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SYNTHESIS AND HIGH PERFORMANCE LIQUID CHROMATOGRAPHY OF ω-(3-SUBSTITUTED-2-OXO-1-PYRIDYL)-ALKYLSULFONATES FOR USE AS WATER TRACING COMPOUNDS

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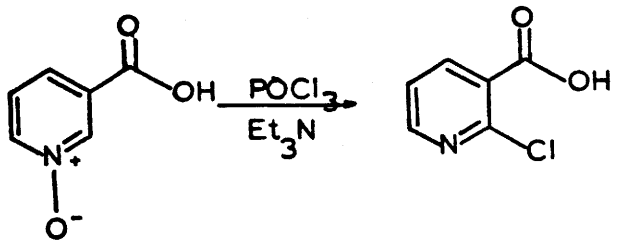
INTRODUCTION

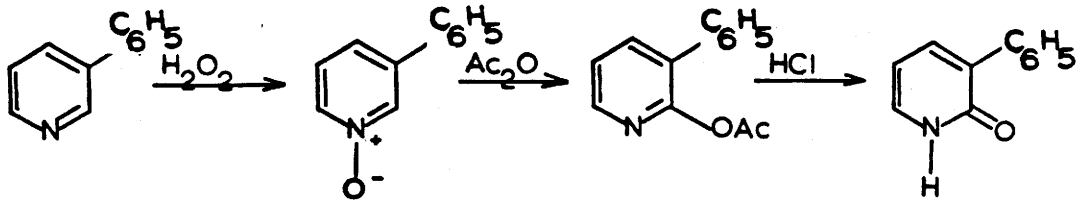
The purpose of this research was to study the synthesis and applications of two new homologous series of 1,3-disubstituted 2-pyridones as possible site-specific water tracing compounds. The compounds were designed to increase the solubility of the parent molecules as well as to create separately identifiable compounds for analysis with high performance liquid chromatography (HPLC). The synthesis of the two specific starting parent molecules of interest, 1-H-2-oxo-3-phenylpyridine (**1**) and 1-H-2-oxo-3-carbamoylpyridine (**4**) are shown in Figure 1. Compound **1** was synthesized by a procedure designed by Bush,[2] following work of Boekelheide,[3,4] which involves rearrangement of a pyridine N-oxide. Compound **4** was synthesized from 2-chloronicotinic acid.[5,6]

The course of this research required a large amount of 2-hydroxynicotinic acid. Since an efficient large-scale synthetic method had not been reported for forming the precursor 2-chloronicotinic acid, we designed such a method based on a literature patent.[7,8]



Method of Synthesis for 2-Chloronicotinic Acid

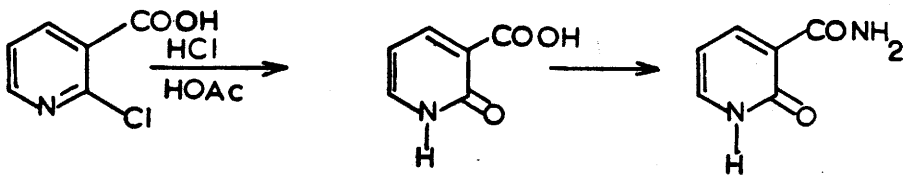
Figure 1. Syntheses of Parent 1-H-2-Oxo-3-substituted-pyridines (1) and (4)



1

Formation of 1-H-2-Oxo-3-phenylpyridine (1) from

3-Phenylpyridine N-Oxide



4

Formation of 1-H-2-Oxo-3-carbomoylpyridine (4) from

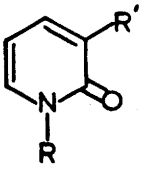
2-Chloronicotinic acid

The use of compounds related to 1 and 4 as water tracers is based on the fact that these 3-substituted-2-pyridones are very strongly fluorescent in the region from 380 to 400 nm. Quantum yields (Φ) of 1, 4, and some related

3-substituted-2 pyridones are shown in Table 1. The fluorescence intensities were also measured in various solvent mixtures of methanol or acetonitrile and water. The intensities did not vary dramatically and were the most intense in 100% water. Lastly, the variation of the 1-methyl-3-carbamoyl-2-pyridone fluorescence intensity with respect to pH was measured by Nelson and Rowe.[9] The results demonstrated only slight variation with respect to these conditions.

In order to study this group of compounds with respect to their suitability

Table 1. Quantum Yields of Fluorescence (Φ) and Molar Absorptivities (ε) of Some 3-Substituted 2-Pyridones Determined in Water Solution.



R'	R	Φ	ε
C_6H_5	-H	.24	9.95×10^3
$CONH_2$	-H	.93	7.50×10^3
C_6H_5	$-CH_3$	.33	9.83×10^3
$CONH_2$	$-CH_3$	.98	8.77×10^3
$CONH_2$	$-CH_2-CH_3$	.93	8.59×10^3
$CONH_2$	$-(CH_2)_2-CH_3$	.92	8.44×10^3
$CONH_2$	$-(CH_2)_3-CH_3$	.93	8.56×10^3

as water tracers, the properties of ideal organic tracing compounds need to be reviewed. Smart and Laidlaw have outlined several qualities desirable in fluorescent water tracing compounds.[10] The detection limit of the compound in question is a major concern. This limit is related to the molar absorptivity, the quantum efficiency of emission, and the transmission of the light energy through available filter combinations of the fluorometer or other detection device in use. Detectability of the compound also depends on background or blank fluorescence, which is usually corrected by subtraction of the difference between natural groundwater fluorescence and a distilled water blank.

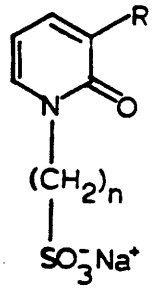
The properties of an organic tracing compound should minimize loss while in transit. There are two main sources of dye loss, nonadsorptive loss and adsorptive loss. Nonadsorptive losses can be due, among other reasons, to photochemical decomposition, chemical decay, pH effects, and biodegradation of the compound by micro-organisms. Adsorption of the tracer onto both organic and inorganic substrates is usually irreversible and can be a high source of loss. In tests conducted by Smart and Laidlaw, adsorption was the least prevalent in compounds containing sulfonic acid groups. This seemed to be due to their low pK_a, which gives an anionic group that repels the usual anionic charges of the adsorbents.

Many of the properties of the 3-phenyl- and the 3-carbamoyl-2-pyridones indicate that they may be useful as water tracers. As already shown these compounds are intensely fluorescent. They show stability toward photochemical decay, since their maximum absorbance, 315-324 nm, is outside that of the normal range of sunlight. The study of fluorescence intensity with respect to pH showed essentially constant intensity over the range of 2-12.

A preliminary test for the biodegradability of the 3-phenyl- and

3-carbamoyl-2-pyridones was conducted in a barnyard humus suspension. The analysis by HPLC showed some loss, and the fluorescent compounds seemed to be adsorbed onto the solid. The 3-carbamoyl-2-pyridone also showed hydrolysis to the 3-carboxylic acid-2-pyridone, both in the slurry test and in water solutions that had been left standing 1 1/2- 2 weeks. In preliminary tests conducted through collaborative efforts with Glenn Thompson, et al. at the University of Arizona, Tucson, both the 3-phenyl- and the 3-carbamoyl-2-pyridones apparently adsorbed to some extent on silica sand columns. In addition, the solubility of both 1-H compounds was somewhat low, 1.3×10^{-3}M for **1**, and 1.0×10^{-2}M for **4**.

The goal of this work was therefore aimed towards the synthesis of several N-substituted pyridone alkyl sulfonates which might show decreased adsorptive properties as well as increased solubility. Alkyl sulfonates of varying chain lengths would be unique in a water system and separately identifiable by HPLC analysis. The synthesis of the six compounds shown below was planned.



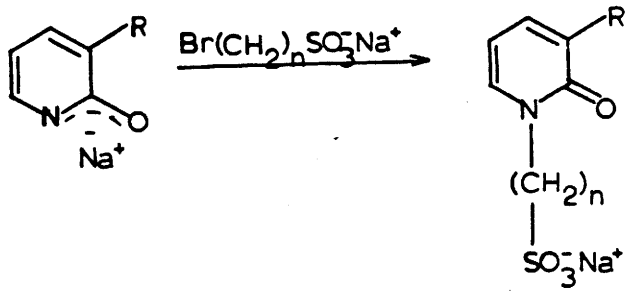
$R=C_6H_5$, n=2,3,4 compounds **15, 16, 17**

$R=CONH_2$, n=2,3,4 compounds **12, 13, 14**

ω-(3-substituted-2-oxo-1-pyridyl)-alkyl sulfonates

The synthesis of these 2-pyridones can be accomplished by reaction of the 2-pyridone sodium salt and a bromoalkyl sulfonate sodium salt as shown

below.[11,12]



Formation of ω-(3-Substituted-2-oxo-1-pyridyl)-alkyl Sulfonates

A series of bromoalkyl sulfonates was therefore needed to form the N-alkyl sulfonated 2-pyridones. Formation of bromoalkyl sulfonates was not described extensively in the literature.[15] It was known that alkyl halides react with sulfite ion to form alkyl sulfonates, a reaction known as the Strecker reaction.[13] There is a brief description of the synthesis of 2-bromoethylsulfonate in Organic Synthesis by limited sulfonation of 1,2-dibromoethane with sodium sulfite.[14] A more general synthetic method was developed using alkyl dihalides to form α,ω-bromoalkyl sulfonates. Similar methods are described in the Russian literature.[16,17]

RESULTS AND DISCUSSION

Preparation of 3-Phenyl and 3-Carbamoyl-2-Pyridones

To obtain sufficient quantities for testing of water tracing properties and preliminary use as tracers, as well as for synthetic modification, the 1-H-3-carbamoyl-2-pyridones were prepared in 50 g batches as outlined in the introduction.

Large Scale Synthesis of 1-H-3-Carbamoyl-2-Pyridone (4)

For further field tests of suitability as a water tracer, roughly 4 kg of **4** was required by collaborators in Arizona. Limited availability of 2-chloronicotinic acid required the synthesis of a large quantity of this compound. (See Experimental Section).

During the following tests, it was found that compound **4** gave inconclusive results, most likely due to the hydrolysis of the carbamoyl-2-pyridone to the 3-carboxylic acid-2-pyridone, (**2**) or a general adsorption of the tracer. Methods were subsequently developed for the sensitive detection of **2**. Thus, **2** may serve as a useful tracer.

Synthesis of α,ω-Bromoalkyl Sulfonates

The formation of 2-bromoethylsulfonate (**7**) followed the method described by Marvel.[14] In the attempt to generalize this reaction, it was noted that both 1,3-dibrompropane and 1,4-dibromobutane were not miscible in the ethanol-water reaction solvent. An attempt at directly following the described procedure was made and both the 3-bromopropylsulfonate (**8**) and 4-bromobutylsulfonate (**9**) were formed, although in low yields of roughly 20%. The insolubility of the starting dibromides facilitated the recovery of the excess. The product had to be

recrystallized several times from 95% ethanol to diminish the amount of sodium bromide in the crude product.

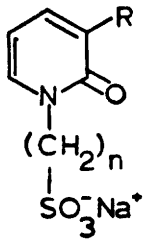
A similar method for formation of the propyl and butyl bromosulfonates described yields of 76% and 15% respectively utilizing 80% ethanol as the reaction solvent and a batch addition of the sodium sulfite.[17]

These reactions are useful because they use mild conditions, utilize inexpensive or easily recoverable starting materials, and have short reaction times. These factors overcome the drawbacks of small yields and difficulty of purification.

Alkylation of 2-Pyridones by α,ω-Bromoalkyl Sulfonates

The sodium salts of **1** and **4** were formed by the methods of Bush,[2] by treatment of 3-phenyl-2-pyridone with sodium methoxide and 3-carbamoyl-2-pyridone with sodium hydroxide. Alkylation of these salts was carried out in acetonitrile. The yields of the reactions for both **1** and **4** with the ethyl, propyl, and butyl bromosulfonates are shown in Table 3. The amount of 1-H-2-pyridone formed was taken as an indication of extent of elimination occurring.[1]

Table 3. Yields of the Alkylsulfonation Reactions



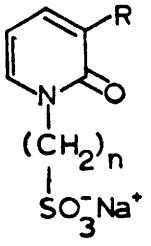
R = C_6H_5		R = $CONH_2$	
n	% Sulfonate	n	% Sulfonate
2	12	2	8
3	41	3	33
4	72	4	64

The isolated products were difficult to purify. The 3-phenyl-2-pyridone alkyl sulfonates were insoluble in ethanol and the 3-carbamoyl-2-pyridone alkyl sulfonates were very soluble so it was not possible to recrystallize them from this solvent. Purification utilizing preparative HPLC was finally used to obtain samples of sufficient purity for analysis.

Spectral Analysis of 2-Pyridone Alkyl Sulfonates

The 3-substituted 2-pyridone-1-alkyl sulfonates were analyzed by ultra-violet and fluorescence spectroscopy. The resultant molar absorptivities (ε) and quantum yields of fluorescence (Φ), are shown in Table 4. The fluorescence intensities are adequate for use as tracing compounds. Proton NMR spectra of the pyridone alkyl sulfonates were obtained to verify the structures.

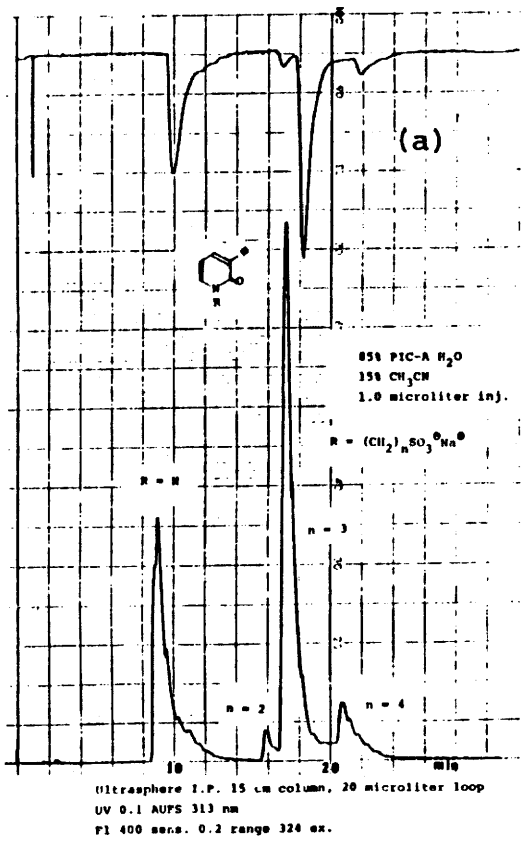
Table 4. Molar Absorptivities and Fluorescence Quantum Yields of the 3-Phenyl- and 3-Carbamoyl-2-Pyridone-1-Alkyl Sulfonates



R	n	ε	Φ	λ max, nm
C_6H_5	2	8.6×10^3	4.7×10^{-3}	283.5
	3	5.9×10^3	9.0×10^{-2}	315.3
	4	2.3×10^3	1.7×10^{-1}	314.9
$CONH_2$	2	6.1×10^3	2.2×10^{-1}	324.7
	3	6.4×10^3	1.3×10^{-1}	325.3
	4	$2/3 \times 10^3$	1.8×10^{-1}	324.5

High Performance Liquid Chromatography (HPLC) of the Pyridone Alkyl Sulfonates

Analytical HPLC separations of the homologous alkyl sulfonate series of the 3-phenyl- and 3-carbamoyl-2-pyridones were developed using ion pairing reagents. These separations, shown in Figure 2, demonstrate that these compounds would be separately identifiable from the same sample if they were to be used as site-specific water tracers. For example, several locations at the same waste disposal site could be marked. Since the syntheses we have developed are general, additional members of a series could be synthesized if needed. Levels of detection of compounds **1**, **4**, **12**, **13**, **14** **16**, and **17** are in the parts-per-trillion range.



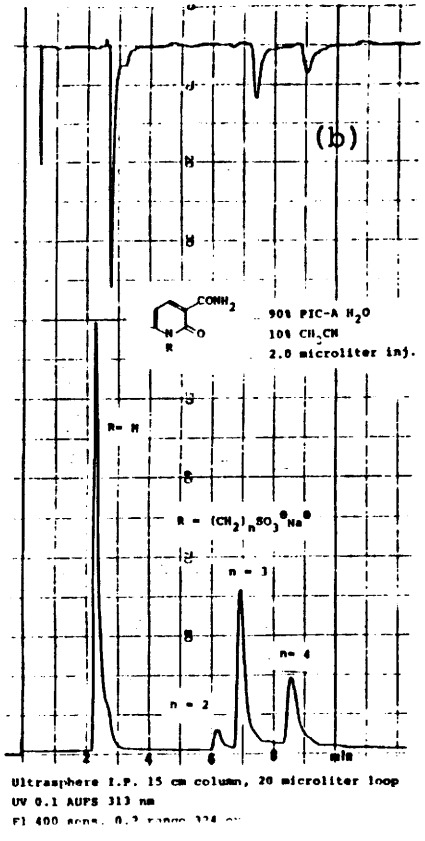


Figure 2.

HPLC Separations of 3-Phenyl-2-pyridone-1-alkyl Sulfonates (a), and 3-Carbamoyl-2-pyridone-1-alkyl Sulfonates (b).

EXPERIMENTAL

Apparatus

HPLC separations were obtained using a system consisting of 2 Waters Associates Model 6000-A Liquid Chromatography pumps, a Model 660 solvent programmer, a Model 440 absorbance detector set at 313 nm, a Schoeffel FS 970 fluorometer with excitation at 320 nm using a Schoeffel 7-54 excitation filter and a Schoeffel KV 370 emission filter. NMR spectra were obtained on a JEOL FS-270 spectrometer and are referenced to tetramethylsilane in chloroform-D, t-butyl-OD in deuterium oxide or DMSO-d_6 as an internal standard. Ultraviolet absorbance data were obtained on a Hitachi 100-80 spectrophotometer. Fluorescence spectra and quantum yields were determined using a Perkin Elmer Hitachi MPF-2A spectrophotometer. Melting points were determined using a Thomas-Hoover Unimelt and are uncorrected. Elemental analyses were obtained from Atlantic Microlabs, Atlanta, Georgia.

Chemicals

All reagents were obtained from Aldrich Chemical Company unless otherwise indicated.

HPLC Separation Conditions

All analytical separations were performed on an Altex Ultrasphere I.P. C18, 5 micron, 4.6 mm x 15 cm column. The 3-carbamoyl-2-pyridone series was separated using a mobile phase of 90% 0.05M tetrabutylammonium phosphate (Waters Associates PIC-A ion pairing reagent) and 10% acetonitrile with a flow rate of 1 mL per minute. The 3-phenyl-2-pyridone series was separated using a mobile phase of 85% 0.05M tetrabutylammonium phosphate and 15% acetonitrile with a flow rate of 1 mL per minute.

Analytical samples of the 3-substituted 2-pyridone-1-alkyl sulfonates were obtained by using a Whatman Partisil M-9 10/50 ODS-2 C18 column. The 3-carbamoyl series compounds were obtained using a mobile phase of 90% water and 10% acetonitrile with a flow rate of 3.3 mL per minute. The 3-phenyl series compounds were obtained using a mobile phase of 85% water and 15% acetonitrile with a flow rate of 3.3 mL per minute. The 1-H-3-pyridone was retained at the head of the column.

Quantum Yields of Fluorescence Measurements

The quantum yields of the 2-pyridones were measured by the relative fluorescence measurement technique of Parker and Rees.[18] Parker and Rees' method compares the fluorescence of the compound of interest to that of a compound with a known fluorescence quantum yield. The compounds herein reported were compared to 1-H-2-oxo-3-carbamoylpyridine (**4**). In the equation,

$$\Phi_2 = \frac{(I_f)_2}{(I_f)_1} \frac{\varepsilon_1 c_1}{\varepsilon_2 c_2} \Phi_1$$

I_f is the intensity of the fluorescent signals of both compounds measured as peak heights in cm, ε is their molar absorptivity, c is their concentration in moles per liter, and Φ is the fluorescence quantum yield of the respective compound. Quantum yield measurements were made in distilled water. Slit settings on the Perkin-Elmer MPF-2A were 8μ for both emission and exitation monochrometers. Spectra were obtained in a reference mode with excitation at 320 nm.

1-H-2-Oxo-3-phenypyridine (**1**). A solution of 3-phenylpyridine (50 g, 332 mmol) and 30% hydrogen peroxide (120 mL) in glacial acetic acid (200 mL) was

refluxed for 5 h and evaporated. Acetic anhydride (300 mL) was added to the residue and refluxed for 24 h and then evaporated to give a dark residue. A 10% HCl solution (100 mL) was added, the residue stirred for 10 h, and then evaporated under vacuum. Recrystallization in benzene was attempted but was ineffective. Purification of the product was obtained by column chromatography of the crude product on silica using chloroform as the mobile phase. The purified product weighed 11.32 g (20%): mp 223.5-225.5°C (previously reported 222-223.5°C).[2] ^{1}H NMR (DMSO-d6): δ 5.38 (t, J=6.2 Hz, 1H), 6.36-6.49 (m, 4H), 6.71-6.18 (m, 3H), 10.92 (s, 1H).

1-H-2-Oxo-3-carboxypyridine (2). A solution of 2-chloronicotinic acid (50 g, 317 mmol), concentrated hydrochloric acid (500 mL), and glacial acetic acid (500 mL was refluxed for 72 h then cooled to crystallize 2-hydroxy-3-carboxypyridine. The yield was 25.75 g (57.3%): mp 257-259°C (lit.[6] mp 258-260°C). ^{1}H NMR (DMSO-d6): δ 7.00 (t, J=7.0 Hz, 1H), 8.26 (dd, $J_{6,5}$=6.0 Hz $J_{6,4}$=2.2 Hz, 1H), 8.71 (dd, $J_{4,5}$=7.0 Hz $J_{4,6}$=2.2 Hz, 1H), 13.56 (s, 1H).

1-H-2-Oxo-3-(methoxycarbonyl)pyridine (3). A solution of 2 (25.75 g, 185 mmol) and freshly distilled boron trifluoride etherate (30 mL) in anhydrous methanol (500 mL) was refluxed for 36 h and then cooled. Water (1000 mL) was added. The solution was extracted with 3 aliquots of chloroform (750 mL) and the chloroform was evaporated under reduced pressure. The resultant residue was recrystallized from water (7 mL per gram of product). The yield was 11.7 g (41%): mp 150-152°C (lit.[6] 151-152°C). ^{1}H NMR ($CDCl_3$): 3.907 (s, 1H), (t, J=6.59 Hz, 3H), 7.78 (d, J=5.13 Hz, 1H) 8.29 (d, J=5.86 Hz, 1H.

1-H-2-Oxo-3-carbamoylpyridine (4). A solution of 3 (10.7g, 77 mmol) and concentrated ammonium hydroxide (486 mL) was allowed to dissolve completely (2 h) and the solution was evaporated under reduced pressure. The residue was

recrystallized from water. The yield was 7.7 g (80%): mp 266-267°C (lit.[6] mp 266-267°C). ^{1}H NMR (DMSO-d6): δ 6.43 (t, J=6.7 Hz, 1H) 7.57 (s, 1H), 7.69 (d, J=4.15 Hz, 1H), 8.31 (d, J=4.15 Hz, 1H), 9.09 (s, 1H), 12.43 (s, 1H).

Nicotinic acid N-oxide (5). A solution of nicotinic acid (1.1 kg, 8.94 mol) and 30% hydrogen peroxide (1500 mL) in glacial acetic acid (12 L) was refluxed in a 22 L reaction vessel for 12 h. Upon cooling a white solid precipitated which was filtered and used for subsequent reactions without further purification. Yield of reaction was approximately 950 g (76%): mp 253-255°C (dec.) lit.[5] 254-256°C (dec.).

2-Chloronicotinic acid (6). Caution. This procedure should be carried out in an efficient hood. A suspension of 5 (1.5 kg, 10 mol) and phosphorus oxychloride (2 kg) was heated at 90°C with stirring in a 12 L four necked flask fitted with a pressure equalizing addition funnel, a thermometer well extending into the solution, and an efficient wide-bore condenser, until a light yellow solution resulted. Triethylamine (1500 mL, 10.7 mol) was slowly added to the solution. Immediately upon addition the solution turned dark red and then dark brown with evolution of a powdery white solid suspension above the surface of the solution. The addition was very exothermic and care must be taken not to evolve too much heat. By controlling the rate of addition of triethylamine, the solution temperature was maintained at 110-120°C for 4 h. After cooling the reaction solution was concentrated by rotary evaporation using an ice-cooled vapor trap to stop any $POCl_3$ vapors. The resultant dark brown syrup as poured over ice (8 L) contained in 3 4 L beakers slowly with stirring to produce a light brown precipitate on the surface of the ice, taking care not to allow the syrup to settle to the bottom of the beaker without hydrolysis. The ice was allowed to melt and the light brown precipitate was filtered and

recrystallized from water. Additional product could be obtained by cooling the filtrate to -10°C. The crude yield of light brown precipitate was 86 g (68%): mp 186-187°C (dec.) lit.[5] 192-193° (dec.).

Large scale preparation of **2**.

A solution of crude **6** (2.0 kg, 12.7 mol) in glacial acetic acid (6 L) and hydrochloric acid (6 L) was refluxed for 48 h. Solution was cooled and concentrated with a rotary evaporator. Precipitated crystals were filtered. Yield was 50%.

Large scale preparation of **4**.

A solution of **3** (1 kg. 7.2 mol) in concentrated ammonium hydroxide (2 L) was stirred for 2 h at room temperature and then concentrated. Yield was 80%.

Large scale preparation of **3**.

A solution of crude **2** (500 g, 3.6 mol) in methanol (8L) with sulfuric acid (200 mL) as the catalyst was refluxed for 36 h. The solution was neutralized with ammonium hydroxide to pH 8, decolorized with activated carbon, and evaporated to dryness. Yield was 85%.

2-Bromoethylsulfonate sodium salt (**7**). A solution of 1,2-dibromoethane (307.5 g, 1.65 mol) in water (225 mL) and 95% ethanol (625 mL) was heated to reflux and stirred while a solution of sodium sulfite (62.5 g, .496 mol) in water (225 mL) was slowly added over a period of 2 h and then refluxed for an additonal 2 h. The excess 1,2-dibromoethane was then distilled off with the ethanol and the resultant aqueous solution was allowed to dry. The residue was recrystallized from 95% ethanol (2 L) and dried in an Abderhalden drying apparatus under vacuum because it was hygroscopic. The yield was 67.7 g (68%).

^{1}H NMR (D_2O): δ 3.43 (t, J=7.32 Hz, 2H), 3.67 (t, J=6.95 Hz, 2H); ^{13}C NMR (D_2O): δ 25.61, 54.66.

3-Bromopropylsulfonate sodium salt (8). A solution of 1,3-dibromopropane (10.9 mL, 20 g, 99 mmol) in 95% ethanol (37.5 mL) and water (13.5 mL) was stirred vigorously and brought to reflux. A solution of sodium sulfite (3.75 g, 29 mmol) dissolved in water (13.5 mL) was slowly added to the refluxing mixture over a period of 2 h and then refluxed for an additional 2 h. The mixture was poured into a separatory funnel and allowed to cool whereupon it separated into a two phase system. The excess 1,3-dibromopropane was drawn off and the remaining solution was evaporated to dryness. The residue was recrystallized from 95% ethanol 3 times. The yield was 1.15 g (17.7%): mp 279-285°C (-HBr), 306° (dec.). ^{1}H NMR (D_2O): δ 2.29 (p, J=7.59 Hz, 2H), 3.07 (t, J=6.59 Hz, 2H), 3.60 (t, J=5.86 Hz, 2H); ^{13}C NMR (D_2O): δ 29.10, 33.20, 51.02.

4-Bromobutylsulfonate sodium salt (9). A solution of 1,4-dibromobutane (12.0 mL, 21.4 g 99 mmol) in 95% ethanol (37.5 mL) and water (13.5 mL) was vigorously stirred and brought to reflux. A solution of sodium sulfite (3.75 g, 29 mmol) in water (13.5 mL) was slowly added to the refluxing mixture over a period of 2 h and then refluxed for an additional 2 h. The mixture was poured in a separatory funnel and allowed to cool and separate into a two phase system. The excess 1,4-dibromobutane was drawn off and the remaining solution was evapoarated to dryness. The residue was recrystallized from 95% ethanol 3 times. The yield was 2.08 g (29.3%). ^{1}H NMR (D_2O): δ 1.88 (m, 2H), 1.97 (m, 2H), 2.89 (m, 2H), 3.45 (m, 2H).

2-Oxo-3-carbamoylpyridine sodium salt (10). A solution of 4 (7.19 g, 52 mmol) and sodium hydroxide (2.6 g, 65 mmol) in water (250 mL) was allowed to stand at room temperature until complete solution occurred. The water was

evaporated under reduced pressure. The yield was 8.2 g (98%).

2-Oxo-3-phenylpyridine sodium salt (11). A solution of sodium metal (0.25 g, 11.3 mmol) and anhydrous methanol (10 mL) was allowed to react to form sodium methoxide. **1** (1.88 g, 11 mmol) was added to the solution and allowed to stand at room temperature for 24 h. The methanol was removed under reduced pressure and the residue was extracted with hot benzene 3 times and dried in the Abderhalden drying pistol for 30 min. The yield was 1.7 g (82%).

2-(2-Oxo-3-carbamoyl-1-pyridyl)-ethylsulfonate sodium salt (12). A solution of **7** (0.264 g, 1.25 mmol) and **10** (0.200 g, 1.25 mmol) in acetonitrile (50 mL) was brought to reflux and stirred for 24 h. The yield of the reaction was 8%, as determined by HPLC. An analytical sample was obtained from the filtered residue of the reaction by preparative HPLC.

3-(2-Oxo-3-carbamoyl-1-pyridyl)-propylsulfonate sodium salt (13). A solution of **8** (0.264 g, 1.17 mmol) and **10** (0.200 g, 1.25 mmol) in acetonitrile (50 mL) was brought to reflux with stirring for 24 h. The yield of the reaction was 33%, as determined by HPLC. An analytical sample was obtained from the filtered residue of reaction by preparative HPLC.

4-(2-Oxo-3-carbamoyl-1-pyridyl)-butylsulfonate sodium salt (14). A solution of **9** (0.299 g, 1.25 mmol) and **10** (0.200 g, 1.25 mmol) in acetonitrile (50 mL) was brought to reflux with stirring for 48 h. The yield of reaction was 64%, as determined by HPLC. An analytical sample was obtained from the filtered residue of reaction by HPLC.

2-(2-Oxo-3-phenyl-1-pyridyl)-ethylsulfonate sodium salt (15). A solution of **7** (0.264 g, 1.25 mmol) and **11** (0.241 g, 1.25 mmol) in acetonitrile (50 mL) was brought to reflux with stirring for 24 h. The yield was 12%, as determined by HPLC. An analytical sample was obtained from the filtered residue of reaction by HPLC.

3-(2-Oxo-3-phenyl-1-pyridyl)-propylsulfonate sodium salt (**16**). A solution of **8** (0.264 g, 1.25 mmol) and **11** (0.241, 1.25 mmol) in acetonitrile (650 mL) was brought to reflux with stirring for 24 h. The yield was 41%, as determined by HPLC. An analytical sample was obtained from the filtered residue of reaction by HPLC. Anal. Calcd. for $C_{14}H_{14}NSO_4Na \cdot H_2O$; C, 50.45; H, 4.8; N, 4.2. Found: C, 50.38; H, 4.83; N, 4.19.

4-(2-Oxo-3-phenyl-1-pyridyl)-butylsulfonate sodium salt (**17**). A solution of **9** (0.371 g, 1.55 mmol) and **11** in acetonitrile (50 mL) was brought to reflux with stirring for 24 h. The yield was 92%, as determined by HPLC. An analytical sample was obtained from the filtered residue of reaction by HPLC.

REFERENCES

1. Tieckelmann, Howard, in "The Chemistry of Heterocyclic Compounds, Pyridine and its Derivatives," Abramovitch, R. A., Ed; Intersciencee: New York, 1974; Vol. 14, Suppl. 3, Chapter 12.
2. Bush, James H. Ph.D. Dissertation, The University of Wyoming, Laramie, Wyoming, 1980.
3. Boekelheide, V.; Linn, W. J., J. Am. Chem. Soc. **1954**, 76, 1286.
4. Cava, M. P.; Winstein, Boris, J. Org. Chem. **1958**, 19, 1633.
5. Taylor, E. C.; Crovetti, Aldo E., J. Org. Chem. **1954**, 19, 1633.
6. Crum, J. D.; Fuchsman, C. H., J. Heterocyclic Chem. **1966**, 3, 252.
7. Clemo, G. R.; Koenig, H., J. Chem. Soc. **1949**, Suppl. 3, S231.
8. Kretzschmar, Egon; et al., E. German Patent 80,209 (Cll. C07d), 1971: Chem. Abstr. **1972**, 76, 72415.
9. Bush, J. H.; Nelson, D. A., Abstracts, Joint Northwest/Rocky Mountain Meeting of the American Chemical Society, Salt Lake City, Utah, June 1980, No. 33.
10. Smart, P. L.; Laidlaw, I.M.S., Water Resources Research **1977**, 13, 15.
11. Hopkins, George C.; et al., J. Org. Chem. **1967**, 32, 4040.
12. Meislich, Herbert, in "The Chemistry of Heterocyclic Compounds, Pyridine and its Derivatives;" Klingsberg, E., Ed.; Interscience: New York, 1962; Part 3, Chapter 12.
13. Gilbert, E. E., "Sulfonation and Related Reactions;" Robert E. Krieger Publishing Co., Huntington, N.Y., 1977; p. 137.
14. Marvel, C. S.; et al., J. Am. Chem. Soc. **1927**, 49, 1833.
15. Yoneda, Gerald S.; et al., J. Org. Chem. **1975**, 40, 375.

16. Lipovich, I. M., J. Appl. Chem. of U.S.S.R. (English Translation) **1945**, 18, 71; Chem. Abstr. **1946**, 40, 6407.

17. Lipovich, I. M.; Mones, E. M., J. Appl. Chem. of U.S.S.R. **1945**, 18, 20; Chem. Abstr. **1945**, 39, 5399.

18. Parker, C. A.; Rees, W. T., Analyst **1960**, 85, 587.