-6; 8-hydroxyquinoline–Ni(II) complex, 14100-15-3; 2′,3′-isopropylidene adenosine 5′-sulfate, 50585-65-4; 2′,3′-isopropylidene adenosine, 362-75-4; Cu, 7440-50-8; riboflavin sulfate, 50585-67-6; riboflavin, 83-88-5; adenosine 5′-sulfate, 2304-12-3; dextran sulfate, 9042-14-2; dextran, 9004-54-0; D-galactose 6-sulfate, 2152-84-3; Ni, 7440-02-0; Co, 7440-48-4; Zn, 7440-66-6; Cd, 7440-43-9; Mn, 7439-96-5; Fe, 7439-89-6.

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Nucleophile-Dependent Displacement of Chloride or Methylsulfinate Ions from 3,5-Dichloro-2,6-bis(methylsulfonyl)pyridine

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3,5-Dichloro-2,6-bis(methylsulfonyl)pyridine was allowed to react with various nucleophiles. It was found that nitrogen and carbon (CN^-) nucleophiles displaced chlorine atom(s) whereas alkoxide and fluoride ions displaced the methylsulfonyl groups. These results were explained using Pearson's hard-soft acid-base concept.

This report describes some of the unexpected results encountered with 3,5-dichloro-2,6-bis(methylsulfonyl)pyridine (1) was allowed to react with various nucleophiles.

It was observed that methylsulfinate ion was displaced from compound 1, 3,5-dichloro-2,6-bis(methylsulfonyl)pyridine, when it was allowed to react with potassium fluo-

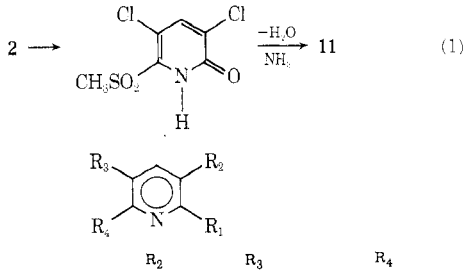
ride or an oxygen nucleophile. The products from these reactions are numbered **2–5.** However, we found that chloride ion was displaced from compound 1 when it was allowed to react with ammonia, dimethylamine, hydrazine, or sodium cyanide. These products are numbered **6–9.**

The question of nucleophile-dependent pathways bears some comment. The isolated products (2–11) from the reaction of 1 and various nucleophiles would indicate complete pathway specificity. However, it seems unlikely that one product was formed to the complete exclusion of another. This is especially true where yields were low. Nevertheless, the isolated products indicate that their reactions appear to follow (at least partially) nucleophile-dependent pathways, and a rationale to explain their results seems needed.

Pearson's[1-4] hard–soft acid–base concept offered one interpretation of these results. If one assumed that the electron density of 1 at C-2 and C-6 was lower than the electron density at C-3 or C-5 (*i.e.*, C-2 and C-6 had greater positive character), as a consequence of being adjacent to the pyridine nitrogen and the greater electron-withdrawing effect of the $-SO_2CH_3$ moiety, then one would expect these centers to be harder acids. Thus, they would prefer reactions with harder bases. On the other hand, if C-3 and C-5 had greater electron density relative to C-2 and C-6, then one would expect these centers to be softer acids and would prefer reactions with softer bases. The results are in agreement with explanation. The harders bases (RO^- and F^-) did indeed react at C-2 whereas the slightly softer bases (R_2NH and CN^-) reacted at C-3.

The electronic character of 1 must also be considered when discussing its reactions. It is well documented that nucleophilic displacements on a pyridine ring usually occur at the 2 and 4 position, whereas displacements at the 3 and 5 positions are exceptional.[5] The very powerful electron-withdrawing effect of the two methylsulfonyl groups on 1 must strongly activate the 3 and 5 positions toward nucleophilic substitution reactions. Thus, differentiation by hard and soft bases for the 2 and 3 positions, respectively, must be a consequence of the unusual electronic character of 1 created by the two methylsulfonyl groups and will not necessarily hold true for other pyridine derivatives.

When compound 2 was treated with ammonia at room temperature, the product was the amide **10.** Compound **11** was the only isolated product when 2 was heated with ammonia. It appeared that compound **2,** which contained a single methylsulfonyl group, behaved more like a "normal" pyridine (preference for displacements at the position adjacent to the nitrogen atom). An alternative explanation for the formation of **11** from 2 was formulated but later rejected. It was possible that 11 could have been formed by a sequence shown in eq 1, since the preparation of 4-aminopyridine from 4-pyridone is a known reaction.[6] However, when 3,5,6-trichloro-2-pyridone was treated with ammonia under the identical conditions, the only product observed was the ammonium salt **12.** Thus, the possibility that **11** was formed by this route seemed remote.



(1)

	R_1	R_2	R_3	R_4
1	SO_2CH_3	Cl	Cl	SO_2CH_3
2	$OCH_2CO_2CH_3$	Cl	Cl	SO_2CH_3
3	$OCH(CH_3)CO_2C_2H_5$	Cl	Cl	SO_2CH_3
4	$OCH(CH_3)CO_2C_2H_5$	Cl	Cl	$OCH(CH_3)CO_2C_2H_5$
5	F	Cl	Cl	F
6	SO_2CH_3	NH_2	Cl	SO_2CH_3
7	SO_2CH_3	$N(CH_3)_2$	Cl	SO_2CH_3
8	SO_2CH_3	$NHN{=}C(CH_3)_2$	Cl	SO_2CH_3
9	SO_2CH_3	CN	CN	SO_2CH_3
10	OCH_2CONH_2	Cl	Cl	SO_2CH_3
11	NH_2	Cl	Cl	SO_2CH_3
12	$O^-NH_4^+$	Cl	Cl	Cl

Experimental Section

Infrared spectra were recorded using a Perkin-Elmer 237B recording spectrometer. Proton nmr spectra were recorded using a Varian A-60 recording spectrometer. Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane, or sodium 2,2-dimethyl-2-silapentane-5-sulfonate for spectra taken in D_2O. Melting points were taken using a Thomas-Hoover melting point apparatus and are corrected. Room temperature was 23 ± 2°.

3,5-Dichloro-2,6-bis(methylsulfonyl)pyridine (1). A three-neck, 5-l. flask was fitted with a stirrer, a Dry Ice condenser, and a gas delivery tube. The flask was charged with 3 l. of methanol and sodium methoxide (238 g, 4.4 mol) and the flask was cooled with an external ice bath. Methyl mercaptan (202 g, 4.2 mol) was weighed into a cold trap and then rapidly distilled into the reaction flask. The ice bath was removed and 2,3,5,6-tetrachloropyridine (434 g, 2 mol) was added portionwise. The reaction mixture was allowed to stir for 1 hr at room temperature and then under reflux for 8 hr.

The crude product, 3,5-dichloro-2,6-bis(methylthio)pyridine, was isolated by pouring the reaction mixture into water, collecting the solid by filtration, washing the solid with water, and air drying. The product was recrystallized from hexane. Only the first fraction (270 g) was isolated. This fraction was recrystallized from methylcyclohexane. Two fractions were collected and combined to yield 223 g, mp 130–133°, of 3,5-dichlorobis(methylthio)pyridine.

The 3,5-dichlorobis(methylthio)pyridine (223 g, 0.94 mol) was dissolved in a solution of acetic acid (2 l.) and acetic anhydride (950 ml). Hydrogen peroxide (820 g of 30%) was added 100 ml at a time to the reaction solution. The temperature rose rapidly, and when it reached 75° the reaction mixture was cooled with an external ice–methanol bath. When the temperature fell below 80° the bath was removed. The temperature gradually rose to 100°. The reaction mixture was heated under reflux for 2 hr using an electric mantle. The reaction mixture was cooled to 60°, and an additional 200 ml of 30% hydrogen peroxide was added. The reaction mixture was refluxed for 1 hr and then allowed to cool and stand overnight at room temperature.

The reaction mixture was poured into water and the white, crystalline solid was collected by filtration and washed with water. It was dried in an evacuated oven (50°, 15 mm) for 18 hr to yield 265 g (93%) of a material identified as the title compound: mp 297–298°; infrared spectrum (mull) 1300 and 1148 cm^{-1} ($-SO_2-$); nmr spectrum (DMSO-d_6, hot) δ 8.86 (1 H, singlet, aromatic proton), 3.61 (6 H, singlet, $-SO_2CH_3$).

Anal. Calcd for $C_7H_7Cl_2NO_4S_2$: C, 27.62; H, 2.32; Cl, 23.3; N, 4.61; S, 21.05. Found: C, 28.2; H, 2.6; Cl, 23.44; N, 5.0; S, 20.82.

The title compound was found to be extremely insoluble. *N*-Methylpyrrolidone was found to be the best aprotic solvent for dissolving 1. The other solvents tested and found inferior were DMSO, DMF, 2-butanone, pyridine, tetrahydrofuran, sulfolane, acetone, acetonitrile, hexamethylphosphortriamide, and nitromethane.

Methyl [3,5-Dichloro-6-(methylsulfonyl)-2-(pyridyl)oxy]acetate (2). A 500-ml flask was charged with acetonitrile (250 ml) and sodium hydride (3.16 g of 50% oil dispersion washed with hexane). This mixture was cooled in an ice bath and methyl glycolate (5.73 g, 0.0658 mol) in acetonitrile (50 ml) was added dropwise over 0.5 hr with constant stirring. 3,5-Dichloro-2,6-bis(methylsulfonyl)pyridine (20.0 g, 0.0658 mol) was added. The reaction mixture was placed under an atmosphere of nitrogen gas and this mixture was gradually heated to 60° and allowed to cool to room temperature over a period of 2.5 hr. The reaction mixture was filtered and the filtrate was concentrated under a reduced pressure. The residual was dissolved in dichloromethane (175 ml), extracted with water (50 ml), and then dried over anhydrous potassium carbonate. The solvent was removed under a reduced pressure to yield a pale-pink solid. This solid was digested with ethanol (100 ml) and two crops of crystals were collected and air dried to yield

11.3 g (55%) of a material identified as the title compound: mp 129–133°; infrared spectrum (mull) 1760 (ester C=O), 1305 and 1140 cm^{-1} ($-SO_2-$); nmr spectrum (DMSO-d_6) δ 8.54 (1 H, singlet, aromatic proton), 5.15 (2 H, singlet, $-OCH_2CO-$), 3.72 (3 H, singlet, $-OCH_3$), 3.38 (3 H, singlet, CH_3SO_2-).

Anal. Calcd for $C_9H_9Cl_2NO_5S$: C, 34.41; H, 2.89; Cl, 22.57; N, 4.46. Found: C, 34.74; H, 3.08; Cl, 22.30; H, 4.45.

Ethyl 2-[3,5-Dichloro-6-(methylsulfonyl)-2-(pyridyl)oxy]propionate (3). A three-neck, 1-l. flask was fitted with a reflux condenser with drying tube (calcium sulfate) and stirring paddle. The flask was charged with freshly distilled *N*-methylpyrrolidone (500 ml) and 3,5-dichloro-2,6-bis(methylsulfonyl)pyridine (26.9 g, 0.0855 mol). This mixture was stirred and heated (100°) until a solution was effected and then allowed to cool to room temperature.

The sodium salt of ethyl lactate was prepared in a three-neck, 500-ml, bottom-draining, ice-jacketed flask which was fitted with a stirring paddle and dropping funnel. This bottom-draining flask was charged with freshly distilled *N*-methylpyrrolidone (400 ml) and sodium hydride (4.25 g of 50% oil dispersion which was washed three times with hexane, 0.0855 mol). This was cooled to 0° by external cooling with crushed ice, and ethyl lactate (10.45 g, 0.0855 mol) was added dropwise to the stirred solution of sodium hydride in *N*-methylpyrrolidone. The cold (0°) solution was stirred for 1 hr and then for 2.5 hr at room temperature. Bubbling and frothing had ceased.

This sodium salt of ethyl lactate was added dropwise through the bottom drain into the flask containing the sulfone. A slight exotherm was noted. This solution was stirred for 20 hr at room temperature. The reaction mixture was filtered, and the filtrate was diluted with a brine solution (1000 ml). This was extracted five times with 250-ml portions of dichloromethane. The dichloromethane eluents were combined, dried (sodium sulfate), and concentrated to a volume of 50 ml under a reduced pressure (2 mm) with warming (bath temperature 75°). The residual was triturated with benzene (200 ml) and a solid (1.3 g) was collected by filtration which proved to be the starting sulfone.

The filtrate was concentrated under a reduced pressure to yield a brown-black oil which was placed on a silica gel column (1.5 × 8.5 in., Merck silica gel) and eluted with benzene (1050 ml) followed by 20% ethyl acetate in benzene (600 ml). Fractions (150 ml) were collected. Fractions 3–11 were pale-orange oils which solidified. The fractions were combined and triturated with ethanol (50 ml), and crystals were collected by filtration to yield 1.6 g (4% based on unrecovered sulfone). A small sample was recrystallized from hot ethanol (5 ml) and the crystals were dried in an evacuated oven (15 mm at 50°) overnight to yield a white, crystalline material identified as the title compound: mp 100.5–101.5; infrared spectrum (mull) 1760 (ester C=O), 1310 and 1197 cm^{-1} ($-SO_2-$); nmr spectrum (acetone-d_6) δ 8.23 (1 H, singlet, aromatic proton), 5.34 [1 H, quartet, spacing = 7 Hz, $OCH(CH_3)CO-$], 4.2 (2 H, quartet, spacing = 7 Hz, OCH_2CH_3), 3.3 (3 H, singlet, CH_3SO_2-), 1.67 (3 H, doublet, spacing = 7 Hz, $CHCH_3$), 1.22 (3 H, triplet, spacing = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{11}H_{13}Cl_2NO_5S$: C, 38.61; H, 3.83; N, 4.09. Found: C, 38.70; H, 3.89; N, 4.21.

Diethyl 2,2′-[(3,5-Dichloro-2,6-pyridinediyl)dioxy]dipropionate (4). A solution of ethyl lactate (10.45 g, 0.0885 mol) in acetonitrile (50 ml) was added dropwise to a mixture of sodium hydride (4.25 g of 50% oil dispersion, 0.0885 mol) and acetonitrile (150 ml). 3,5-Dichloro-2,6-bis(methylsulfonyl)pyridine was added in one portion to this solution. The mixture was placed under an atmosphere of nitrogen gas and refluxed for 15 hr.

A white solid was collected by filtration and the filtrate was diluted with water (200 ml). This was extracted twice with 250-ml portions of chloroform. The chloroform eluents were combined, dried (magnesium sulfate), and concentrated under a reduced pressure to yield a brown oil. The oil was triturated with ethanol (75 ml) and water (50 ml) was added. A precipitate was collected by vacuum filtration and dried in an evacuated oven (25 mm at 50°) for 2 hr to yield 3.3 g (20% based on ethyl lactate present). A small sample was further purified by molecular distillation (bath temperature 110°, 0.1 mm) to yield a white solid which was shown to be the title compound mixed with a hydrocarbon: mp 90–91.5°; infrared spectrum (mull) 1750 cm^{-1} (ester C=O); nmr spectrum ($CDCl_3$) δ 7.65 (1 H, singlet, aromatic proton), 5.05 [2 H, quartet, spacing = 7H_3, $-COCH(CH_3)O-$], 4.23 (4 H, quartet, spacing = 7 Hz, CH_3CH_2O-), 1.62 (6 H, doublet, spacing = 7 Hz, $-CHCH_3$), 1.28 (6 H, triplet, spacing = 7 Hz, CH_3CH_2-), 1.5–0.7 δ (6 H, multiplet near base line, mineral oil).

Anal. Calcd for $C_{15}H_{19}Cl_2H_2O_6C_2H_6$: C, 49.8; H, 5.37; Cl, 17.3; N, 3.41. Found: C, 50.13; H, 5.63; Cl, 17.1; N, 3.4.

3,5-Dichloro-2,6-difluoropyridine (5). A three-neck, 500-ml flask was fitted with a reflux condenser with a drying tube, a stirring paddle, and a well containing a thermocouple which was connected to a controller. 3,5-Dichloro-2,6-bis(methylsulfonyl)pyridine (5.0 g), potassium fluoride [5.0 g, previously dried at 100° (15 mm) over 15 hr], and dimethyl sulfoxide (250 ml, dried by storage over 3A molecular sieves) were charged into the flask. The reaction was stirred and heated at 105° for 20 hr. The reaction mixture was diluted with water (200 ml) and then steam distilled. The condensate, approximately 200 g, was saturated with sodium chloride and extracted twice with 100-ml portions of dichloromethane. The combined dichloromethane eluents were dried (Na_2SO_4) and concentrated under a reduced pressure to yield a pale-yellow liquid. A vapor phase chromatograph of this liquid indicated that the major components were (in order of elution) dichloromethane, dimethyl sulfoxide, and a third material. The conditions of the chromatograph were the following: column, 2 ft × 0.125 in. (o.d.) glass packed with 5% 410 silicone gum on a Chromosorb Q (60/80 mesh); temperature program from 50 to 150° at an increase of 11°/min; helium flow 40 ml/min. This third material was identified as the title compound, as its proton and ^{19}F nmr spectrum were identical with those of an authentic sample of 3,5-dichloro-2,6-difluoropyridine.[7,8]

3-Amino-5-chloro-2,6-bis(methylsulfonyl)pyridine (6). A three-neck, 1-l. flask was equipped with a Dry Ice condenser and stirring paddle. The flask was charged with *N*-methylpyrrolidone (1 l.) and 3,5-dichloro-2,6-bis(methylsulfonyl)pyridine (20 g, 0.065 mol). The contents of the flask were heated to 90° to effect dissolution. When the temperature had fallen to 40°, anhydrous ammonia (2.80 g, 0.165 mol) was distilled into the flask. The reaction mixture turned very dark blue in color. An aliquot of this blue solution was kept for several days with no diminution of the blue color. An electron spin paramagnetic resonance spectrum of this blue solution revealed no paramagnetic species present.

The dark-blue solution was heated at 70° for 15 hr, after which time the solution was an amber color. A white solid (2.1 g, water soluble) was collected by filtration and the solvent was removed from the filtrate by distillation (bath temperature 80°, 2 mm). The residual material was triturated with benzene (250 ml) and hexane was added until the solution became cloudy. Crystals, which formed after several hours at room temperature, were collected by filtration to yield 10.28 g (two crops, 57%). A small sample was digested in refluxing ethanol and after cooling to room temperature crystals were collected by filtration and air dried to yield a white, crystalline solid identified as the title compound: mp 227–230° with slight decomposition; infrared spectrum (mull) 3340 and 3445 (NH stretch), 1290 and 1130 cm^{-1} ($-SO_2-$); nmr spectrum (DMSO-d_6) δ 8.12 (1 H, singlet, aromatic proton), 7.92 (2 H, broad singlet, $-NH_2$), 3.42 (6 H, two peaks separated by 3 Hz, CH_3SO_2-).

Anal. Calcd for $C_7H_9ClN_2O_4S_2$: C, 30.37; H, 3.28; N, 10.12. Found: C, 30.09; H, 3.49; N, 9.80.

3-Chloro-5-(dimethylamino)-2,6-bis(methylsulfonyl)pyridine (7). The same experimental procedure was utilized as described for the preparation of 3-chloro-5-amino-2,6-bis(methylsulfonyl)pyridine except that the experiment was conducted with 10 g (0.0328 mol) of 3,5-dichloro-2,6-bis(methylsulfonyl)pyridine and 2.96 g (0.0656 mol) of anhydrous dimethylamine. Two crops of crystals were collected from benzene–hexane to yield 8.8 g (86%). A small sample was recrystallized from hot ethanol and white crystals were collected by filtration which were identified as the title compound: mp 180–181°; infrared spectrum (mull) 1127 and 1305 cm^{-1} ($-SO_2$); nmr spectrum (DMSO-d_6) δ 7.73 (1 H, singlet, aromatic proton), 3.42 (6 H, singlet, CH_3SO_2-), 3.15 [6 H, singlet, $N(CH_3)_2$].

Anal. Calcd for $C_9H_{13}ClN_2O_4S_2$: C, 34.56; H, 4.19; N, 8.96. Found: C, 34.13; H, 4.36; N, 8.85.

[5-Chloro-2,6-bis(methylsulfonyl)-3-pyridyl]hydrazone of Acetone (8). A three-neck, 1-l. flask which was fitted with a drying tube (calcium sulfate) and stirring paddle was charged with *N*-methylpyrrolidone (800 ml) and 3,5-dichloro-2,6-bis(methylsulfonyl)pyridine (10.0 g, 0.0328 mol). This mixture was stirred and heated to 90°, at which temperature a solution was effected. The solution was cooled to 30°, and then triethylamine (3.0 ml, 0.0328 mol) and hydrazine (1.11 g of 95% material, 0.0328 mol) were added. This solution was stirred for 2.5 hr at room temperature. The reaction mixture was concentrated to a volume of 100 ml by distillation (bath temperature 75°, 3 mm). Crystals (2.7 g) were collected by filtration which proved to be triethylamine hydrochloride. The mother liquors were diluted with acetone (10 ml)

and then with water (ca. 50 ml) until the cloud point. Crystals formed and three crops were collected and air dried to yield 5.9 g (53%). A small sample was recrystallized from hot ethanol and the crystals were washed with hexane and air dried to yield a pale-yellow material, identified as the title compound: mp 170–172; infrared spectrum (mull) 3315 (NH), 1580 (C=N-), 1293 and 1130 cm^{-1} (-SO_2-); nmr spectrum ($CDCl_3$ plus 2 drops of DMSO-d_6) δ 9.86 (1 H, broad singlet, NH), 8.14 (1 H, singlet, aromatic proton), 3.33 (6 H, two singlets separated by 3.5 Hz, CH_3SO_2-), 2.12 (3 H, singlet, =CCH_3), 1.97 (3 H, singlet, =CCH_3).

Anal. Calcd for $C_{10}H_{14}ClN_3O_4S_2$: C, 35.35; H, 4.15; N, 12.37. Found: C,35.55; H, 4.16; N, 11.95.

2,6-Bis(methylsulfonyl)-3,5-dicarbonitrilepyridine (9). 3,5-Dichloro-2,6-bis(methylsulfonyl)pyridine (10.0 g, 0.0394 mol) was dissolved in *N*-methylpyrrolidone (500 ml) by heating to 100°. This solution was cooled to 30° and sodium cyanide (1.93 g, 0.0394 mol) was added to this solution. The reaction mixture turned dark brown colored and it was allowed to stir at room temperature for 5 days. The reaction was concentrated by distillation of the solvent (bath temperature 75°, 2 mm) to a volume of 50 ml. This was triturated with water (200 ml) and then mixed with dichloromethane (100 ml). A solid formed which collected in the dichloromethane layer. This solid was collected by filtration to yield 2.6 g, which proved to be unreacted starting material (mp 287–294°). The aqueous layer was extracted three more times with 150-ml portions of dichloromethane. The eluents were combined, dried (sodium sulfate), filtered, and concentrated under a reduced pressure to yield a black liquid.

The black liquid was placed on a silica column (Merck silica gel, 0.05–0.2 mm) whose dimensions were 1.5 (diameter) × 16 in. This column was slowly eluted with benzene (4.0 l.), 5% ethyl acetate in benzene (1.8 l.), 10% ethyl acetate in benzene (2.0 l.), and 25% ethyl acetate in benzene (3.5 l.). The last 2.5 l. of the 25% ethyl acetate–benzene eluent yielded a solid when it was concentrated under a reduced pressure. It was crystallized from DMSO–water. This crystalline solid was dried in an evacuated oven (50°, 15 mm) for 14 hr to yield 120 mg (2.1% based on available cyanide) of a material identified as the title compound: mp 255.5–256.5 dec; infrared spectrum (mull) 2250 (very weak, -C≡N), 1328 and 1147 (-SO_2-), 990 cm^{-1} (CH_3- on SO_2); nmr spectrum (DMSO-d_6) δ 8.99 (1 H, singlet, aromatic proton), 3.59 (6 H, singlet, CH_3SO_2-).

Anal. Calcd for $C_8H_7N_3O_4S_2$: C, 37.89; H, 2.47; N, 14.73. Found: C, 38.05; H, 2.74; N, 14.80.

[(3,5-Dichloro-6-(methylsulfonyl)-2-(pyridyl)oxy]acetamide (10). A Hoke high-pressure, 30 ml, stainless-steel bomb was charged with methyl [(3,5-dichloro-6-(methylsulfonyl)-2-(pyridyl)oxy]acetate (**2**, 5.0 g, 0.0159 mol) and anhydrous ammonia (13 g). The bomb was sealed and allowed to sit at room temperature for 17 hr. The contents of the bomb were mixed with dichloromethane (50 ml) and the ammonia was allowed to evaporate. The mixture was gently refluxed for several minutes, diluted with an additional 100 ml of dichloromethane, and then triturated with water (100 ml). Crystals formed at the water-organic interface. Three crops were collected and air dried to yield 4.18 g (94%). A small sample was recrystallized from ethanol and the crystals were dried in an evacuated oven (50°, 15 mm) for 14 hr. This material was identified as the title compound: mp 166.5–167.5; infrared spectrum (mull) 3470, 3380, 3200 (NH), 1690 (amide C=O), 1130 and 1305 cm^{-1} (-SO_2-); nmr spectrum (DMSO-d_6) δ 8.45 (1 H, singlet, aromatic proton), 7.0–7.7 (2 H, multiplet, -NH_2), 485 (2 H, singlet, -OCH_2CO-), 3.4 (3 H, singlet, CH_3-SO_2-).

Anal. Calcd for $C_8H_8Cl_2N_2SO_4$: C, 32.12; H, 2.70; N, 9.37. Found: C, 31.6; H, 2.70; N, 9.32.

2-Amino-3,5-dichloro-6-(methylsulfonyl)pyridine (11). A Hoke high-pressure, 30-ml, stainless-steel bomb was charged with 3.5 g (0.0117 mol) of [(3,5-dichloro-6-(methylsulfonyl)-2-(pyridyl)oxy]acetamide (**10**) and anhydrous ammonia (10.0 g). The bomb was placed in an oil bath and heated at 100° for 18 hr. The contents of the bomb were removed and the ammonia was allowed to evaporate. The residue was triturated with chloroform several times. The chloroform solutions were combined and concentrated under a reduced pressure to yield a sticky, white solid (2.1 g). A thin layer chromatogram (silica plates eluted with chloroform) indicated that at least five compounds were present. This mixture was triturated with 18% aqueous hydrochloric acid (75 ml). The insoluble material was collected by filtration to yield 0.95 g (28%) of a white solid. This material was recrystallized from hot ethanol (20 ml). The crystals were collected by filtration and dried in an evacuated oven (15 mm, 60°) for 48 hr to yield buff-colored crystals (0.32 g) of a material identified as the title compound: mp 185–187°; infrared spectrum (mull) 3480 and 3300 (NH stretch), 1310 and 1140 cm^{-1} (-SO_2-); nmr spectrum (DMSO-d_6) δ 8.03 (1 H, singlet, aromatic proton), 7.14 (2 H, broad singlet, -NH_2), 3.34 (3 H, singlet, CH_3SO_2-).

Anal. Calcd for $C_6H_6Cl_2N_2O_2S$: C, 29.89; H, 2.51; N, 11.62. Found: C, 29.73; H, 2.71; N, 11.61.

3,5,6-Trichloro-2-pyridinol Ammonium Salt (12). A 30-ml, stainless-steel bomb was charged with 3,5,6-trichloro-2-pyridinol (5 g)[9] and anhydrous ammonia (20 g). The bomb was heated on a steam bath for 18 hr. The ammonia was evaporated to yield a white, water-soluble solid (4 g) which was identified as the title compound: infrared spectrum (mull) 3300–2400 cm^{-1} (broad absorption, NH_4^+; nmr spectrum (D_2O) δ 7.58 (singlet, aromatic proton); mp 208–209°.

Anal. Calcd for $C_5H_4Cl_3N_2 \cdot 0.1H_2O$: C, 49.3; N, 12.99; H_2O, 0.90. Found: C, 49.0; N, 12.7; H_2O, 0.84.

Registry No.—**1**, 51230-78-5; **2**, 51230-79-6; **3**, 51230-80-9; **4**, 51230-81-0; **5**, 698-51-1; **6**, 51230-82-1; **7**, 51230-83-2; **8**, 51230-84-3; **9**, 51230-85-4; **10**, 51230-86-5; **11**, 51230-87-6; **12**, 51230-88-7; 2,3,5,6-tetrachloropyridine, 2402-79-1; 3,5-dichlorobis(methylthio)pyridine, 51230-89-8; methyl glycolate, 96-35-5; ethyl lactate sodium salt, 39979-94-7; ethyl lactate, 97-64-3.

References and Notes

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