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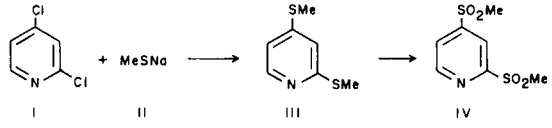
Received July 1, 1983

Dihalogenated pyridines, some activated with carboxylic, ester or cyano group, were allowed to react with sodium alkylmercaptides. After hydrolysis of the ester or cyano group followed by decarboxylation, bis-alkylthiopyridines with substituents at 2,3-, 2,4-, 2,5-, 2,6- and 3,5-positions were prepared. These compounds were oxidized to bis-alkylsulfonylpyridines.

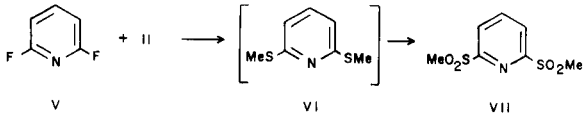
J. Heterocyclic Chem., **21**, 97 (1984).

For a synthesis project, we needed bis-alkylsulfonylpyridines, or thier precursors, *i.e.* bis-alkylthiopyridines. All possible isomers are known in the literature [3-13]. They were prepared by multistep reaction schemes which usually involve diazotization. As an explosive intermediate was reported in one case [6] and others looked potentially dangerous, elimination of the diazotization step seemed desirable.

2,4- And 2,6-bis-methylthiopyridines (III and VI) were prepared in our laboratory directly from the reaction of 2,4-dichloropyridine with sodium methylmercaptide in dimethylformamide (Method I) and 2,6-difluoropyridine with sodium methylmercaptide in dimethylsulfoxide (Method II). Both methods were simpler than that reported [5, 7-10] for the preparation of compounds III and VI. Compound III was isolated and oxidized to 2,4-bis-methylsulfonylpyridine (IV). Intermediate VI was not isolated, but oxidized to 2,6-bis-methylsulfonylpyridine (VII).



I II III IV



V VI VII

Displacement of a halogen or nitro group at the 3 and 5 positions by mercaptide did not look promising at the beginning. Wuest and Sakel [14] reported a 14% yield of 3-mercaptopyridine from 3-bromopyridine with potassium hydrosulfide in the presence of copper. Binz and Räth [15] reported that only the 2-chloro group was displaced in a group of 2,5-disubstituted pyridines.

R = NO_2, Br, Cl, I.

Fitch *et al* [16] reported displacement of the 5-nitro group in methyl 5-nitropicolinate.

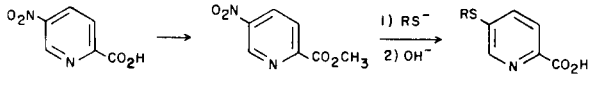


Table I

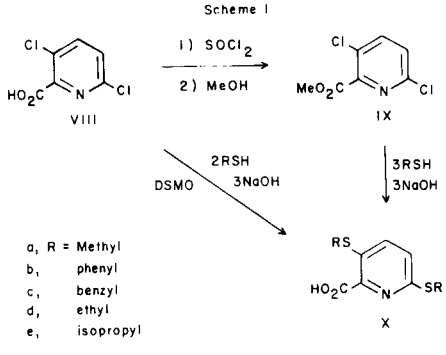
bis-Alkylthiopyridinecarboxylic Acids and Nitrile

Compound	Substituents R_2	R_3	R_4	R_5	R_6	Mp (°C)	Method of Preparation (% Yield)	Formula	Analysis Calcd./Found C	H	N
X-a	CO_2H	*S*-methyl			*S*-methyl	142-144	III (82)	$C_8H_9NO_2S_2$	44.63	4.42	6.51
							IV (65)		44.58	4.22	6.42
X-b	CO_2H	*S*-phenyl			*S*-phenyl	131-132	III (72)	$C_{18}H_{13}NO_2S_2$	63.69	3.86	4.13
									63.32	3.96	4.05
X-c	CO_2H	*S*-benzyl			*S*-benzyl	129	III (44)	$C_{20}H_{17}NO_2S_2$	65.37	4.66	3.81
									64.99	4.85	3.65
XIII-a	CO_2H			*S*-methyl	*S*-methyl	152	IV (89)	$C_8H_9NO_2S_2$	44.63	4.22	6.51
									44.38	4.37	6.34
XIII-d	CO_2H			*S*-ethyl	*S*-ethyl	112-113	IV (95)	$C_{10}H_{13}NO_2S_2$	49.35	5.38	5.76
									49.24	5.53	5.66
XVIII-a	CN	*S*-methyl		*S*-methyl		115.5-116	XI (95)	$C_8H_8N_2S_2$	48.95	4.11	14.27
									48.66	4.20	14.23

As the acid was converted to the ester before the displacement followed by rehydrolysis to the acid, it was uncertain whether the reaction would proceed with the acid.

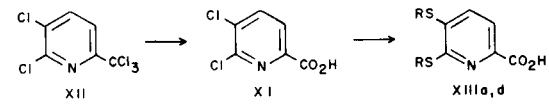
In our initial approach, 3,6-dichloropyridine-2-carboxylic acid (VIII) [17] was converted to its methyl ester IX. When the ester was allowed to react with three equivalents of methylmercaptide, displacement of the chloro groups and cleavage of the ester took place and the acid Xa was obtained upon acidification (Method III). Later, acid VIII was converted to X directly with three equivalents of sodium hydroxide and 2.2 equivalent of alkanethiol in dimethylsulfoxide (Method IV). The esterification step was eliminated as summarized in Scheme I.

Scheme I



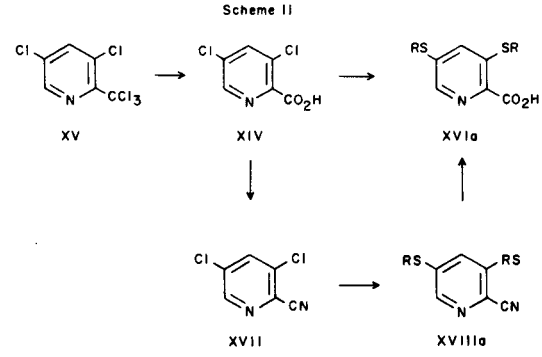
Compounds Xa-c are listed in Table I. Also prepared were ethyl and isopropyl compounds which were decarboxylated without purification of the intermediates (Method V).

5,6-Dichloropyridine-2-carboxylic acid (XI), which was obtained from hydrolysis of 2,3-dichloro-6-trichloromethylpyridine (XII) [18], gave 5,6-bis-alkylthiopyridine-2-carboxylic acids XIII.



3,5-Dichloropyridine-2-carboxylic acid (XIV), which was obtained from the hydrolysis of 3,5-dichloro-2-trichloromethylpyridine (XV) [19], gave the bis-alkylthio compound in very poor yield. The acid was converted to nitrile and 3,5-bis-methylthio groups were introduced into the molecule (Scheme II). The nitrile was hydrolyzed to the acid, compounds XIII and XVIII are listed in Table I.

Scheme II



Decarboxylation of 2-pyridinecarboxylic acids was carried out with or without solvents (Methods VI and VII). Low melting compounds were melted, decarboxylated and distilled over by means of Kügelrohr apparatus. With high melting compounds, the presence of a solvent decreased tarring. Common high boiling solvents, like decalin, diphenyl ether, *o*-dichlorobenzene, were all satisfactory. The bis-alkylthiopyridines can be isolated by extraction into 6*N* hydrochloric acid, basified and extracted into an organic solvent. Or the bis-alkylthiopyridine in hydro-

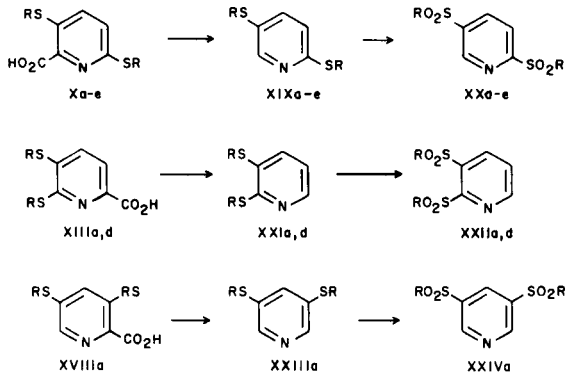
Table II

bis-Alkylthiopyridines

Compound	Substituents R_2	R_3	R_4	R_5	R_6	Mp or Bp (mm Hg)	Method of Preparation (% Yield)	Formula	Analysis Calcd./Found C	H	N
III	*S*-methyl		*S*-methyl			99 (0.05) [a]	I (88)	$C_7H_9NS_2$	49.08	5.30	8.18
									48.72	5.29	8.22
XIX-a	*S*-methyl			*S*-methyl		90 (0.1)	VI (79)	$C_7H_9NS_2$	49.08	5.30	8.18
									49.28	5.35	8.04
XIX-c	*S*-benzyl			*S*-benzyl		77	VI (98)	$C_{19}H_{17}NS_2$	70.55	5.30	4.33
									70.49	5.32	4.33
XXI-a	*S*-methyl	*S*-methyl				85 (0.3)	VI (45)	$C_7H_9NS_2$	49.08	5.30	8.18
									49.05	5.12	8.09
XXI-d	*S*-ethyl	*S*-ethyl				95 (0.3)	VI (67)	$C_9H_{13}NS_2$	54.23	6.57	7.03
									54.11	6.48	7.00
XXIII-a		*S*-methyl		*S*-methyl		90 (0.05) [b]	VI (76)	$C_7H_9NS_2$	49.08	5.30	8.18
									48.79	5.25	8.11

[a] Reported bp 130° (2 Torr) [5]. [b] Reported bp 135° (0.0001 Torr) [12].

chloric acid can be oxidized without isolation as shown in Method V. The bis-alkylthiopyridines are listed in Table II.



Oxidation of the bis-alkylthiopyridines to the corresponding sulfones was carried out with hydrogen peroxide in acetic acid or in trifluoroacetic acid or in sodium hypochlorite solution (methods VIII-X). The bis-alkylsulfonylpyridines are listed in Table III.

All compounds were identified by proton magnetic resonance spectra, infrared spectra and elementary analysis. In Table IV are listed the proton chemical shifts of the methyl compounds. Other alkyl compounds have similar spectra of their aromatic protons, and are not listed.

All the bis-alkylsulfonylpyridines, except XXIV, have an alkylsulfonyl group at the 2-position. They are reactive toward nucleophilic displacement. The results will be reported in a separate article.

EXPERIMENTAL

Melting points were taken with Thomas-Hoover Capillary Melting Point Apparatus and were not corrected. Infrared spectra were recorded with a Perkin-Elmer Infrared Spectrophotometer Model 297. Proton magnetic resonance spectra were recorded with a Varian T-60 Spectrometer. Preparative liquid chromatography separation was run with Waters Associates Prep LC System 500 with silica gel. Microanalyses were done by M. Gade.

Method I.

2,4-bis-Methylthiopyridine (III).

A suspension of 20.8 g (0.52 mole) of sodium hydroxide in 200 ml of dimethylformamide was cooled to $<5°$. To this suspension was added 25 g (0.52 mole) of methanethiol. The whole was stirred at room temperature under a Dewar condenser filled with Dry-Ice/dichloromethane until all sodium hydroxide disappeared. To this sodium methylmercaptide mixture was added 35 g (0.236 mole) of 2,4-dichloropyridine (I). The reaction mixture was heated at 140° for 6 hours. After cooling, the reaction mixture was poured into 400 g of ice and extracted with dichloromethane. The organic layer was dried, concentrated and distilled to give 35.4 g (88%) of product bp 99°/0.05 mm.

Method II.

2,6-bis-Methylsulfonylpyridine (VII).

Pulverized sodium hydroxide, 82.3 g (2.2 moles), was added to 300 ml of dimethylsulfoxide and chilled in Dry-Ice/dichloromethane mixture. Chilled methanethiol, 90 g (1.87 moles) was added quickly through a Dry-Ice cooled dropping funnel, followed by 107.6 g (0.93 mole) of 2,6-difluoropyridine. As a result of the exothermic reaction the reaction tempe-

Table III

bis-Alkylsulfonylpyridines

Compound	Substituents R_2	R_3	R_4	R_5	R_6	Mp (°C)	Method of Preparation (% Yield)	Formula	Analysis Calcd./Found C	H	N
IV	SO_2methyl		SO_2methyl			167-168	X (89)	$C_7H_9NO_4S_2$	35.73	3.85	5.95
									35.35	3.80	5.68
VII	SO_2methyl				SO_2methyl	193-195	II (56) [a]	$C_7H_9NO_4S_2$	35.73	3.85	5.95
									35.66	3.71	5.99
XX-a	SO_2methyl			SO_2methyl		205-207	VIII (75)	$C_7H_9NO_4S_2$	35.73	3.85	5.95
									35.91	3.97	5.98
XX-b	SO_2phenyl			SO_2phenyl		202-205	VI-VIII (47) [a]	$C_{17}H_{13}NO_4S_2$	56.81	3.64	3.90
									56.88	3.75	3.99
XX-c	SO_2benzyl			SO_2benzyl		265 dec	IX (87)	$C_{19}H_{17}NO_4S_2$	58.89	4.42	3.62
									58.29	4.52	3.59[c]
XX-d	SO_2ethyl			SO_2ethyl		148-150	V (52) [b]	$C_9H_{13}NO_4S_2$	41.05	4.97	5.32
									40.63	5.02	5.33
XX-e	SO_2-isopropyl			SO_2-isopropyl		181	III-VII-IX (54) [b]	$C_{11}H_{17}NO_4S_2$	45.34	5.88	4.81
									45.47	5.88	4.73
XXII-a	SO_2methyl	SO_2methyl				175-176	IX (65)	$C_7H_9NO_4S_2$	35.73	3.85	5.95
									35.35	3.80	5.68
XXII-d	SO_2ethyl	SO_2ethyl				132	IX (65)	$C_9H_{13}NO_4S_2$	41.05	4.97	5.32
									41.08	5.06	5.29
XXIV-a		SO_2methyl		SO_2methyl		229-231	X (81)	$C_7H_9NO_4S_2$	35.73	3.85	5.95
									35.63	3.91	5.83

[a] Overall yield of two-step preparation. [b] Overall yield of three-step preparation. [c] A more satisfactory analysis was unobtainable.

Table IV

PMR Data for bis-Alkylthiopyridinecarboxylic Acid, bis-Alkylthiopyridines and bis-Alkylsulfonylpyridines

Compound	Substituents and Chemical Shifts (ppm-TMS)										Solvents
	R_2 (or R_6)		R_3 (or R_5)		R_4		R_5 (or R_3)		R_6 (or R_2)		
III	S-Me	2.52 (s)	H	6.93 (d)	S-Me	2.40 (s)	H	6.80 (q)	H	8.24 (d)	Deuteriochloroform
IV	SO_2-Me	3.48 (s)	H	8.48 (d)	SO_2-Me	3.40 (s)	H	8.30 (q)	H	8.17 (d)	DMSO-d_6
VI	S-Me	2.52 (s)	H	6.82 (t)	H	7.18 (q)	H	6.82 (t)	S-Me	2.52 (s)	Deuteriochloroform
VII	SO_2-Me	3.34 (s)	H	8.40 (t)	H	8.40 (t)	H	8.40 (t)	SO_2-Me	3.34 (s)	DMSO-d_6
X-a	CO_2H		S-Me	2.60 (s)	H	7.63 (d)	H	7.37 (d)	S-Me	2.45 (s)	DMSO-d_6/Deuteriochloroform
XIX-a	H	8.40 (d)	S-Me	2.42 (s)	H	7.42 (q)	H	7.09 (d)	S-Me	2.54 (s)	Deuteriochloroform
XX-a	H	9.30 (d)	SO_2-Me	3.37 (s)	H	8.68 (q)	H	8.32 (d)	SO_2-Me	3.42 (s)	DMSO-d_6
XIII-a	CO_2H		H	7.48 (d)	H	7.60 (d)	S-Me	2.52 (s)	S-Me	2.57 (s)	DMSO-d_6
XXI-a	H	8.22 (q)	H	6.90 (q)	H	7.32 (q)	S-Me	2.42 (s)	S-Me	2.56 (s)	Deuteriochloroform
XXII-a	H	9.11 (q)	H	8.10 (q)	H	8.70 (q)	SO_2-Me	3.50 (s)	SO_2-Me	3.55 (s)	DMSO-d_6
XVI-a	CO_2H		S-CH_3	2.67 (s)	H	7.55 (d)	S-Me	2.51 (s)	H	8.30 (d)	DMSO-d_6
XXIII-a	H	8.22 (d)	S-Me	2.48 (s)	H	7.39 (t)	S-Me	2.48 (s)	H	8.22 (d)	Deuteriochloroform
XXIV-a	H	9.46 (d)	SO_2-Me	3.48 (s)	H	8.78 (t)	SO_2-Me	3.48 (s)	H	9.46 (d)	DMSO-d_6

rature rose to 105°. The reaction mixture was then heated to 130° for 2 hours, cooled, diluted with ice water and filtered. The solid was washed with CHLOROETHENE* NU [20] and the filtrate extracted with the same. The organic layer was dried and concentrated under reduced pressure to give an orange-brown oil. The oil was dissolved in 500 ml of trifluoroacetic acid and oxidized with 318 g of 30% hydrogen peroxide at 65 to 75° for 2 hours. After cooling and diluting with 1500 g of ice-water mixture, the solid was collected by filtration. It was washed with water, ethanol and ether to give 123.3 g of product, 56% overall yield of the two-step procedure.

Method III.

Synthesis of 3,6-bis-Alkylthiopyridine-2-carboxylic Acid from Methyl 3,6-Dichloropyridine-2-carboxylate. 3,6-bis-Methylthiopyridine-2-carboxylic Acid (Xa).

Methanethiol, 30.3 g (0.69 mole), was dissolved in 200 ml of dimethylformamide at below 0°. To this solution was added 70.6 g (0.69 mole) of potassium *t*-butoxide at such a rate that the reaction temperature was kept below 10°. The resulting white slurry was added to a mixture of 39.35 g (0.19 mole) of methyl 3,6-dichloropyridine-2-carboxylate in 100 ml of dimethylformamide at 80°. After the addition was complete, the temperature was raised to 100° and maintained for 2 hours. Upon cooling, the paste-like reaction mixture was diluted with ether and filtered. The solid was dissolved in water, extracted with dichloromethane. The aqueous layer was acidified with concentrated hydrochloric acid to *p*H 3. The solid was collected by filtration and dried on a porous plate to give 37 g (82%) of bright yellow solid. Small portion was recrystallized from ethanol to give bright yellow plates, mp 142-144°.

Method IV.

Synthesis of bis-Alkylthiopyridine-2-carboxylic Acids from Dichloropyridine-2-carboxylic Acids.

3,6-bis-Methylthiopyridine-2-carboxylic Acid (Xa).

A solution of sodium methylmercaptide was prepared by addition of 66.4 g (1.38 moles) of methanethiol to a chilled mixture of 76 g (1.9 moles) of sodium hydroxide in 300 ml of dimethylsulfoxide under a Dry-Ice condenser. A solution of 100 g (0.52 mole) of 3,6-dichloropyridine-2-carboxylic acid in 300 ml of dimethylsulfoxide was added. The reaction mixture was heated to 130-135° for 2 hours. After cooling, the reaction mixture was diluted with ice-water and acidified with hydrochloric acid. The precipitate was collected by filtration, dried and recrystallized from dichloromethane to give 72.6 g (65%) of product, identical to that prepared in Method III.

Method V.

2,5-bis-Ethylsulfonylpyridine (XX-d).

Sodium hydroxide 160 g (4.0 moles) was weighed into a reaction flask, and covered with 1 ℓ of dimethylsulfoxide which was then cooled in an ice bath (~ 10°) and then 149 g of ethanethiol was added. The mixture was stirred at room temperature for 1 hour and then 3,6-dichloro-2-pyridinecarboxylic acid (192 g) was added and the resulting mixture was heated at 130° for 6 hours. After cooling, the reaction mixture was poured into 5 kg of ice, and acidified with 140 ml of concentrated hydrochloric acid. A solid formed which was collected by filtration. The aqueous filtrate was decanted into a separatory funnel and extracted with 2 ℓ of 1,1,1-trichloroethane. The solid was dissolved in 1 ℓ of dichloromethane. The organic solutions were combined, washed with 1 ℓ of water, dried, and concentrated to give 273 g of crude 3,6-bis-ethylthio-2-pyridinecarboxylic acid. The crude 3,6-bis-ethylthio-2-pyridinecarboxylic acid was dissolved in 100 ml of 1,2-dichlorobenzene and added in small portions to 500 ml of 1,2-dichlorobenzene heated at 160°. After the addition was complete, heating was continued for 2 hours. The reaction was chilled in ice and extracted three times with 200 ml of 6*N* hydrochloric acid.

The acid solution was put in a large container equipped with a mechanical stirrer. To this fast stirring solution was added 4 ℓ of 5.25% sodium hypochlorite solution. An off-white precipitate was formed which was collected by filtration, washed with water and dried to give 136.7 g of the product, 2,5-bis-ethylsulfonylpyridine, mp 148-150°.

Method VI.

Decarboxylation of bis-Alkylthiopyridine-2-carboxylic Acid in Decalin.

2,5-bis-Methylthiopyridine (XIXa).

To 75 ml of decalin was added portionwise while heating 59.5 g (0.28 mole) of 3,6-bis-methylthiopyridine-2-carboxylic acid. When the mixture reached 155° gas bubbles began to appear. The reaction was heated at 175° until no more bubbles appeared. Upon cooling the decalin solution was treated with 40 ml of 6*N* hydrochloric acid in 3 portions. The resulting solid and aqueous layers were collected. The solid was covered with water and an attempt was made to free it from the decalin. The aqueous layers and solid were then made basic with 50% sodium hydroxide and extracted with ether. The ether solution was treated with charcoal, dried and ether removed. This resulted in a yellow oil, 31 g (66%). A portion of this oil was distilled with Kügelrohr distillation apparatus (80°/0.1 mm). The sample contained some decalin.

Method VII.

Decarboxylation of bis-Alkylthiopyridine-2-carboxylic Acid.

2,5-bis-Methylethylthiopyridine (XIXe).

3,6-bis-Methylethylthiopyridine-2-carboxylic acid, 142 g (0.52 mole) was placed in a round bottom flask and warmed gently to 130° with a Kügelrohr apparatus under vacuum. An oil came out, and was purified by a second distillation at 150-160°/5 mm to give 80 g (66%) of product.

Method VIII.

Oxidation of bis-Alkylthiopyridine to bis-Alkylsuolfonylpryidine in Acetic Acid-Hydrogen Peroxide.

2,5-bis-Methylsulfonylpyridine (XXa).

2,5-bis-Methylthiopyridine, 26 g (0.15 mole) was dissolved in 60 ml of acetic acid and 75 g (0.66 mole) of 30% hydrogen peroxide was added dropwise. After about ¼-⅓ of the oxidant had been added, the reaction exothermed to 95°. Addition was stopped and the reaction was cooled to 75° with an ice bath. The addition was resumed and the temperature was kept at 75° for 4 hours. After cooling, the solid was filtered off, washed with water, ethanol, and ether. A portion was recrystallized from acetonitrile resulting in a white solid, mp 205-207°.

Method IX.

Oxidation of bis-Alkylthiopyridine to bis-Alkylsulfonylpyridine in Trifluoroacetic Acid-Hydrogen Peroxide.

2,5-bis-Methylethylsulfonylpyridine (XXe).

Trifluoroacetic acid, 400 ml, was placed in a flat-bottom, 2 ℓ, 3-necked flask equipped with magnetic stirrer, thermometer, reflux condensor, and dropping funnel. 2,5-bis-Methylethylthiopyridine, 74.40 g (0.327 mole) was added and the solution was heated to 54°. Hydrogen peroxide, 30%, 163.3 g (1.309 mole) was dropped in while the reaction temperature was maintained at 70-75°.

The flask was placed in a water bath for better regulation. There was no reaction initiation period observed; the exotherm was regular and proportional to the rate of addition. After about 60% of the peroxide had been added, the solution underwent a very rapid exotherm to 110° and was cooled by ice to 70° (the rapid exotherm was caused by the sudden addition of a large amount of peroxide). Upon completion of addition peroxide, the solution, which had originally been dark brown, had faded to a light yellow-gold. The solution was heated at 54° for 1-½ to 2 hours, with the color fading to light yellow during the heating. The solution was then allowed to cool overnight to room temperature. The cooled solution was added to 700 ml of ice-cold water and resulted in the immediate precipitation of a large amount of white solid. The mixture was allowed to settle and was filtered and washed thoroughly with water. The excess hydrogen peroxide of the filtrate was neutralized with sodium bisulfite, and the solid was washed twice with ethanol and three times with anhydrous ether. The crude product was a clean, snow-white powder, weighed 83.14 g (87%), mp 181°.

Several grams were recrystallized from acetonitrile and gave tiny, white needles.

Method X.

2,4-bis-Methylsulfonylpyridine (IV).

In an Erlenmyer flask was placed 3.4 g (0.02 mole) of 2,4-bis-methylthiopyridine. To this oil was added 30 g of Chlorox® solution (5.25% sodium hypochlorite). An exotherm was observed. After the initial reaction subsided, another 100 g (0.092 mole total) of Chlorox solution was added in small portions. The reaction mixture was stirred at room temperature for 2 hours and the white precipitate collected by filtration. It was washed with water and vacuum dried to give an analytically pure sample.

Method XI.

3,5-bis-Methylthio-2-pyridinecarbonitrile (XVIIIa).

3,5-Dichloro-2-pyridinecarbonitrile (60 g, 0.347 mole) and methanethiol (42 ml, 0.763 mole) were stirred in 200 ml of tetrahydrofuran at 5° under positive pressure of nitrogen. A solution of potassium *t*-butoxide (93.48 g, 0.833 mole) in 500 ml of tetrahydrofuran was added at a rate to maintain the temperature below 15°. The reaction mixture was stirred for an additional 15 minutes, then poured into 2 ℓ of an ice water slurry. The slurry was stirred well for 5 minutes, then the solid was collected by filtration and dried to give 54.58 g (0.329 mole, 95%) of 3,5-bis-methylthio-2-pyridinecarbonitrile, mp 115.5-116°.

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