saturated sodium bicarbonate solution. The latter in turn was acidified in the cold with hydrochloric acid and the desired compound was isolated by ether extraction. Removal of the ether afforded a tan-colored, crystalline material (761 mg, 92.5%), mp 80–85°, whose tlc (1:1 ether–benzene, containing a trace of formic acid) showed only one spot. Because the diacid **25** was very soluble in all of the common solvents, a specimen was purified by preparative tlc, mp 84–86°, ir (neat melt) 1785, 1735, 1220, 1165, and 970 cm^{-1}.

Anal. Calcd for $C_{19}H_{32}O_6$: C, 64.02; H, 9.05. Found: C, 64.39; H, 9.23.

2,3-Bis(methoxycarbonyl)-4-*n*-tridecylbutyrolactone. The dicarboxylic acid (124 mg) was treated with a solution of diazomethane in ether until a faint yellow color persisted. The solvent was removed under reduced pressure and the residue was recrystallized from methanol. This afforded the pure diester: mp 43–45°; ir (film) 1635 (CO_2CH_3) and 1675 cm^{-1} (γ-lactone); nmr 3.63 (CO_2CH_3, s), 3.87 (CO_2CH_3, s), and 4.47 ppm (CHO–, m). Both signals due to the hydrogens α to the ester functions lie partially under the methoxy hydrogen peaks and could not be accurately identified.

Anal. Calcd for $C_{19}H_{34}O_6$: C, 65.59; H, 9.44. Found: C, 65.57; H, 9.48.

***dl*-Protolichesterinic Acid (16).** The dicarboxylic acid (504 mg) was treated at room temperature with a solution prepared from 0.6 ml of formalin and 0.2 ml of diethylamine. As the solid dissolved a substantial amount of gas evolution occurred. Stirring was continued for 3.5 hr and ether, followed by saturated sodium chloride solution containing a few drops of hydrochloric acid, was added to the reaction mixture. The ether extract was washed with salt solution and then dried ($MgSO_4$). Removal of the ether under reduced pressure then led to an oil which rapidly crystallized. The crude solid (192 mg, ~40% yield) had mp 65–83° and after one crystallization from acetic acid had mp 90–92° (160 mg). Further crystallization from the same solvent provided the analytically pure *dl*-protolichesterinic acid: mp 92–93.5°; ir ($CHCl_3$) 1715 (CO_2H), 1760 (γ-lactone), 1665, and 960 cm^{-1} (=CH_2); nmr 3.64 ($CHCO_2H$, m), 4.80 (CHO, m), 6.0 (=CH, d, J = 3.0 Hz), 6.43 (=CH, d, J = 2.8 Hz), and 15.3 ppm (CO_2H, s). Both spectra were identical with that of an authentic specimen. When the latter was mixed with our material no depression in melting point was observed, mmp 92–93°.

Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94. Found: C, 70.18; H, 9.91.

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Registry No.—**4** (R = H; R′ = Ph), 6005-95-4; **4** (R = H; R′ = 1-hexyl), 26613-70-7; **4** (R = H; R′ = *n*-butyl), 26449-01-4; **6** (R = H; R′ = Ph), 26613-71-8; **6** (R = H; R′ = 1-hexyl), 26798-41-4; **6** (R = H; R′ = *n*-butyl), 26449-03-6; **6** [R = (1′-pyrrolidinylcarbonyl)methyl, R′ = 1-octyl], 51175-39-4; **7** (R = H; R′ = Ph), 1008-76-0; **15**, 39949-70-7; **16**, 51260-32-3; **18a** (R = H), 51175-40-7; **18a** (R = Me), 51175-41-8; **18b** (R = H), 51175-42-9; **18b** (R = Me), 51202-16-5; **19**, 51175-43-0; **21**, 51175-44-1; **22** (R = H), 51175-45-2; **22** (R = Me), 51202-17-6; **25**, 51175-46-3; γ-decanoic lactone, 706-14-9; γ-octanoic lactone, 104-50-7; methyl 3-methoxycarbonyl-4-oxoheptadecanoate, 51175-47-4; tetradecylaldehyde, 124-25-4; dimethyl maleate, 624-48-6; trimethyl 1,1,2-ethenetricarbonyl-4-oxoheptadecanoate, 51175-47-4; tetradecylaldehyde, 40967-67-7; tricarballylic acid, 99-14-9; 2,3-bis(methoxycarbonyl)-4-*n*-tridecylbutyrolactone, 51202-18-7.

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A Metal-Catalyzed Reaction of 8-Quinolyl Sulfate and Its Application to the Preparation of Biochemically Related Sulfate Esters

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The effect of Cu(II) and 8-hydroxyquinoline–Cu(II) complex on the hydrolysis and alcoholysis of 8-quinolyl sulfate in polar solvents was examined. The hydrolysis rate of 8-quinolyl sulfate in dimethylformamide containing water (1%, v/v) at 20° gave good pseudo-first-order plots (k_{obsd} 6.5 × 10^{-3} hr^{-1}), while it was markedly enhanced by the addition of Cu(II) (0.5 molar equiv) or 8-hydroxyquinoline–Cu(II) complex (0.1 molar equiv), although no satisfactory pseudo-first-order plots were obtained in these cases. Both Cu(II) and its 8-hydroxyquinoline complex also accelerated the alcoholysis of 8-quinolyl sulfate in dimethylformamide or pyridine containing ethanol (10%, v/v each). The effect of 8-hydroxyquinoline–Cu(II) complex was more than that of Cu(II) in both the hydrolysis and alcoholysis of 8-quinolyl sulfate. The factors (water content, solvent, metal ion) which affect this metal-catalyzed reaction were examined and a possible mechanism for this reaction was discussed. This metal-catalyzed reaction of 8-quinolyl sulfate was applied successfully for the preparation of D-galactose 6-sulfate, adenosine 5′-sulfate, and dextran sulfate.

Recently, the reactions of 8-quinolyl derivatives of amino acids[1] and phenylphosphoric acid[2] and their application to the synthesis of peptides and phosphate esters have been reported. In 1967, Hay and Edmonds[3] reported a kinetic study of the hydrolysis of 8-quinolyl sulfate catalyzed by cupric ions in aqueous media, and, in 1971, Murakami and Sunamoto[4] reported the solvolysis of 8-quinolyl dihydrogen phosphate in the presence of some bivalent

Table I
Rate of Solvent Catalytic Decomposition of 8-Quinolyl Sulfate in Some Organic Solvents[a]

Solvent	Decomposition of 8-quinolyl sulfate, % (20°) 1 hr	8 hr	32 hr	72 hr	192 hr	k_{obsd} (10^{-2} hr^{-1})	Decomposition of 8-quinolyl sulfate, % (60°) 5 min	10 min	20 min	40 min	k_{obsd} (10^{-2} min^{-1})
Pyridine	4.8	33.4	74.1	96.4		4.70	30.9	54.2	90.2	97.9	[b]
Dimethylformamide		4.0	17.8	37.8	72.2	0.65	4.9	13.4	28.4	52.4	1.76
Dimethyl sulfoxide		5.9	19.1	36.1	66.8	0.64	7.2	15.2	27.7	47.0	1.62

[a] The reaction was carried out in the indicated solvent containing water (1%, v/v). [b] Satisfactory pseudo-first-order plots were not obtained.

Table II
Effect of Cu(II) Ion on the Decomposition of 8-Quinolyl Sulfate in Pyridine and Dimethylformamide Containing Water (1%, v/v each)[a]

Cu(II) added, molar equiv	Decomposition of 8-quinolyl sulfate, % Pyridine 15 min	30 min	60 min	Dimethylformamide 15 min	30 min	60 min
0			9.5		2.0	2.2
0.05	23.9	31.8	42.6	25.3	37.9	54.6
0.1	37.8	47.3	57.0	35.6	49.9	70.2
0.3	44.7	60.8	80.8	59.1	78.4	91.0
0.5	66.7	76.4	88.0	79.7	93.4	98.9
1.0	79.7	93.7	99.2	91.0	97.4	98.9

[a] The reaction was carried out in the presence of the indicated amount of $CuCl_2$ at 20°.

Table III
Effect of Water Content in Solvents on the Cu(II)-Catalyzed Decomposition of 8-Quinolyl Sulfate[a]

Water content, %, v/v	Decomposition of 8-quinolyl sulfate, % Pyridine 15 min	30 min	60 min	Dimethylformamide 15 min	30 min	60 min
0	62.1	79.1	78.0	25.9	27.4	27.4
0.5	68.0	82.8	92.9	84.4	94.9	100.2
5	53.1	65.1	77.7	77.5	88.3	93.9
25	10.8	18.2	29.8	36.0	52.2	71.5
100			2.5			2.5

[a] The reaction was carried out in the presence of 0.6 molar equiv of $CuCl_2$ at 20°.

metal ions. More recently, the alcoholysis and phosphorolysis of 8-quinolyl phosphoryl esters with metal ions have been demonstrated in this laboratory.[5]

This paper describes the work on the metal-catalyzed reaction of 8-quinolyl sulfate in organic solvents and its application for the preparation of biochemically related sulfate esters.

Reports on the reliable preparative method for 8-quinolyl sulfate and its characteristics are not found to the best of our knowledge. 8-Quinolyl sulfate was successfully prepared by sulfating 8-hydroxyquinoline with $ClSO_3H$ in *N,N*-dimethylaniline and isolated in the free ester form. 8-Quinolyl sulfate was fairly stable in water for at least 120 hr at 20°, but it was gradually hydrolyzed in moist pyridine. At an elevated temperature (60°), the hydrolysis in moist pyridine was remarkable. Some of polar solvents other than pyridine could also accelerate the hydrolysis, and good pseudo-first-order plots were obtained in every case except pyridine (60°), values of the rate constants (k_{obsd}) of which are listed in Table I.

As shown in Table II, addition of a catalytic amount of Cu(II) considerably enhanced the rate of hydrolysis of 8-quinolyl sulfate in moist pyridine or dimethylformamide at 20°. When the amount of Cu(II) used was more than 0.5 molar equiv, 8-quinolyl sulfate decomposed almost quantitatively within 1 hr and a stoichiometric amount of 8-hydroxyquinoline–Cu(II) complex (2:1) was isolated from the reaction mixture. The data in Table II also indicate that, in the presence of Cu(II), the solvent effect of dimethylformamide is larger than that of pyridine. No satisfactory pseudo-first-order plots were obtained for the metal-catalyzed hydrolysis of 8-quinolyl sulfate shown in Table II.

Although data are not shown here, a higher water content in pyridine or dimethylformamide gave a negative effect on the rate of catalytic hydrolysis of 8-quinolyl sulfate by the solvent. The data shown in Table III also indicate that the water content in pyridine or dimethylformamide markedly affects the rate of decomposition of 8-quinolyl sulfate in the presence of Cu(II). The decomposition of 8-quinolyl sulfate, which depends on both Cu(II) and the organic solvent used, seems to proceed most rapidly in the presence of a minimum amount of water necessary for the hydrolysis of 8-quinolyl sulfate.

The rate of Cu(II)-catalyzed decomposition of 8-quinolyl sulfate was measured in various polar solvents containing water (Table IV). The decomposition of 8-quinolyl sulfate in dioxane or tetrahydrofuran containing water (10%, v/v), which is comparable to that in dimethylformamide, was remarkable. The data in Table IV also indicate that 8-quinolyl sulfate was alcoholyzed effectively in ethanol containing water (10%, v/v), suggesting its promising ability for the sulfation of hydroxylic compounds.

The effect of metal ions other than Cu(II) which can form a metal complex with 8-hydroxyquinoline was examined. As shown in Table V, none of the metal ions tested except Cu(II) displayed any marked effect in dimethylformamide, but they, except Cd(II) and Mn(II), were moderately effective in pyridine. The data in Table V also indicate that the acetate anion has a marked accelerative effect on this reaction. A similar effect of cupric acetate was observed on the reaction of 8-quinolyl phosphoryl esters.[5] Though experimental data are not shown here, the hydrolysis rate of 8-quinolyl sulfate in the absence of Cu(II) was not affected by the presence of an acetate ion (added as sodium acetate to the reaction system), and this effect of acetate ion is probably cooperative (or synergistic) with Cu(II) in the reaction step at which Cu(II) takes part in this reaction.

In contrast to the good pseudo-first-order plots of the solvent-catalyzed hydrolysis rate of 8-quinolyl sulfate in the absence of a metal ion, the presence of a metal ion markedly enhanced the hydrolysis rate and the rate turned away from the pseudo-first-order plots, not giving a satisfactory rate constant. When a metal ion was present, the color of the reaction solution changed with progress of the reaction, and a stoichiometric amount of 8-hydroxyquinoline–metal complex was recovered from the solution at the end of the reaction. This fact clearly indicates that there is a correlation between metal complex formation and progress of the reaction. To examine the possible participation of the complex formed in this reaction, the decomposition of 8-quinolyl sulfate with the isolated 8-hydroxyquinoline–Cu(II) (2:1) or 8-hydroxyquinoline–Ni(II) (2:1) complex was examined. As can be seen from Table VI, the effect of 0.1 molar equiv each of the 8-hydroxyquinoline complex of Cu(II) and Ni(II) was fair-

Table IV
Effect of Solvents on the Cu(II)-Catalyzed Decomposition of 8-Quinolyl Sulfate[a]

Solvent	Decomposition of 8-quinolyl sulfate, %: H_2O (10%, v/v) 30 min	H_2O (10%, v/v) 60 min	H_2O (1%, v/v) 30 min	H_2O (1%, v/v) 60 min
Pyridine	51.8	60.8	76.8	89.7
Dimethylformamide	84.1	93.4	93.1	97.7
Dimethyl sulfoxide	32.8	45.8	49.9	71.2
Dioxane	82.1	92.0	*c*	
Tetrahydrofuran	98.3	97.7	*c*	
Ethanol	65.3 (57.2)[b]	68.9 (60.8)[b]	*c*	

[a] The reaction in the indicated solvent containing water (1 or 10%, v/v) was carried out in the presence of 0.6 molar equiv of $CuCl_2$ at 20°. [b] The parenthesized figures are the yield of ethyl sulfate. [c] Data could not be obtained owing to a poor solubility of 8-quinolyl sulfate in these solvents.

Table V
Effect of Metal Ions on the Decomposition of 8-Quinolyl Sulfate[a]

Metal ion	Decomposition of 8-quinolyl sulfate, %: Pyridine 15 min	Pyridine 30 min	Dimethylformamide 15 min	Dimethylformamide 30 min
Cu(II)	61.8	76.8	82.6	93.1
Cu(II)[b]	99.1		98.8	100.0
Ni(II)	33.6	45.5		6.3
Co(II)	32.0	42.9		4.8
Zn(II)	22.8	36.7		5.0
Cd(II)	5.2	8.0	*c*	*c*
Mn(II)	*c*	*c*		2.6
Fe(III)	47.2	52.2		13.9
Nil		<5.0		<2.0

[a] The reaction was carried out in pyridine or dimethylformamide containing water (1%, v/v each) with 0.6 molar equiv of metal chloride at 20°. [b] Cupric acetate was used. [c] Could not be determined owing to a poor solubility of the metal chlorides in these solvents.

ly larger than that of 0.1 molar equiv each of Cu(II) and Ni(II), respectively. It is interesting that the 8-hydroxyquinoline–metal complex displayed a marked effect on the decomposition of 8-quinolyl sulfate in polar solvents, in contrast to the absence of any effect in 8-hydroxyquinoline–metal complexes on the decomposition of 8-quinolyl phosphoryl esters under similar conditions.[5] Together with the results obtained by the Cu(II)-catalyzed hydrolysis of 8-quinolyl sulfate, which gave no satisfactory pseudo-first-order plots, the data in Table VI suggest that the rate of metal-catalyzed decomposition of 8-quinolyl sulfate would be correlated with the rate of formation of 8-hydroxyquinoline–metal complex in the solvent used, and catalytic activity of the metal complex formed during the reaction would be more essential for this reaction.

Alcoholysis of 8-quinolyl sulfate in polar solvents containing alcoholic compounds was examined in the presence or absence of metal catalysts, and the result obtained is summarized in Table VII. The alcoholysis occurred to a fair extent in the absence of Cu(II) at a higher temperature (60°), but not at a lower temperature (20°). In the presence of Cu(II) (0.6 molar equiv), 8-quinolyl sulfate was almost quantitatively alcoholyzed in pyridine or dimethylformamide within 1 hr at 20°, indicating an evident enhancement of the reactivity of 8-quinolyl sulfate with Cu(II). Further, it was confirmed that 0.1 molar equiv of 8-hydroxyquinoline–Cu(II) (2:1) complex affected the alcoholysis more seriously than did Cu(II).

From the results obtained as above, three possible mechanisms (A, B, and C in Chart I) are conceivable for the Cu(II)-catalyzed reaction of 8-quinolyl sulfate. As shown in Chart I, a greater part of this reaction will proceed along routes B and C, which include the formation of 8-hydroxyquinoline–Cu(II) complex from the decomposition of 8-quinolyl sulfate with Cu(II) and the decomposition of 8-quinolyl sulfate catalyzed by the complex formed, respectively. Contribution of route A to this reaction at 20° seems to be rather small (see Table I). Each of routes A, B, and C would produce a common reactive species (supposedly, SO_3–solvent adduct). When an appropriate nucleophile exists, the adduct reacts rapidly with it to afford a corresponding product such as inorganic sulfate or sulfate esters.

Chart I

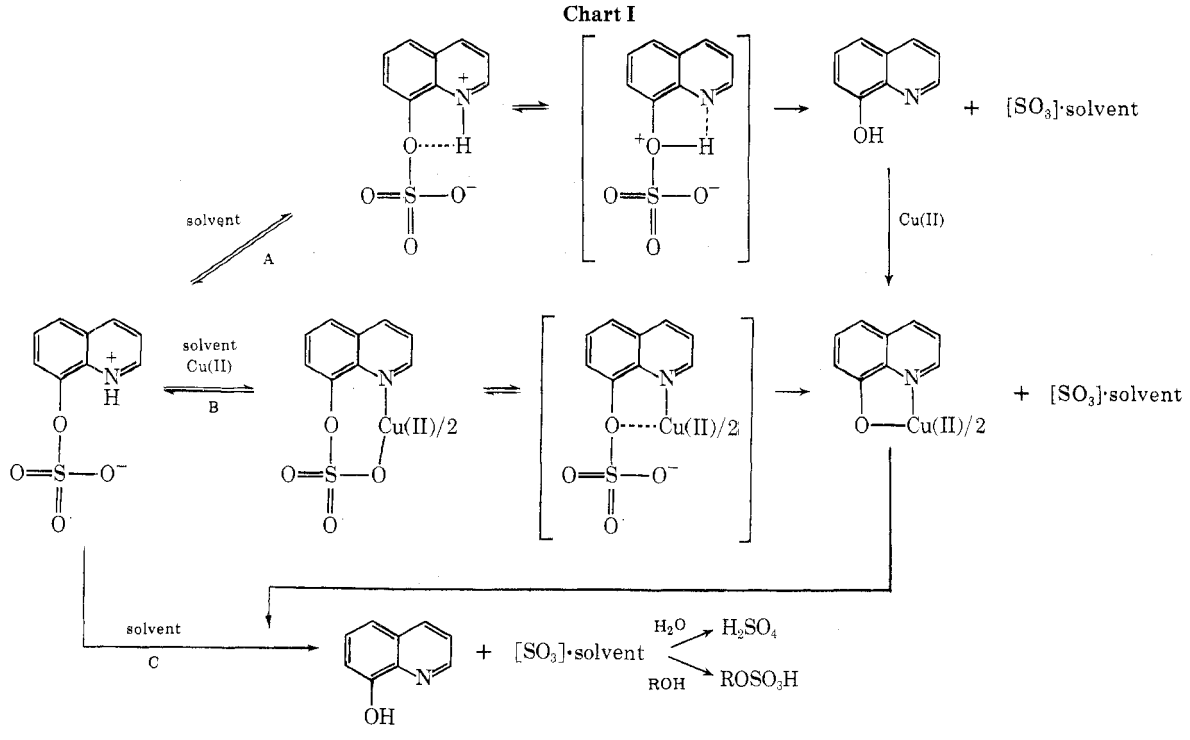

Table VI
Effect of 8-Hydroxyquinoline–Metal Complex on the Decomposition of 8-Quinolyl Sulfate[a]

Metal or 8-hydroxyquinoline–metal complex	Decomposition of 8-quinolyl sulfate, %: Pyridine 15 min	Pyridine 30 min	Pyridine 60 min	Dimethylformamide 15 min	Dimethylformamide 30 min	Dimethylformamide 60 min
Cu(II)	37.8	47.3	57.0	35.6	49.9	70.2
8-Hydroxyquinoline–Cu(II)	63.3	74.2	89.1	65.0	80.2	93.7
Ni(II)	14.0	19.1	27.5	3.9	5.1	5.6
8-Hydroxyquinoline–Ni(II)	21.1	35.3	48.9	8.4	13.2	19.2

[a] The reaction was carried out in pyridine or dimethylformamide containing water (1%, v/v each) with 0.1 molar equiv of the indicated metal ion or 8-hydroxyquinoline–metal complex at 20°.

which was dried over P_2O_5 *in vacuo* for 2 hr at 130°, yield 0.40 g. For preparing 8-hydroxyquinoline–Ni(II) (2:1) complex, an EtOH solution (20 ml) of 8-hydroxyquinoline (4 mmol) was mixed with an aqueous solution (10 ml) of $NiCl_2 \cdot 6H_2O$ (2 mmol), and the resultant solution was concentrated *in vacuo* to one-third the original volume and diluted with water (40 ml). The precipitate formed was collected, washed with water, and dried over P_2O_5 *in vacuo* for 2 hr at 130°, yield 0.34 g. Satisfactory analytical data for C, H, N were obtained on both of the 8-hydroxyquinoline–metal complexes ($C_{18}H_{12}N_2O_2Cu$ and $C_{18}H_{12}N_2O_2Ni$) prepared as above.

Reagents and Solvents. Other reagents, which were all special reagent grade, were used without further purification. Dextran (Lot No. KL-2269, mol wt 11,000 by viscosity determination) was obtained from Meito Sangyo Co. Ltd., Nagoya. Organic solvents were dehydrated and redistilled by a conventional method.

Analytical Methods. Inorganic sulfate was determined by Dodgson's turbidimetric method.[7] For fluorometric measurement, an Aminco-Bowman spectrofluorometer was used. Paper electrophoreses were carried out on Toyo Roshi No. 50 filter paper at 22 V/cm for 30–60 min, using one of the following buffer solutions. Samples were applied on a line positioned at 4.5 cm from the center of the filter paper (25 × 9 cm): (a) 0.05 *M* ammonium acetate, pH 7.0; (b) pyridinium acetate solution, pH 5.8 (pyridine:AcOH: BuOH:H_2O = 5:1:5:250, v/v).

Table VII
Alcoholysis of 8-Quinolyl Sulfate in Polar Solvents with or without Metal Catalyst[a]

ROH	Solvent	Alcoholysis of 8-quinolyl sulfate, %: Without metal catalyst 20°	Without metal catalyst 60°	Cu(II) (0.6 molar equiv) 20°	8-Hydroxyquinoline–Cu(II) (0.1 molar equiv) 20°
Ethanol	Pyridine	14.9	100.0	95.7	96.5
	Dimethylformamide	3.4	87.2	98.2	92.3
	Dimethyl sulfoxide	2.3	68.4	52.2	58.0
Cyclohexanol	Pyridine	15.1	99.3	91.3	
	Dimethylformamide	2.0	85.3	98.5	
	Dimethyl sulfoxide	3.1	67.5	50.1	

[a] The reaction was carried out in the indicated solvent containing ethanol or cyclohexanol (10%, v/v) for 1 hr.

Applicability of this reaction to the sulfation of biochemical materials such as nucleosides and vitamins was examined. When an equimolar mixture of 2′,3′-isopropylidene adenosine and 8-quinolyl sulfate was allowed to react for 1 hr at 20° in the presence of $CuCl_2$ (0.6 molar equiv), the yield of 2′,3′-isopropylidene adenosine 5′-sulfate was 71%. When 2 molar equiv of 2′,3′-isopropylidene adenosine was allowed to react with 8-quinolyl sulfate under the same conditions, the sulfation of 2′,3′-isopropylidene adenosine advanced almost quantitatively (98%). As can be seen from Table VIII, riboflavin was sulfated effectively by 8-quinolyl sulfate in the presence of Cu(II) under mild conditions. Sulfation in dimethyl sulfoxide, which is a good solvent for riboflavin, was evidently less than that in dimethylformamide, although data are not shown here.

The preparation of D-galactose 6-sulfate, adenosine 5′-sulfate, and dextran sulfate was successfully achieved by the method involving the use of 8-quinolyl sulfate and cupric catalysts.

Table VIII
Yield and Composition of Riboflavin Sulfates formed by the Cu(II)-Catalyzed Alcoholysis of 8-Quinolyl Sulfate with Riboflavin[a]

Molar ratio of riboflavin to 8-quinolyl sulfate	Yield and composition of riboflavin sulfates, %: Unreacted riboflavin	Riboflavin sulfate: Mono-	Di-	Tri-
1:1	56.8	19.0	23.5	0.7
1:2	27.2	28.3	42.7	1.8
1:5	2.0	16.5	67.8	13.7

[a] A mixture composed of the indicated molar ratio of riboflavin and 8-quinolyl sulfate in dimethylformamide was allowed to react in the presence of $CuCl_2$ (0.6 molar equiv) for 5 hr at 20°.

Experimental Section

Synthesis of 8-Quinolyl Sulfate. A $CHCl_3$ solution (50 ml) of *N,N*-dimethylaniline (12.7 ml, 0.1 mol) was mixed with a $CHCl_3$ solution (9 ml) of $ClSO_3H$ (2.7 ml, 0.04 mol) below 5° under stirring. To the mixture, a solution of 8-hydroxyquinoline (4.35 g, 0.03 mol) in $CHCl_3$ (25 ml) was added and the mixture was stirred for 1 hr at 0°. After standing overnight at room temperature, the crystalline precipitate formed was collected and recrystallized from water to thin yellow needles, mp 158–162° dec. The crystals were dried over P_2O_5 *in vacuo* for 3 hr at 80°. Yield was 4.90 g (72.6%).

Anal. Calcd for $C_9H_7NO_4S$: C, 47.97; H, 3.11; N, 6.22; S, 14.21. Found: C, 47.77; H, 3.09; N, 6.20; S, 13.96. Uv max (0.1 *N* HCl): 240.8 nm (ϵ 5.25 × 10^4); ir (KBr) 1045 (SO), 1240–1275 cm^{-1} (SO_2). The crystals of 8-quinolyl sulfate and its aqueous solution were highly fluorescent [excitation λ_{max} (H_2O) (pH 4.45) 316 nm, emission λ_{max} (H_2O) (pH 4.45) 475 nm].[6]

Preparation of 8-Hydroxyquinoline–Metal Complexes. 8-Hydroxyquinoline–Cu(II) (2:1) complex was prepared by mixing an EtOH solution (20 ml) of 8-hydroxyquinoline (4 mmol) with an aqueous solution (10 ml) of $CuCl_2 \cdot 2H_2O$ (2 mmol), followed by filtration and washing with water of the precipitate formed,

Determination of the Metal-Catalyzed Decomposition of 8-Quinolyl Sulfate in Organic Solvents. General Procedure. 8-Quinolyl sulfate (*ca.* 60 mg) was weighed into a volumetric flask (10-ml volume) and dissolved in 5 ml of the indicated solvent. A necessary amount of the metal salt (or 8-hydroxyquinoline–metal complex) was added to the flask, the content of which was diluted to 10 ml with the solvent. The stoppered flask was immersed in an oil bath kept at a constant temperature. All these operations must be carried out quickly below 15°. Aliquots (1 ml each) were removed periodically from the flask and diluted tenfold with cold water. After keeping in ice-water for at least 1 hr, the mixture was filtered to remove 8-hydroxyquinoline–metal complex present or formed during the reaction.

Turbidimetric analysis of inorganic sulfate was carried out on the filtrate obtained as above. A corresponding amount of the solvent used must be added to the standard solutions for the turbidimetry. The amount of 8-quinolyl sulfate was fluorometrically determined by measuring the fluorescence intensity of the filtrate at 475 nm using an excitation wavelength of 316 nm.[6]

Determination of 2′,3′-Isopropylidene Adenosine 5′-Sulfate

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-