The Direct Thionation and Aminoalkylation of Pyridine 1-Oxides and Related Reactions (1)

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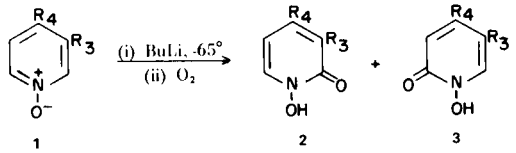
The reaction of lithiopyridine 1-oxides with oxygen gives poor yields of 1-hydroxy-2-pyridones. The reaction with sulfur, however, is a convenient route to the 1-hydroxy-2-pyridinethiones which have useful antibacterial and antifungal activity. Reaction with ethylene oxide gives mainly polymeric products, but addition to Shiff's bases promises to be a convenient mode of mono-, and particularly di-α-aminoalkylation of pyridine 1-oxides.

The substitution of hydrogen in pyridine 1-oxide and its derivatives has been achieved in a number of cases by base-induced proton-abstraction followed by treatment *in situ* with a suitable electrophile. In this way, hydroxyalkylation (2), acylation (3), carboxylation (3), halogenation (1,4), and chloromercuration (4) were conveniently carried out. We now report the action of a number of electrophiles upon 2-lithiopyridine 1-oxides leading to methods for the direct thionation and aminoalkylation of the parent heterocycle.

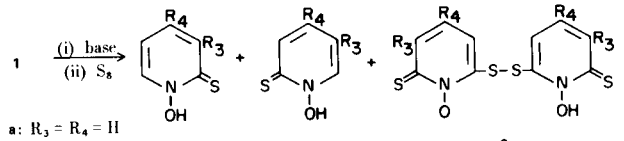
1-Hydroxy-2-pyridones have been shown (5) to have marked antibacterial activity. Of the 2-, 3-, and 4-hydroxypyridine 1-oxides only the first possessed significant antibacterial activity (6). 1-Hydroxy-2-pyridinethiones have been synthesized from 2-bromopyridine 1-oxides by treatment with thiourea, followed by hydrolysis of the isothiouronium salts (7). These, and their zinc chelates, have been shown to have marked and useful antibacterial activity (7). It would be of interest, therefore, to develop one-step syntheses of these compounds from the parent heterocycle.

Treatment of 2-lithiopyridine 1-oxide with oxygen did not yield any of the desired hydroxamic acid. On the other hand, 2-lithio-4-methylpyridine 1-oxide did give 1-hydroxy-4-methyl-2-pyridone (**2b**), albeit in low yield. Treatment of the lithio derivative of 3,4-dimethylpyridine 1-oxide (**1d**) with oxygen gave 1-hydroxy-3,4-dimethyl-2-pyridone (**2d**) (10%) and 1-hydroxy-3,4-dimethyl-6-pyridone (**3d**) (13.9%), whose spectral properties were consistent with the assigned structures, and which gave the characteristic hydroxamic acid red color with ferric chloride.



a: $R_3 = R_4 = H$
b: $R_3 = H$; $R_4 = Me$
d: $R_3 = R_4 = Me$

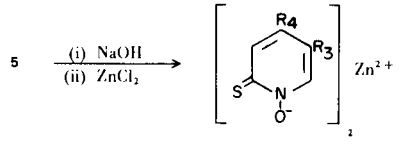
A general method of preparing cyclic thiohydroxamic acids has been developed which involves the addition of elemental sulfur to lithiopyridine 1-oxides. Treatment of lithiopyridine 1-oxide with sulfur in tetrahydrofuran at -65° gave 1-hydroxy-2-pyridinethione (**4a**) (8%) together with a brown plastic-like solid. The latter was not affected by lithium aluminum hydride and was not, therefore, a pyridine polysulfide (*vide infra*). When the reaction was carried out in ether at room temperature the yield of **4a** was only slightly higher. An improvement was achieved by using lithium hydride in dimethoxyethane containing some diethyleneglycol monomethyl ether as the base instead of butyllithium: **4a** was obtained in 19% yield. When methoxyethanol was used instead, the yield was still higher (21.5%). This base was, however, less effective than BuLi in the reactions with substituted pyridine 1-oxides.



a: $R_3 = R_4 = H$
b: $R_3 = H$; $R_4 = CH_3$
c: $R_3 = CH_3$; $R_4 = Cl$
d: $R_3 = R_4 = CH_3$

Reaction of 2-lithio-4-methylpyridine 1-oxide (from **1b** and BuLi) with sulfur gave **4b** (38.7%). When the anion was generated using lithium hydride in dimethoxyethane containing some methoxyethanol the yield of **4b** was only 5.5%. When 4-chloro-3-methylpyridine 1-oxide (**4c**) was

treated with BuLi at -65° and then with sulfur **5c** (11.5%) was obtained. The structure assignment is based on the known orientation on hydroxyalkylation of the anion of **4c** (2) and the infrared, n.m.r. and mass spectra of the compound (see Experimental). Thiohydroxamic acid **5c** was rather unstable and decomposed quite vigorously, so that its purification proved to be difficult. The zinc chelate (**7c**) (86%) was stable, however, and could be analyzed.



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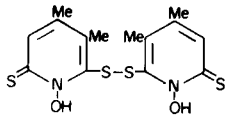
The lithio derivatives of 3,4-dimethylpyridine 1-oxide (**1d**) (from BuLi in tetrahydrofuran at -65°) was treated with sulfur to give 1-hydroxy-3,4-dimethyl-2-pyridinethione (**4d**) (12.5%), 1-hydroxy-3,4-dimethyl-6-pyridinethione (**5d**) (24.1%), and 2,2′-(1,1′-dihydroxy-4,4′,5,5′-tetramethyldipyridyl-6,6′-thione)disulfide (**6d**) (37.4%) (or its isomer **8**). The structure of the disulfide was supported by its



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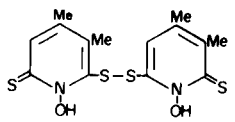

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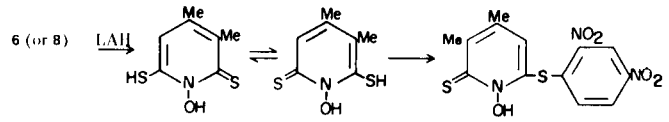
molecular weight, elemental analysis, nmr and mass spectrum. It was reduced quantitatively with lithium aluminum hydride to give 3,4-dimethyl-1-hydroxy-2-mercapto-6-pyridinethione (**10**) which, with 2,4-dinitrochlorobenzene, gave a 2,4-dinitrophenylthioether (assumed to be **11**). The unsymmetrical structure **9** for the disulfide could be elimi-



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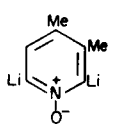
nated on the basis of its nmr spectrum in perdeuteriopyridine which exhibited a 2H singlet at δ 7.06 due to the pyridine α-protons and only two 6H singlets at δ 2.5 and 1.9, respectively, due to the two types of methyl groups. The data could not allow a distinction to be made between the two symmetrical structures **6** and **8** but our preference is for the sterically less hindered one, **6**. The formation of **6** (or **8**) suggests the intermediacy of the dilithio derivative (**12**), whose presence has been noted previously (2-4).



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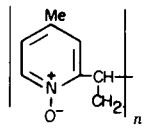
The relative orientation of **4d** and **5d** was easily established on the basis of their nmr spectra. Preferential formation of **5d** once again (2) suggests that metallation occurs at the least hindered α-carbon atom. Other reaction conditions and the use of other possible sources of sulfur are given in Table I. Treatment of **5d** with 2,4-dinitrochlorobenzene did not give a 2,4-dinitrophenylether. All the cyclic thiohydroxamic acids prepared here gave the characteristic purple color with ferric chloride and formed zinc chelates readily.

Since the reaction of organolithium reagents with epoxides is a convenient method for the synthesis of β-substituted ethanols (8) it was hoped that 2-lithiopyridine 1-oxides would yield 2-pyridylethyl alcohols. These on dehydration would give 2-vinylpyridine 1-oxides which, on polymerization, would lead to poly-(2-vinylpyridine 1-oxides), of interest in the treatment of the pathogenic effects of silica in animals (9). Treatment of 2-lithiopyridine 1-oxide in THF at -15° with a five molar excess of ethylene oxide gave 2-*n*-butylpyridine (9.5%) and a mixture of pyridine 1-oxide and a higher molecular weight product which could not be resolved by column chromatography. Pyridine 1-oxide probably arises by hydrogen-abstraction, either from THF, ethylene oxide or both. Similar results were obtained when ether was used as the solvent, either at -15° or at 25°.

Reaction of lithio-4-methylpyridine 1-oxide with ethylene oxide in ether at 25° for 2 hours gave an elastic-like hygroscopic solid whose molecular weight (osmometric) in chloroform was 812. This corresponds to a telomer (**13**) of 4-methyl-2-vinylpyridine 1-oxide where n = 6. When the reaction time was lengthened to 10 hours, a product



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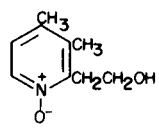

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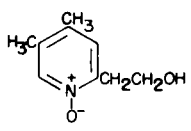

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of molecular weight 1866 was obtained, corresponding to **13** (n = 14). A portion of this product was purified by precipitation with ether from acetone solution. Its nmr spectrum (rather rough integral since accurate integration was not possible) exhibited a 1H multiplet at δ 8.6-7.8 assigned to C_6-H, a 2H multiplet at δ 7.5-6.5 due to C_3-H and C_5-H, a complex 3-4 H multiplet at δ 4.5-3.4 assigned to -CH- and $-CH_2-$, and complex multiplets at δ 3.0-0.7 probably due to $-CH_2-$ and $-CH_3$ groups. The presence of cross-linkages is possible since 2,6-disubstituted products have been isolated in the cases of alkylation, bromination, chlorination, and thionation.

Lithio-3,4-dimethylpyridine 1-oxide did not react with ethylene oxide in tetrahydrofuran at -65°. When the re-

TABLE 1

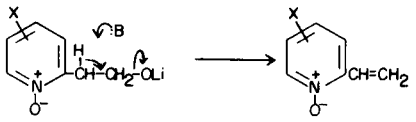
Direct Thionation of Lithiopyridine 1-Oxides

1	Reagent	Base	Solvent	(temp. °C)	Yields of products (%) 4	5	6
$R_3 = R_4 = H$	S_8	*n*-BuLi	THF (a)	(-65°)	7.9		
			Ether	(25°)	10.1		
		$LiNH_2$	DME (b)	(80°)	---		
		LiOMe	DME	(80°)	---		
		LiOMe	DME-ME (c) (10:1 v/v)	(80°)	---		
		LiH	DME	(80°)	12.0		
			DME-DEME (d) (50:4 v/v)	(80°)	19.5		
			DME-ME (50:4 v/v)	(80°)	21.5		
	C_2H_4S	LiH	DME-ME	(80°)	---		
$R_3 = H$; $R_4 = Me$	S_8	*n*-BuLi	THF	(-65°)	38.7		
		LiH	DME-ME	(80°)	5.2		
		$NaNH_2$	lig. NH_3	(-33°)	---		
$R_3 = Me$; $R_4 = Cl$	S_8	*n*-BuLi	THF	(-65°)		11.45	
$R_3 = R_4 = Me$	S_8	*n*-BuLi	THF	(-65°)	12.5	24.1	37.4
			Ether	(25°)	7.9	7.3	21.1
	S_2Cl_2	*n*-BuLi	THF	(-65°)	4.6	7.5	
	C_2H_4S	*n*-BuLi	Ether	(25°)	7.7	11.0	
	S_8	LiH	DME	(80°)	0.9		
			DME-ME		5.2	5.5	

(a) Tetrahydrofuran. (b) Dimethoxyethane. (c) 2-Methoxyethanol. (d) Diethyleneglycol monomethyl ether.

action was carried out in ether at 25° for 16 hours two products were isolated. The first was a viscous yellow oil whose infrared and nmr spectrum indicated this to be a mixture of 2-(3,4-dimethyl-2-pyridyl)ethanol 1-oxide (**14**) and 2-(4,5-dimethyl-2-pyridyl)ethanol 1-oxide (**15**). This was supported by the presence of an M^+ · ion in the mass spectrum at m/e 167 ($C_9H_{13}NO_2$) and an $(M-H_2O)^+$ · peak at m/e 149. Unfortunately, no satisfactory elemental analyses could be obtained on this material. The second product was an elastic-like solid whose nmr spectrum suggested it to be a 2,6-disubstituted pyridine polymer. When the oil which is probably a mixture of **14** and **15** was stirred with concentrated sulfuric acid for 30 minutes at room temperature an elastic-like solid was obtained identical (ir and nmr) with the above polymer. Authentic 2-(2′-pyridyl)-ethanol 1-oxide (10) is not dehydrated under the same conditions but is on heating with concentrated acid. The same type of polymeric product was obtained when an 8-molar excess of ethylene oxide was used. The molecular weight of the polymers varied from 1215 to 2222 depending on the reaction time.

In all probability, the 2-(1′-oxido-2′-pyridyl)ethoxide (**16**) is formed in all cases and undergoes base-catalyzed β-elimination to give the 2-vinylpyridine 1-oxide (**17**) which then polymerizes in the presence of strong base. Vinylpyridines are known (9) to polymerize almost quantitatively in the presence of *n*-butyllithium. Authentic 2-



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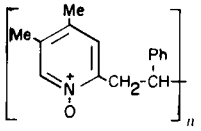
vinylpyridine 1-oxide polymerizes on standing at room temperature with *n*-butyllithium. To avoid this polymerization which apparently requires the presence of a base an inverse addition procedure was used whereby a solution of lithio-3,4-dimethylpyridine 1-oxide (free of **1d**) was added dropwise to a 4-molar excess of ethylene oxide. Compound **1d** (38%) was isolated (probably resulting from hydrogen abstraction by the anion) together with the oil identical with what appears to be the mixture of **14** and **15** (*vide supra*). While again this oil could not be resolved or obtained analytically pure, this inverse addition procedure seems to be more promising in that no polymeric product was formed.

Lithio-3,4-lutidine 1-oxide did not react with cyclohexene oxide under a variety of conditions but did react (direct addition) with styrene oxide in ether at room temperature to give a mixture of telomers. These could be resolved to some extent by chromatography on alumina to give a major product, M.W. 653 (osmometric) in chloroform solution corresponding to **18** (n = 3; Calcd. M.W. 675). Minor fractions corresponding to n = 2 and n = 4 were also obtained. The ir and nmr spectra of these frac-

tions were consistent with the proposed structure. The same product (identical ir) was obtained when the inverse addition procedure was used so that this method provided no improvement here.



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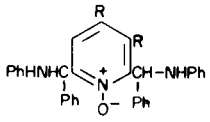
The reaction of organolithium reagents with Schiff bases is a convenient method of preparing substituted amines (11). Treatment of lithio-3,4-dimethylpyridine 1-oxide in the THF at -65° with *N*-benzylideneaniline gave 2,6-*bis*-(α-anilinobenzyl)-3,4-dimethylpyridine 1-oxide (**19**; R = Me) (62%) and 2-(α-anilinobenzyl)-4,5-dimethylpyridine 1-oxide (**20**) (12%). The infrared, mass, and nmr spectra were consistent with the assigned structures and eliminated alternative structures such as **21** for the 2:1 product, for instance. Thus, no resonances due to pyridine α-protons



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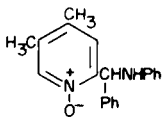

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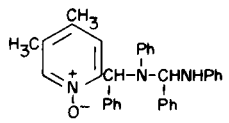

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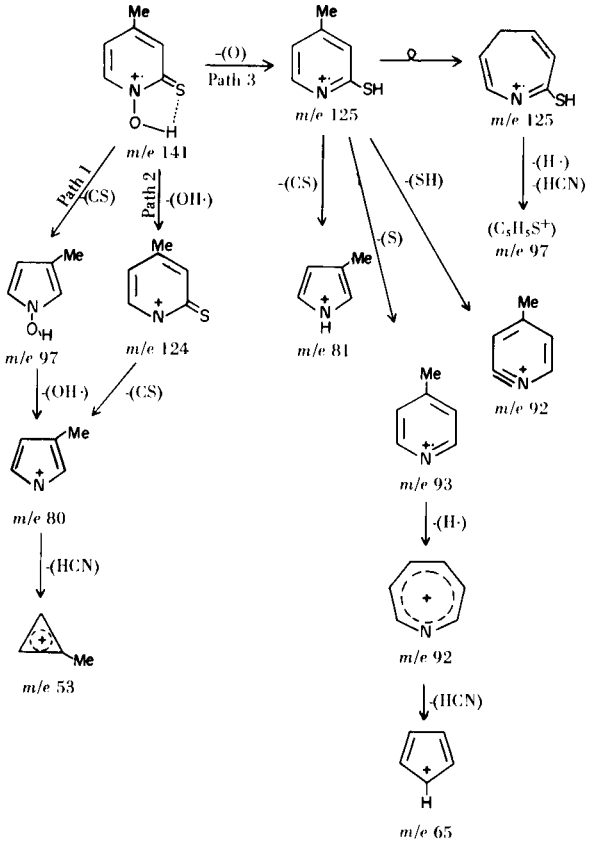
were observed in the spectrum of **19**, nor were fragments observed at m/e 363 and 273, corresponding to $PhCH{=}\overset{+}{N}(Ph)CH(Ph)NHPh$ and $PhN{=}\overset{+\cdot}{C}H(Ph)NHPh$, respectively. When the reaction was carried out in ether at 25° the yields were lower: (**19**, 31%; **19**, 17.5%). The only product obtained from lithiopyridine 1-oxide and benzylidine aniline was **19** (R = H) (41%). This reaction therefore showed promise for the synthesis of aminoalkylated pyridine 1-oxides.

Mass Spectra.

There does not appear to have been any study made of the mass spectra of cyclic thiohydroxamic acids though the spectra of 1-hydroxy-2-pyridone (12) and of 2-pyridinethione and 2-alkylthiopyridines (13) have been interpretted. We have made tentative mass spectral assignments based on comparison with these molecules. Firm assignments will have to wait until high resolution spectra and isotopic labelling studies are available. We illustrate these with the mass spectrum of 1-hydroxy-4-methyl-2-pyridinethione (**4b**) (Scheme 1). The molecular ion at m/e 141 could undergo various modes of fragmentation. Loss of CS (path 1) would lead to a hydropyrrole cation [by analogy with 2-pyridinethione (13)] at m/e 97 followed by consecutive loss of ·OH (to m/e 80) and HCN (to m/e 53). Alternatively (path 2), it could start by losing ·OH to give m/e 124 which then fragments as does 2-pyridinethione. A third alternative would involve initial loss of oxygen [as in the cases of 1-hydroxy-2-pyridones (12)] (path 3) followed by fragmentations typical of pyridinethiones and alkylthiopyridines.

Amine **19** did not exhibit a parent ion at m/e 485 but did show an ($M^{+\cdot}$-O) fragment at m/e 469 (14) and an ion at m/e 468 ($M^{+\cdot}$-OH). The diamine **20** also did not show a molecular ion at m/e 304 but did show an ion at m/e 288 (loss of oxygen) and at m/e 287 (loss of OH).

(SCHEME 1)



Biological Testing.

Some of the cyclic thiohydroxamic acids prepared above were evaluated for their antibacterial and antifungal activities by the Warner Lambert Research Institute. The bacterial test organisms were *S. aur.*, *E. coli*, and *P. vulg.* and the minimal concentration of thiohydroxamic acid required to prevent growth in the absence of serum varies from 4 to 1000 μg/ml, with **5d** being the most active against *S. aur.*, and **10** being the most active against *E. coli* and *P. vulg.* These activities were maintained in the presence of serum. The minimal concentration needed to inhibit the growth of the fungal test organisms *C. alb.*, *T. ment.*, *A. nigr.*, *S. schn.*, *M. cani* and *C. neof.* varied from 8 to 125 μg/ml. On the other hand, the disulfide **6** was inactive both as an antibacterial and as an antifungal agent, and this is most likely due to its very low solubility.

EXPERIMENTAL

Nmr spectra were recorded on a Varian A60 or HA100 Mc spectrometer, mass spectra were determined on an MS-12 or CEC 21-104 single focussing mass spectrometer using an ionization voltage of 70eV, and solution molecular weights were determined on a Hitachi Perkin-Elmer Model 115 osmometer.

1-Hydroxy-4-methyl-2-pyridone.

4-Picoline 1-oxide (1.53 g.) in anhydrous tetrahydrofuran (70 ml.) was cooled to -65°, flushed with dry oxygen-free nitrogen and treated with *n*-butyllithium (1.8 g., in hexane solution) slowly with stirring. The dark brown solution was stirred for 1 hour and then dry oxygen was bubbled into the reaction mixture (30 ml./minute) for 15 minutes. The mixture was allowed to come to room temperature and water (40 ml.) was added. The mixture was acidified to *p*H 2 with 18% hydrochloric acid, extracted with chloroform (8 x 75 ml.), the extracts dried (sodium sulfate) and evaporated under reduced pressure to give a greenish brown tarry semi-solid. This was chromatographed on a 2.5 x 50 cm silica gel column. Elution with ether gave 1-hydroxy-4-methyl-2-pyridone (0.223 g., 12.7%), m.p. 131-132° (from acetone) [lit. (15), m.p. 129-130°]; nmr (deuteriochloroform): δ 7.58 (d, 1, $J_{5,6}$ = 7 Hz, C_6-H), 6.44 (d, $J_{3,5}$ = 2 Hz, C_3-H), 6.10 (q, 1, $J_{5,6}$ = 7 Hz, $J_{3,5}$ = 2 Hz, C_5-H), 2.18 (s, 3, $ArCH_3$), 12.08 (s, 1, OH, exchanges with deuterium oxide); mass spectrum (relative abundance): m/e 125 ($M^{+\cdot}$, 71), 109 (71), 97 (15), 81 (18), 80 (100), 53 (65).

The aqueous layer was adjusted to *p*H 12 and extracted with chloroform to give 4-picoline 1-oxide (0.325 g.), identical with an authentic sample.

Reaction of Lithio-3,4-pyridine 1-Oxide with Oxygen.

Using the same procedure as above 3,4-lutidine 1-oxide (1.72 g.), *n*-butyllithium (1.8 g.) in hexane, and oxygen gave a brown solid which was chromatographed on silica gel (2.5 x 52 cm). Elution with benzene-ether (3:1 v/v) gave 1-hydroxy-3,4-dimethyl-2-pyridone (0.194 g., 10%), m.p. 169-170° (recrystallized from acetone and then sublimation at 100°/0.125 mm): ir (potassium bromide): 3115 (m), 2500 (m), 1620 (s), 1500 cm^{-1} (s); nmr (deuteriochloroform): δ 11.26 (s, 1, OH, exchanges with deuterium oxide), 7.50 (d, 1, $J_{5,6}$ = 7 Hz, C_6-H), 6.10 (d, 1, $J_{5,6}$ = 7 Hz, C_5-H), 2.16 (s, 3, $ArCH_3$), 2.10 (s, 3, $ArCH_3$); mass spectrum (relative abundance): m/e 139 ($M^{+\cdot}$, 100), 123 (91), 111 (19), 110 (21), 95 (25), 94 (76), 80 (25), 67 (41), 41 (41), 39 (54).

Anal. Calcd. for $C_7H_9NO_2$: C, 60.42; H, 6.52. Found: C, 60.36; H, 6.61.

Continued elution with benzene-ether gave 1-hydroxy-3,4-dimethyl-6-pyridone (0.27 g., 13.9%), m.p. 195° (recrystallized from acetone and then sublimation at 125°/0.175 mm); ir (potassium bromide): 3100 (m), 2700 (m), 1660 (s), 1580 (s), 1490 cm^{-1} (s); nmr (deuteriochloroform): δ 11.18 (s, 1, OH, exchanges with deuterium oxide), 7.46 (s, 1, C_2-H), 6.46 (s, 1, C_5-H), 2.12 (s, 3, $ArCH_3$), 2.05 (s, 3, $ArCH_3$); mass spectrum (relative abundance): m/e 139 ($M^{+\cdot}$, 100), 123 (54), 111 (21), 110 (23), 95 (17), 94 (7), 80 (15), 67 (35), 41 (38), 39 (50).

Anal. Calcd. for $C_7H_9NO_2$: C, 60.42; H, 6.52. Found: C, 60.51; H, 6.52.

Elution with alcohol gave a brownish-black semi-solid. This was dissolved in ethanol (20 ml.), precipitated with water, and heated on a steam bath for 2 hours with 18% hydrochloric acid. Extraction with chloroform and work up gave more **3d** (19 mg., 1%; overall yield 14.9%), m.p. 195°.

1-Hydroxy-2-pyridinethione.

(a) In Tetrahydrofuran.

Pyridine 1-oxide (1.9 g.) in anhydrous tetrahydrofuran (70 ml.) at -65° was heated with *n*-butyllithium (2.56 g.) in hexane under dry, oxygen-free nitrogen. The brown solution was stirred for 1 hour after which sulfur (1.28 g.) was added. Stirring was continued for 30 minutes and the mixture was then allowed to come to room temperature. It was then poured into water (40 ml.), acidified to *p*H 2 with 18% hydrochloric acid and extracted with chloroform (8 x 50 ml.). The dried (magnesium sulfate) extracts were evaporated to give a black semi-solid which was extracted with hot 95% ethanol (60 ml.). An insoluble brown plastic like solid (1.9 g.) was filtered. Evaporation of the alcohol gave a brown solid which was chromatographed on a column of silica gel (2.5 x 60 cm). Elution with light petroleum-benzene (1:1 v/v) gave 1-hydroxy-2-pyridinethione (0.20 g., 7.9%), m.p. 68° [lit. (7), 68-70°], identical with an authentic sample. Elution with ether gave a black tar (0.345 g.) which could not be characterized.

(b) In Ether.

Pyridine 1-oxide (1.9 g.) suspended in anhydrous ether (75 ml.) at -65° was treated with *n*-butyllithium (2.56 g.) in hexane under dry nitrogen. After stirring for 20 minutes the solution was warmed to room temperature, sulfur (1.28 g.) was added and stirring was continued for 30 minutes. Water (30 ml.) was added and the sulfur (0.40 g.) which precipitated was filtered. Work up as above gave 1-hydroxy-2-pyridinethione (0.256 g., 10.1%), m.p. 68°.

1-Hydroxy-4-methyl-2-pyridinethione.

Prepared as above from 4-picoline 1-oxide (2.18 g.), *n*-butyllithium (2.56 g.) and sulfur (1.28 g.) in THF at -65°, 1-hydroxy-4-methyl-2-pyridinethione (1.092 g., 38.7%) had m.p. 59° [lit. (7), 59-61°]; nmr (deuteriochloroform): δ 7.9 (d, 1, J = 7 Hz, C_6-H), 7.46 (d, 1, $J_{3,5}$ = 2 Hz, C_3-H), 6.54 (q, 1, $J_{5,6}$ = 7 Hz, $J_{3,5}$ = 2 Hz, C_5-H), 2.24 (s, 3, $ArCH_3$), 11.8 (br s, 1, OH, exchanges with deuterium oxide); mass spectrum (relative abundance): m/e 141 ($M^{+\cdot}$, 100), 125 (13), 124 (15), 97 (25), 93 (40), 92 (16), 81 (8), 80 (22), 63 (18), 53 (26), 39 (40).

4-Chloro-1-hydroxy-3-methyl-6-pyridinethione.

Prepared as above from 4-chloro-3-picoline 1-oxide (2.86 g.), *n*-butyllithium (2.56 g.), and sulfur (1.28 g.) a brown semi-solid was obtained and extracted with ethanol. Filtration, evaporation of the alcohol, and chromatography on a silica gel column gave 4-chloro-1-hydroxy-3-methyl-6-pyridinethione (0.395 g., 11.45%), m.p. 99-101° (from ethanol); ir (potassium bromide): 3100 (m), 2750 (w), 1600 (m), 1550 cm^{-1} (s); nmr (deuteriochloroform): δ 9.9 (br s, 1, OH exchanges with deuterium oxide), 7.9 (s, 1, C_2-H), 7.64 (s, 1, C_5-H), 2.26 (s, 3, $ArCH_3$); mass spectrum (relative abundance): m/e 177 (37), 176 (9), 175 ($M^{+\cdot}$, ^{35}Cl, 100), 161 (4), 160 (6), 159 (11), 158 (13), 127 (19). A solution of the chloro compound (87.5 mg.) in 0.5 *N* sodium hydroxide (1 ml.) was added to a solution of zinc chloride (34 mg.) in water (3 ml.). The zinc salt was washed with water, ethanol, and ether to give pure product (89 mg., 86%), m.p. 292-294° dec.

Anal. Calcd. for $C_{12}H_{10}Cl_2N_2O_2S_2Zn$: C, 34.77; H, 2.69. Found: C, 34.99; H, 2.69.

Reaction of Lithio-3,4-dimethylpyridine 1-Oxide with Sulfur.

(a) In Tetrahydrofuran.

Using the same procedure as above, 3,4-lutidine 1-oxide (2.46 g.), *n*-butyllithium (2.56 g.) and sulfur (1.28 g.) at -65° gave a yellow solid which was extracted with warm ethanol (60 ml.). 2,2′-(1,1′-Dihydroxy-4,4′,5,5′-tetramethyldipyridyl-6,6′-dithione)-

disulfide (1.39 g., 37.4%) was insoluble and was filtered. After recrystallization from chloroform it had m.p. 186-187°; ir (potassium bromide): 3050 (w), 2325 (w), 1570 (m), 1550 (m), 1490 (s), 1440 cm^{-1}; nmr (perdeuteriopyridine): δ 7.06 (s, 2, C_3-H, C_3'-H), 2.50 (s, 6, $ArCH_3$), 1.9 (s, 6, $ArCH_3$).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S_4$: C, 45.14; H, 4.33; M 372. Found: C, 45.25; H, 4.24; M (osmometer), 370.

Evaporation of the alcohol extract above gave a yellow solid which was chromatographed in silica gel (2.5 x 60 cm). Elution with light petroleum-benzene (1:1 v/v) gave sulfur (50 mg.). Further elution with light petroleum-benzene (1:1 v/v) gave 1-hydroxy-3,4-dimethyl-2-pyridinethione (0.388 g., 12.5%), m.p. 128-129° (from benzene followed by sublimation at 125°/1.75 mm); ir (potassium bromide): 3100 (m), 2700 (m), 1610 (m), 1560 (s), 1480 cm^{-1} (s); nmr (deuteriochloroform): δ 12.35 (br s, 1, OH exchanges with deuterium oxide), 7.88 (d, 1, $J_{5,6}$ = 6 Hz, C_6-H), 6.56 (d, 1, $J_{5,6}$ = 6 Hz, C_5-H), 2.42 (s, 3, $ArCH_3$), 2.26 (s, 3, $ArCH_3$); mass spectrum (relative abundance): m/e 155 ($M^{+\cdot}$, 100), 140 (6), 139 (29), 138 (84), 94 (18), 92 (35).

Anal. Calcd. for C_7H_9NOS: C, 54.18; H, 5.84. Found: C, 54.18; H, 5.96.

Continued elution with light petroleum-benzene (1:1 v/v) gave 1-hydroxy-3,4-dimethyl-6-pyridinethione (0.748 g., 24.1%), m.p. 121-122° (from benzene followed by sublimation at 125°/1.75 mm); ir (potassium bromide): 3110 (w), 1620 (m), 1540 (s), 1460 cm^{-1} (s); nmr (deuteriochloroform): δ 10.47 (br s, 1, OH exchanges with deuterium oxide), 7.78 (s, 1, C_2-H), 7.36 (s, 1, C_5-H), 2.16 (s, 3, $ArCH_3$), 2.13 (s, 3, $ArCH_3$); mass spectrum (relative abundance): m/e 155 ($M^{+\cdot}$, 100), 141 (10), 139 (11), 138 (20), 125 (13), 111 (18), 107 (29).

Anal. Calcd. for C_7H_9NOS: C, 54.18; H, 5.84. Found: C, 53.85; H, 5.86.

The zinc salt of **4d** was prepared in 98.4% yield and had m.p. 283-285° dec. (from dioxane).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S_2Zn$: C, 44.99; H, 4.31. Found: C, 44.54; H, 4.28.

The zinc salt of **5d** (98.5%) had m.p. >300° (dioxane).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S_2Zn$: C, 44.99; H, 4.31. Found: C, 44.57; H, 4.56.

(b) In Ether.

When the reaction was carried out in ether at 25° as described above using 3,4-lutidine 1-oxide (1.23 g.), *n*-BuLi (1.28 g.) and sulfur (0.64 g.) followed by extraction and chromatography **6** (0.392 g., 21.1%), **4d** (0.123 g., 7.9%), and **5d** (0.113 g., 7.3%) were obtained.

Reaction of Lithio-3,4-dimethylpyridine 1-Oxide with Other Sulfur Compounds.

(a) With Sulfur Monochloride.

3,4-Lutidine 1-oxide (1.23 g.) in anhydrous THF (70 ml.) at -65° was treated with *n*-BuLi (1.28 g.) and then with sulfur monochloride (0.844 g.) in anhydrous THF (10 ml.) for 30 minutes. The solution was allowed to warm to room temperature and water (60 ml.) was added. Extraction with chloroform (6 x 75 ml.) gave a black oil (0.96 g.) which was chromatographed on silica gel to give a yellow oil (0.096 g.) which did not contain nitrogen and was not examined further. Elution with methanol gave 3,4-lutidine 1-oxide (0.104 g.). The aqueous layer was acidified with 18% hydrochloric acid, extracted with chloroform (6 x 50 ml.) and the dried (sodium sulfate) extract was evaporated and chromatographed on silica gel (2.5 x 40 cm) to give **4d** (0.072 g., 4.6%), m.p. 126-127°, and **5d** (0.116 g., 7.5%), m.p. 120-121°.

(b) With Ethylene Sulfide.

3,4-Lutidine 1-oxide (2.46 g.) in anhydrous ether (70 ml.) was treated with *n*-BuLi (2.56 g.) and then with ethylene sulfide (2.4 g.) in dry ether (25 ml.) for 2 hours at room temperature. Acidification and work up as above gave **4d** (0.24 g., 7.7%) and **5d** (0.343 g., 11%).

1-Hydroxy-3,4-dimethyl-2-sulfhydro-6-pyridinethione (**10**).

2,2'-(1,1'-Dihydroxy-4,4',5,5'-tetramethyldipyridyl-6,6'-dithione)disulfide (**6**) (1.0 g.) was added over a period of 10 minutes to a stirred suspension of lithium aluminum hydride (0.076 g.) in dry THF (25 ml.). The reaction mixture was stirred for 1 hour at room temperature and then boiled under reflux for 30 minutes. It was cooled to 0° and water (20 ml.) was added. The resulting green suspension was acidified to *p*H 2 with 18% hydrochloric acid and diluted to a volume of 150 ml. with water. Extraction with chloroform (3 x 50 ml.), drying (sodium sulfate) and evaporation of the chloroform *in vacuo* gave 1-hydroxy-3,4-dimethyl-2-sulfhydro-6-pyridinethione (0.99 g., 98.5%), m.p. 120-122° (from carbon tetrachloride); ir (potassium bromide): 2350 (m), 1530 (s), 1450 (m), 1400 cm^{-1} (s); nmr (deuteriochloroform): δ 8.68 (br s, 2, SH and OH, exchanges with deuterium oxide), 6.68 (s, 1, C_5-H), 2.25 (s, 3, $ArCH_3$), 2.19 (s, 3, $ArCH_3$); mass spectrum (relative abundance): m/e 187 ($M^{+\cdot}$, 60), 171 (100), 170 (72), 155 (9), 152 (6), 143 (14), 139 (27), 138 (27), 136 (35), 127 (26), 119 (41), 117 (41).

Anal. Calcd. for $C_7H_9NOS_2$: C, 44.89; H, 4.84. Found: C, 45.29; H, 5.02.

The zinc salt was obtained as a yellow solid, m.p. >300°, after washing with dioxane.

Anal. Calcd. for $C_{14}H_{16}N_2O_2S_4Zn$: C, 38.40; H, 3.68. Found: C, 38.45; H, 3.09.

1-Hydroxy-4,5-dimethyl-2-(2',4'-dinitrophenylthio)-6-pyridinethione (**11**).

A solution of 1-hydroxy-3,4-dimethyl-2-sulfhydro-6-pyridinethione (0.187 g.) and sodium ethoxide (0.002 mole) in ethanol (3 ml.) was added to a solution of 2,4-dinitrochlorobenzene (0.404 g.) in absolute ethanol (3 ml.) and stirred at room temperature (4.5 hours). It was then poured into water (50 ml.), extracted with chloroform (3 x 50 ml.), the extracts dried (sodium sulfate) and evaporated to give 2,4-dinitrophenetole (0.265 g.), m.p. 86° [lit. (16), 85°]. The basic aqueous layer was brought to *p*H 2 and extracted with chloroform (3 x 50 ml.). The dried (sodium sulfate) extract was evaporated to give **11** (0.209 g., 59.2%), m.p. 175-177° (from chloroform-carbon tetrachloride, 4:1 v/v).

Anal. Calcd. for $C_{13}H_{11}N_3O_5S_2$: C, 44.18; H, 3.12. Found: C, 44.19; H, 3.20.

Reaction of Pyridine 1-Oxide with Lithium Hydride and Sulfur.

A mixture of pyridine 1-oxide (0.95 g.) and lithium hydride (0.795 g.) suspended in anhydrous dimethoxyethane (50 ml.) and 2-methoxyethanol (4 ml.) was heated with sulfur (0.32 g.) for 18 hours at 80°. The mixture was acidified, the precipitated sulfur was filtered and the product was extracted and chromatographed as before to give 1-hydroxy-2-pyridinethione (0.273 g., 21.5%).

The other reactions summarized in Table I were carried out similarly.

Reaction of Lithio-4-methylpyridine 1-Oxide with Ethylene Oxide.

4-Picoline 1-oxide (1.53 g.) suspended in anhydrous ether (75 ml.) was treated with *n*-BuLi (1.8 g.) in hexane under nitrogen at -65°. The dark brown solution was stirred for 1 hour and then

ethylene oxide (2.46 g.) in ether was added and the temperature was raised to room temperature. After stirring for 2 hours water (30 ml.) was added and the mixture was extracted with chloroform (6 x 75 ml.), the extract dried (sodium sulfate) and evaporated. Chromatography on a column of alumina (2.5 x 35 cm) gave a brown stretchy semi-solid [1.8 g., 95% calcd. as poly-(4-methyl-2-vinylpyridine 1-oxide)]. *M* (chloroform) (osmometer): Found: 812.

The reaction was repeated but for 10 hours this time. The dark brown product had *M* (chloroform) 1866. It was dissolved in acetone and reprecipitated with ether repeatedly to give a brown stretchy hygroscopic solid. The nmr spectrum of this product was not well resolved and the integral could not be measured accurately; nmr (deuteriochloroform): δ 8.6-7.8 (m, 2, C_6-H), 7.5-6.5 (m, 2, C_3-H, C_5-H), 4.5-3.4 (m, 4, -C*H*-, -CH_2-), 3.0-0.7 (m, -CH_2-, -CH_3).

Reaction of Lithio-3,4-dimethylpyridine 1-Oxide with Ethylene Oxide.

(a) In Tetrahydrofuran.

3,4-Lutidine 1-oxide (1.72 g.) in anhydrous THF (60 ml.) at -65° was treated under dry nitrogen with *n*-BuLi (1.8 g.) in hexane and ethylene oxide (3.69 g.) in dry THF (10 ml.). The temperature was raised to -15° and kept there for 3 hours. The usual work-up gave a viscous orange oil which was chromatographed on a column of alumina (2.5 x 40 cm). Elution with ether-methanol (5:1 v/v) gave a yellow oil (0.722 g.) which appears to be a mixture of 3,4-lutidine 1-oxide and a higher molecular weight product in a ratio of 2:1 as calculated from the nmr spectrum: nmr (deuteriochloroform): δ (3,4-lutidine 1-oxide portion): 7.92 (d, 2, $J_{5,6}$ = 7 Hz, C_5-H), 7.01 (d, 1, $J_{5,6}$ = 7 Hz, C_5-H), 2.19 (s, 3, $ArCH_3$), 2.15 (s, 3, $ArCH_3$); (higher molecular weight portion): 7.73 (s, 1, C_6-H), 7.21 (s, 1, C_3-H), 4.96 (br s, 1, OH), 3.86 (t, 2, *J* = 6 Hz, -CH_2-), 3.30 (s, 3, -C*H*-), 3.04 (t, 2, *J* = 6 Hz, -CH_2-), 2.22 (s, 3, $ArCH_3$), 2.10 (s, 3, $ArCH_3$).

Further elution with ether-methanol (2:1 v/v) gave a viscous yellow oil (0.225 g.), b.p. 140°/0.075 mm; ir (film): 3325 (s), 1460 (s), 1200 cm^{-1} (s); nmr (deuteriochloroform): δ 8.14-7.88 (m, 2, C_6-H, C_2-H), 7.16-6.88 (m, 2, C_3-H, C_5-H), 4.80 (s, 2H, OH exchanges with deuterium oxide), 3.90 (t, 2, *J* = 6 Hz, CH_2), 3.60 (s, 2, C*H*), 3.30 (t, 2, *J* = 6 Hz, CH_2), 3.20 (t, 2, *J* = 6 Hz, CH_2), 2.26 (s, 3, $ArCH_3$), 2.21 (s, 3, $ArCH_3$), 1.94 (s, 3, $ArCH_3$): mass spectrum (relative abundance): m/e 167 ($M^{+\cdot}$, $C_9H_{13}NO_2$, 5), 165 (11), 151 (21), 150 (38), 149 (14), 148 (16), 137 (17), 135 (26), 134 (61), 133 (20), 132 (29), 123 (54), 121 (100), 120 (64), 107 (65), 106 (51), 79 (49), 78 (18), 77 (64), 67 (27), 65 (32), 53 (90), 52 (21), 51 (39), 45 (30), 41 (36), 39 (65). An analytically pure same of the mixture of alcohols **14** and **15** could not be obtained.

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.67; H, 7.78. Found: C, 63.00; H, 7.88.

Elution with methanol gave a brown elastic solid (0.160 g.) which was dissolved in ethanol and precipitated with ether three times to give a pale yellow elastic solid which begins to decompose at 69°.

(b) In Ether.

3,4-Lutidine 1-oxide (1.72 g.) suspended in dry ether (75 ml.) at -65° was treated with *n*-BuLi (1.8 g.) and then allowed to come to room temperature under dry nitrogen. Ethylene oxide (2.46 g.) in dry ether (10 ml.) was added and the reaction mixture was then stirred for 16 hours at room temperature. Work-up as above gave the mixture of **14** and **15** (1.95 g.) as a yellow oil, identical with that obtained in THF, and an elastic-like solid (0.574 g.) whose ir and nmr spectra were identical to those of the product obtained above.

(c) In Ether - Inverse Addition.

The reaction was the same as under (b) above except that the reddish-brown solution of lithio-3,4-lutidine 1-oxide was added dropwise over a period of 20 minutes to a solution of ethylene oxide (2.46 g.) in dry ether (20 ml.). Work-up and chromatography gave 3,4-lutidine 1-oxide (0.65 g.), m.p. 135°, and the mixture of alcohols **14** and **15** (0.984 g.), identical with that obtained above.

Reaction of Lithio-3,4-dimethylpyridine 1-Oxide with Styrene Oxide.

Using the same procedure as above 3,4-lutidine 1-oxide (1.72 g.) in anhydrous ether (70 ml.) at -65° was treated with *n*-BuLi (1.8 g.), and then with styrene oxide (3.36 g.) in dry ether (10 ml.) at room temperature. The mixture was stirred for 12 hours at room temperature, water (40 ml.) was added and the mixture extracted with chloroform (6 x 75 ml.). The extracts were dried (sodium sulfate), evaporated and the residual orange oil triturated with light petroleum (b.p. 30-60°) to remove styrene oxide. The oil was dried *in vacuo* to give a flaky yellow solid (3.19 g.), m.p. 80-110°. It was purified by dissolving it in benzene and reprecipitation with light petroleum. *M* (chloroform) (osmometer) 653; ir (potassium bromide): 3130, 1490 (w), 1140 (s); nmr (deuteriochloroform): δ 7.88 (br s, 1, C_2-H), 7.14 (m, 6, C_3-H, C_6H_5), 3.4 (m, 3, C*H*, CH_2), 2.14 (m, 6, $ArCH_3$). There was no change in the spectrum on addition of deuterium oxide. The highest peak in the mass spectrum was at m/e 316 (2) [121 (100)].

Anal. Calcd. for $(C_{13}H_{16}NO)_n$: C, 77.21; H, 7.98. Found: C, 76.26; H, 7.02.

A portion of the reaction product (1.147 g.) was chromatographed on an alumina column (2.5 x 30 cm). Elution with ether gave an orange solid (51 mg.). Elution with ether-methanol (3:1 v/v) gave an orange solid (0.895 g.). Elution with methanol gave an orange-brown solid (92 ml.). The infrared spectra (potassium bromide) of these three fractions were identical. An analytically pure sample could not be obtained (suggesting the presence of 2,6-disubstituted *N*-oxide residues).

2,6-*Bis*(α-*N*-Phenylaminobenzyl)pyridine 1-Oxide.

Benzylideneaniline (3.62 g.) was added to a solution of the anion from pyridine 1-oxide (0.95 g.) and *n*-BuLi (1.28 g.) in THF (70 ml.) at -65°. After 1 hour, water (40 ml.) was added and the mixture was worked up. Chromatography of the product on silica gel (2.5 x 42 cm) and elution with light petroleum (b.p. 30-60°)-benzene (1:1 v/v) gave a mixture of benzylideneaniline and benzaldehyde (1.86 g.). Elution with benzene gave aniline (0.255 g.). Elution with benzene-ether (3:1 v/v) gave 2,6-*bis*(α-*N*-phenylaminobenzyl)pyridine 1-oxide (1.87 g., 40.9%), m.p. 105° (75% ethanol); ir (potassium bromide): 3400 (m), 3100 (m), 1590 (s), 1490 (s), 1230 cm^{-1} (s); nmr (deuteriochloroform): δ 7.60-6.85 (m, 17, C_3-H, C_4-H, C_5-H, ArH), 6.80-6.15 (m, 8, C*H*, 6 ArH), 4.44 (s, 2, N*H*, exchanges with deuterium oxide); mass spectrum (relative abundance): m/e 440 (8), 439 (12), 338 (8), 337 (30), 336 (22), 335 (24), 260 (28), 259 (20), 245 (36), 183 (34), 182 (80), 181 (46), 180 (100), 167 (20), 105 (22), 104 (16), 95 (24), 93 (78), 78 (26), 77 (100), 51 (38).

Anal. Calcd. for $C_{31}H_{27}N_3O$: C, 81.36; H, 5.95. Found: C, 81.31; H, 6.08.

Reaction of Lithio-3,4-dimethylpyridine 1-Oxide with Benzylideneaniline.

The reaction was carried out as above using 3,4-lutidine 1-oxide

(1.23 g.), *n*-BuLi (1.28 g.) and benzylideneaniline (3.62 g.) to give 2,6-*bis*(α-*N*-phenylaminobenzyl)-3,4-dimethylpyridine 1-oxide (**18**; R = Me) (3.0 g., 61.8%), m.p. 125° (from ethanol); ir (potassium bromide): 3350 (m), 1580 (s), 1480 (s), 1430 (s), 1255 cm^{-1} (s); nmr (deuteriochloroform): δ 7.45-6.85 (m, 15, C_5-H, 14 ArH), 6.75-6.30 (m, 6, ArH), 6.11 (br s, 2, C*H*), 4.51 (s, 2, N*H*, exchanges with deuterium oxide), 2.23 (s, 3, $ArCH_3$), 2.11 (s, 3, Ar CH_3); mass spectrum (relative abundance): m/e 469 (1), 468 (2), 392 (3), 377 (1), 182 (20), 181 (26), 180 (34), 93 (100), 77 (29).

Anal. Calcd. for $C_{33}H_{31}N_3O$: C, 81.64; H, 6.44. Found: C, 81.95; H, 6.74.

Elution with ether-methanol (10:1 v/v) gave 2-(α-*N*-phenylaminobenzyl)-4,5-dimethylpyridine 1-oxide (0.368 g., 12.1%), m.p. 212-213°; ir (potassium bromide): 3330 (m), 3300 (m), 3100 (w), 1700 (m), 1590 (s), 1490 (s), 1440 (s), 1260 cm^{-1} (s); nmr (deuteriochloroform): δ 7.98 (s, 1, C_6-H), 7.5-7.0 (m, 8, C_3-H, 7 ArH), 6.8-6.45 (m, 3, ArH), 6.15 (d, 1, J = 3 Hz, C*H*), 4.78 (s, 1, N*H*, exchanges with deuterium oxide), 2.16 (s, 3, $ArCH_3$), 2.10 (s, 3, $ArCH_3$); mass spectrum (relative abundance): m/e 288 (31), 287 (65), 210 (8), 209 (31), 196 (61), 195 (22), 182 (37), 180 (37), 167 (45), 106 (13), 77 (100), 41 (67).

Anal. Calcd. for $C_{20}H_{20}N_2O$: C, 78.91; H, 6.62. Found: C, 78.85; H, 6.77.

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