Halogenation of Pyridine 1-Oxides (1)

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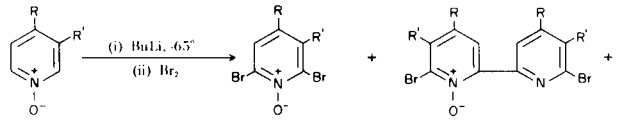
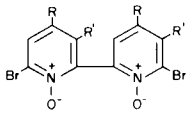
The chlorination and bromination of α-lithiopyridine 1-oxides has been studied. Only dihalogenated pyridine 1-oxides are formed. In the case of bromination dipyridyl derivatives are also formed, and, indeed, predominate. Chloromercuration of the lithiopyridine 1-oxides gave highly insoluble, unresolvable mixtures of pyridylmercury derivatives. These could be brominated readily to give mixtures of 2-bromo- and 2,6-dibromopyridine 1-oxides.

Base-catalyzed proton-abstraction from pyridine 1-oxides (2) has been applied to the synthesis of alkyl- (3) and acylpyridine 1-oxides (4). Treatment of the *N*-oxide with *n*-butyllithium in a non-protic solvent yields 2- and 2,6-dipyridyl 1-oxide anions which, on treatment with appropriate electrophiles, give the 2- and 2,6-substituted pyridine 1-oxides. In the present paper we describe the reaction of the α-pyridyl-1-oxide anions with halogens and with mercuric chloride.

The reaction of lithiopyridine 1-oxides with bromine gave a variety of dihalogenated products (Table I). Thus, pyridine 1-oxide with butyllithium at -65° followed by treatment with bromine gave 2,6-dibromopyridine 1-oxide (**1a**; R = R′ = H) (3.1%), 6,6′-dibromo-2,2′-dipyridyl 1-oxide (**2a**; R = R′ = H) (6.2%), and 6,6′-dibromo-2,2′-dipyridyl 1,1′-dioxide (**3a**; R = R′ = H) (8.2%). **1a** (R = R′ = H) had the same melting point as the known compound (5) and its structure was confirmed by nmr and mass spectrometry.



1 2 (R′ = H)



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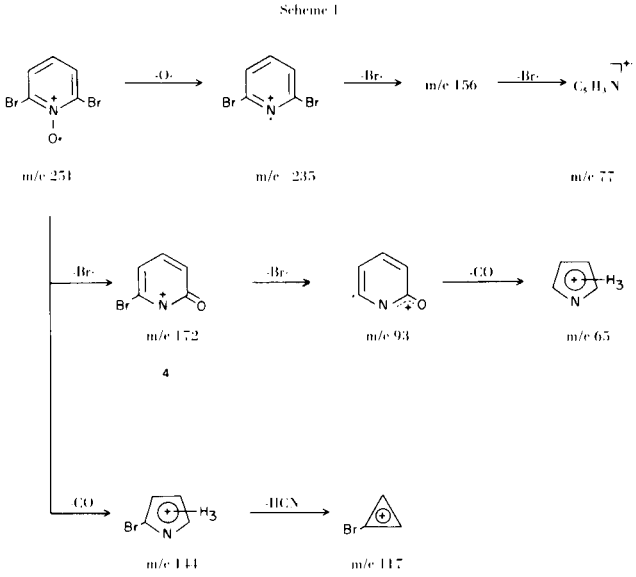
It exhibited a 2H doublet ($J_{3,4} = J_{4,5}$ = 8 Hz) at τ 2.36 (C_3-H, C_5-H) and a 1H triplet at τ 3.08 (C_4-H). The mass spectrum showed the expected isotope cluster for two bromine atoms in the parent ion at m/e 251 (M^+, ^{79}Br), 253 (base peak), and 255 (^{81}Br). A fragment ion at m/e 172 is best accounted for by loss of a bromine atom (M^+-79) from the parent ion and rearrangement of the *N*-oxide to a pyridone cation (**4**) to explain the subsequent fragmentations: loss of CO to give *m/e* 144, or of bromine and then CO to yield an ion at *m/e* 93. A possible fragmentation pathway is illustrated in Scheme 1.

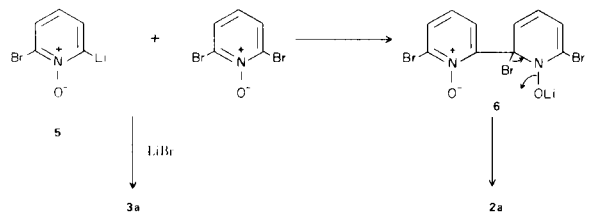
Scheme I



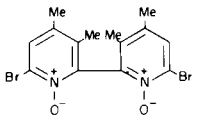
The structure of **2a** (R = R′ = H) followed from its analysis and spectral properties. The probable nmr assignments are as follows: τ 0.98, 1H quartet ($J_{3,4}$ = 8 Hz, $J_{3,5}$ = 1 Hz), C_3-H; τ 1.73, 1H quartet ($J_{3',4'}$ = 8 Hz, $J_{3',5'}$ = 2 Hz), C_3′-H; τ 2.25, 1H quartet ($J_{4',5'}$ = 8 Hz, $J_{3',5'}$ = 2 Hz), C_5′-H; τ 2.35, 1H triplet (J = 8 Hz), C_4′-H; τ 2.48, 1H quartet ($J_{4,5}$ = 8 Hz, $J_{3,5}$ = 1 Hz), C_5-H; and τ 2.85, 1H triplet (J = 8 Hz), C_4-H. The parent ion cluster in the mass spectrum was consistent with the formula $C_{18}H_6Br_2N_2O$, and an M^+-16 fragment ion was present at *m/e* 312.

The infrared, nmr and mass spectral data, and elemental analysis were in agreement with the structure **3a** (R = R′ = H) proposed for the third product formed. The nmr spectrum in deuteroacetic acid exhibited a 2H multiplet at τ 2.30-2.55 due to C_3-H and C_3′-H and a 4H multiplet at τ 2.60-2.85 due to C_5-H, C_5′-H, C_4-H and C_4′-H.

No 2-bromopyridine 1-oxide could be isolated under any of the reaction conditions used, even when phenol was added at -65° to remove unreacted bromine before the mixture was allowed to warm to room temperature. Neither did decrease in the relative amounts of butyllithium or of bromine lead to any monobromo derivative. It is conceivable that any 2-bromopyridine 1-oxide formed could have reacted with 2-lithio-6-bromopyridine 1-oxide to give the product of nucleophilic addition-elimination, namely 6,6′-dibromo-2,2′-dipyridyl 1-oxide (**2a**). The fact that no **2c** (R = R′ = Me) is formed in the reaction with 3,4-lutidine 1-oxide, nor is any monobromo-3,4-lutidine-1-oxide isolated in this reaction, speaks against this possibility. It seems more likely that the 2,6-dianion is formed which reacts with bromine to give initially 2-bromo-6-lithiopyridine 1-oxide (**5**), and this with more bromine gives **1**. Addition of **5** to **1a** and elimination of lithium hypobromite would lead to **2a** while Fittig coupling of **5** and **1a** (or oxidation of two molecules of **5**) would lead to **3a** as would elimination of lithium bromide from the σ-complex **6**. [An alternative to the formation of the dianion is that the mono-anion is formed first; this reacts with bromine to give 2-bromopyridine 1-oxide, which forms the 6-lithio-2-bromopyridine 1-oxide derivative with excess butyllithium present faster than the latter can react with bromine (the inductive effect of the 2-Br substituent presumably increasing the acidity of C_6-H sufficiently to facilitate greatly this proton-abstraction, so that all the monobromopyridine 1-oxide is consumed). This appears to be a less likely alternative].



The reaction of lithio-4-picoline 1-oxide with bromine proceeded similarly (Table I). On the other hand, lithio-3,4-lutidine 1-oxide only gave products corresponding to **1b** and to **3b**, none of the dipyridyl mono-*N*-oxide (**2b**) being formed in this case. The positions of the β-methyl groups in **3c** in the case of the reaction with 3,4-lutidine 1-oxide could be assigned on the basis of the nmr data. In principle, three isomers could be formed: the two symmetrical compounds **7** and **8**, and **3c**. If a symmetrical product had been formed, one would have expected to see only one 2H proton due to the β-protons and two



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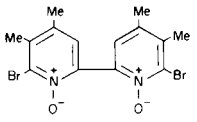

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methyl singlets due to the β- and γ-methyl groups. In actual fact, the compound exhibited a 1H singlet at τ 2.50 (C_3-H or C_5′-H), a 1H singlet at τ 2.88 (C_5′-H or C_3-H) and four 3H singlets at τ 7.58, 7.74, 7.82, and 8.04, respectively, as expected for the unsymmetrically substituted dipyridyl **3c**, (R = R′ = Me). This product probably arises, therefore, by the nucleophilic addition of 2-bromo-6-lithio-3,4-dimethylpyridine 1-oxide to C_2 in 2,6-dibromo-3,4-dimethylpyridine 1-oxide, followed by elimination of lithium bromide, this orientation being consistent with the known directive effect of a 3-methyl group upon the addition of organolithium compounds to pyridines (6). The possibility of a Fittig reaction between 6-bromo-2-lithio-3,4-dimethylpyridine 1-oxide and the C_6-Br group in **1** (R = R′ = Me) cannot be dismissed, however.

Control experiments were carried out in which the bromination was attempted without the prior addition of butyllithium. No halogenated products were formed, in agreement with the findings of Mosher and Welsh (7) who reported that bromination of pyridine 1-oxide could not be effected at 110° in the presence of iron powder.

Chlorination of lithiopyridine 1-oxide gave only 2,6-dichloropyridine 1-oxide (4.5%), none of the dipyridyls analogous to **2** and **3** being formed. The mass spectral fragmentation of this compound was similar to that of **1** (R = R′ = H). Lithio-3,4-lutidine 1-oxide gave 2,6-dichloro-3,4-lutidine 1-oxide (8.8%) and again no binuclear products were isolated.

In view of the fact that no products of monobromination were formed in the above reactions and that dipyridyl formation accompanied the formation of bromination products we studied the chloromercuration of the lithiopyridine 1-oxides.

Treatment of pyridine 1-oxide in tetrahydrofuran or in ether with butyl lithium at -65° followed by one equivalent of mercuric chloride gave a mixture of organo-mercury compounds. These were insoluble in all organic solvents except boiling acetic acid from which they did not crystallize out. No way was found to effect resolution of this mixture. The mass spectrum indicated the presence of (1-oxido-2-pyridyl)mercuric chloride (**9a**) (*m/e* 330; M^+, ^{202}Hg) and di-(1-oxido-2-pyridyl)mercury (**10a**) (*m/e* 390) (the mass spectral patterns were characteristic of

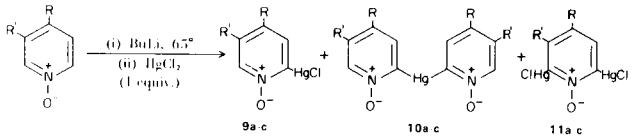
TABLE 1

Reaction of 2,6-Dilithiopyridine 1-Oxides with Bromine at -65°

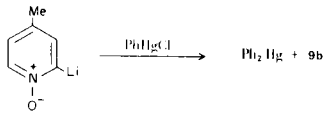
N-oxide	Solvent	Excess bromine removed	Products (%) 1	2	3
Pyridine	THF-ether	-----	3.1	6.2	8.2
	THF-ether	Phenol	4.0	-----	4.1
	HMPT-ether	-----	0.8	-----	1.15
4-Picoline	THF	-----	4.6	18.1	12.7
3,4-Lutidine	THF	$Na_2S_2O_3$	12.8	-----	4.3
	THF	Phenol	23.3	-----	1.6
	THF	Phenol and then N_2	8.9	-----	2.4

the isotopic distribution for Hg and Cl), as well as that of a dimercurated species. Similar mixtures of products (**9b** and **10b**; **9c** and **10c**) were obtained from 4-picoline 1-oxide and 3,4-lutidine 1-oxide, and these, too, could not be resolved into their pure components. Attempts to convert the mixtures of **9** and **10** to the pure diarylmercury by treatment of excess sodium iodide solution (8) or to the pure arylmercuric chloride by treatment with mercuric chloride (9) failed, probably due to the insolubility of the compounds.

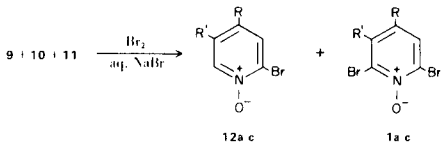
In an attempt to avoid the formation of **9b** the reaction was carried out using only half an equivalent of mercuric chloride, but no products were isolated. In order to avoid coupling side reactions, lithio-4-picoline 1-oxide was treated with one equivalent of phenylmercuric chloride in anhydrous tetrahydrofuran. The only products siolated, however, were diphenylmercury and impure **9b**. None of the desired 2-phenylmercury derivative was obtained.



a: R R' H
b: R Me; R' H
c: R R' Me



Using the procedure of van Ammers and den Hertog (10) the arylmercury compound mixture could be converted to the corresponding bromopyridines by heating the mixture with bromine and sodium bromide and then reducing the bromo *N*-oxides formed with iron and acetic acid. We have found it more useful for preparative purposes to omit the reduction step and to isolate the bromo *N*-oxides by column chromatography. In this way, not only were 2-bromopyridine 1-oxides (**12a-c**) obtained but so were 2,6-dibromopyridine 1-oxides (**1a-c**), thus confirming the presence of appreciable amounts of 2,6-dichloromercury derivatives (**11**) in the reaction mixtures. Treatment of the lithiopyridine 1-oxide intermediates with two equivalents of mercuric chloride gave complex product mixtures from which only the 2,6-dibromo derivatives (**1**) were obtained on heating with bromine-aqueous sodium bromide. These data are consistent with the formation of 2,6-dilithio intermediates in this reaction. The yields of **1** obtained in this way were: **1a**, 17%; **1b**, 32%; **1c**, 36%.



Treatment of lithio-4-picoline 1-oxide with triphenyllead chloride or with trimethylsilyl chloride gave only recovered starting material.

EXPERIMENTAL

Nmr spectra were determined on a Varian HA-100 instrument and mass spectra on a CEC 104 single focussing spectrometer.

Reaction of Lithiopyridine 1-Oxide with Bromine.

Pyridine 1-oxide (0.95 g., 0.01 mole) in anhydrous THF (20 ml.) and ether (20 ml.) was cooled to -65° and *n*-butyllithium (1.28 g., 0.02 mole) in hexane solution was added slowly to the stirred solution under nitrogen. After 1 hour, the dark brown solution was treated with bromine (1.6 g., 0.02 mole) in dry ether (10 ml.), the solution stirred for a further 15 minutes and then allowed to warm to room temperature. It was poured into water (50 ml.), extracted with chloroform (5 x 30 ml.), the extracts dried (potassium carbonate) and evaporated to give a dark viscous oil which was chromatographed on a 2.5 x 10 cm. silica gel

column. Elution with benzene gave *6,6'-dibromo-2,2'-dipyridyl 1-oxide* (**2a**) (0.102 g., 6.2%), m.p. 209-211° dec. (from acetone); ν max (potassium bromide) 1265 cm^{-1} ($\overset{+}{N}$-$\bar{O}$); mass spectrum (70 eV) 332 (33), 330 (68), 328 (37) (M^+), 316 (2), 314 (4), 312 (2) (M^+-O), 170 (100).

Anal. Calcd. for $C_{10}H_6Br_2N_2O$: C, 36.36; H, 1.82. Found: C, 36.40; H, 1.83.

Further elution with benzene gave 2,6-dibromopyridine 1-oxide (**1a**) (0.078 g., 3.1%), m.p. 187-188° dec. (from acetone) [lit. (5) 186.5-188.5° dec.]. Elution with chloroform gave a black semi-solid which, on trituration with acetone, gave *6,6'-dibromo-2,2'-dipyridyl 1,1'-dioxide* (**3a**) (0.023 g., 1.3%), m.p. 232-234° dec. (from acetone); ν max (potassium bromide) 1265, 1250 cm^{-1}; mass spectrum (70 eV) 348 (50), 346 (100), 344 (54) (M^+), 331 (18), 329 (34), 327 (18) (M^+-OH).

Anal. Calcd. for $C_{10}H_6Br_2N_2O_2$: C, 34.70; H, 1.75. Found: C, 34.16; H, 1.79.

The aqueous layer from the original extraction was made basic with potassium carbonate and extracted with chloroform (5 x 30 ml.). The extracts were dried (potassium carbonate) and evaporated to give a yellow semi-solid which, on trituration with acetone, gave more 6,6'-dibromo-2,2'-dipyridyl 1,1'-oxide (0.12 g., 6.9%). The overall yield of **3a** (R = R' = H) was 8.2%.

In one case, phenol (0.6 g.) was added to the reaction mixture before it was allowed to warm to room temperature. No **2** was obtained in this case and a mixture of bromophenols (0.152 g.) was isolated by column chromatography.

Reaction of Lithio-4-picoline 1-Oxide with Bromine.

4-Picoline 1-oxide (1.09 g., 0.01 mole) in dry THF (40 ml.) was treated with *n*-butyllithium (1.28 g., 0.02 mole) in hexane and then with bromine (1.6 g., 0.02 mole) as described above for pyridine 1-oxide. The mixture was worked up as above and chromatographed on a column of silica gel. Elution with benzene-ether (3:1 v/v) gave *6,6'-dibromo-4,4'-dimethyl-2,2'-dipyridyl 1-oxide* (**2b**) (0.321 g., 18%), m.p. 166-167° (acetone); ν max (potassium bromide) 1255 cm^{-1} ($\overset{+}{N}$-$\bar{O}$); nmr (deuteriochloroform) τ: 1.18 (1H, s, C_5'-H); 2.04 (1H, d, $J_{3,5}$ = 3 Hz, C_3-H); 2.68 (1H, s, C_3'-H); 7.6 (6H, s, 2 CH_3); mass spectrum (70 eV) 360 (52), 358 (100), 356 (54) (M^+), 344 (2), 342 (4), 340 (2) (M^+-O).

Anal. Calcd. for $C_{12}H_{10}Br_2N_2O$: C, 40.25; H, 2.81; N, 7.82. Found: C, 40.54; H, 2.76; N, 7.78.

Elution with ether gave *2,6-dibromo-4-methylpyridine 1-oxide* (**1b**) (0.122 g., 4.6%), m.p. 154-155°; ν max (potassium bromide) 1245 cm^{-1}; nmr (deuteriochloroform) τ: 2.50 (2H, s, C_3-H, C_5-H); 7.70 (3H, s, CH_3); mass spectrum (70 eV) 269 (48), 267 (100), 265 (50) (M^+), 253 (2), 251 (4), 249 (2) (M^+-O).

Anal. Calcd. for $C_6H_5Br_2NO$: C, 27.0; H, 1.89. Found: C, 27.25; H, 1.96.

Further elution with ether-ethanol and ethanol gave *6,6'-dibromo-4,4'-dimethyl-2,2'-dipyridyl 1,1'-dioxide* (**3b**) (0.237 g., 12.7%) m.p. 219-222° dec. (acetic acid); ν max (potassium bromide) 1240 cm^{-1}; nmr (CD_3CO_2D) τ: 2.5 (2H, d, $J_{3,5} = J_{3',5'}$ = 3 Hz, C_5-H, C_5'-H); 2.86 (2H, d, J = 3 Hz, C_3-H, C_3'-H); 7.92 (6H, s, 2 CH_3); mass spectrum (70 eV) 376 (51), 374 (100), 372 (57) (M^+), 359 (21), 357 (40), 355 (21) (M^+-OH).

Anal. Calcd. for $C_{12}H_{10}Br_2N_2O_2$: C, 38.53; H, 2.69. Found: C, 38.73; H, 2.86.

Reaction of Lithio-3,4-lutidine 1-Oxide with Bromine.

The bromination was carried out as before using 3,4-lutidine 1-oxide (0.86 g.), butyllithium (0.90 g.) and bromine (1.12 g.), and phenol (0.45 g.) was added prior to allowing the reaction mixture to warm up to room temperature. Chromatography as before gave 2,6-dibromo-3,4-dimethylpyridine 1-oxide (**1c**) (0.457 g., 23.3%) m.p. 144° (from acetone); ν max (potassium bromide) 1260 cm^{-1} ($\overset{+}{N}$-$\bar{O}$); nmr (deuteriochloroform) τ: 2.62 (1H, s, C_5-H); 7.62 (3H, s, C_3-CH_3); 7.68 (3H, s, C_4-CH_3); mass spectrum (70 eV) 283 (33), 281 (72), 279 (34) (M^+), 267 (7), 265 (16), 263 (8) (M^+-O), 65 (100).

Anal. Calcd. for $C_7H_7Br_2NO$: C, 29.92; H, 2.51; N, 4.98. Found: C, 30.22; H, 2.52; N, 4.80.

Elution with ether-ethanol (5:1 v/v) gave a brown oil which, on trituration with acetone (8 ml.), gave *6,6'-dibromo-3',4,4'-5-tetramethyl-2,2'-dipyridyl 1,1'-dioxide* (**3c**) (22 mg., 1.6%), m.p. 200-202° dec.; ν max (potassium bromide) 1260 cm^{-1}; mass spectrum (70 eV) 404 (3), 402 (7), 400 (3) (M^+), 387 (47), 385 (80), 383 (40) (M^+-OH).

Anal. Calcd. for $C_{14}H_{14}Br_2N_2O_2$: C, 41.82; H, 3.51; N, 6.97. Found: C, 42.03; H, 3.74; N, 6.71.

2,6-Dichloropyridine 1-Oxide.

Pyridine 1-oxide (0.95 g., 0.01 mole) in THF (20 ml.) and ether (20 ml.) was cooled to -65° and treated with *n*-butyllithium (1.28 g., 0.02 mole) in hexane as usual. After 1 hour at -65° the dark solution was treated with chlorine gas (30 ml./min.) for 15 minutes, the mixture stirred under nitrogen for a further 15 minutes and then allowed to come to room temperature. Water was added and the mixture was basified with potassium carbonate. It was extracted with chloroform (5 x 30 ml.), the extract dried (potassium carbonate) and evaporated to give a brown viscous oil which was chromatographed on a silica gel column (2.5 x 20 cm.). Elution with benzene gave butyl chloride (80 mg.). Elution with benzene-ether (3 1 v/v) gave 2,6-dichloropyridine 1-oxide (74 mg., 4.5%), m.p. 139-140° [lit. (11) m.p. 139.5-140.5°]; ν max (potassium bromide) 1265 cm^{-1}; mass spectrum (70 eV) 167 (18), 165 (22), 163 (46) (M^+), 151 (3), 149 (12), 147 (21) (M^+-O), 128 (7) (M^+-Cl), 63 (100).

Only uncharacterizable tars were eluted subsequently.

2,6-Dichloro-3,4-dimethylpyridine 1-Oxide.

Prepared as above from 3,4-lutidine 1-oxide (0.86 g.), butyllithium (1.28 g.) and chlorine gas, it was obtained by chromatography and elution with benzene-ether (3:1 v/v). Recrystallization from acetone gave the *N*-oxide (0.117 g., 8.8%), m.p. 165-166°; ν max (potassium bromide) 1275 cm^{-1} ($\overset{+}{N}$-$\bar{O}$); nmr (deuteriochloroform) τ: 2.75 (1H, s, C_5-H); 7.62 (3H, s, C_3-CH_3); 7.68 (3H, s, C_4-CH_3); mass spectrum (70 eV) 195 (10), 193 (66), 191 (100) (M^+), 177 (6), 175 (7) (M^+-O).

Anal. Calcd. for $C_7H_7Cl_2NO$: C, 43.78; H, 3.67. Found: C, 44.21; H, 3.74.

Reaction of Lithiopyridine 1-Oxides with Mercuric Chloride (1 equiv.).

n-Butyllithium (0.05 mole) in hexane was added slowly to a stirred suspension of the *N*-oxide (0.025 mole) in anhydrous THF (150 ml.) under dry nitrogen at -65°. The solution was stirred at -65° for 1 hour or warmed to 0° and immediately cooled down to -65° again, and treated dropwise with a solution of mercuric chloride (0.025 mole) in anhydrous THF. This resulted in decoloration and formation of a yellow precipitate. After a further 15 minutes at -65° the mixture was warmed to room temperature, water (100 ml.) was added and the solid was filtered and dried. It was then heated at 100° under vacuum to remove all traces of elemental mercury.

A. Pyridine 1-Oxide.

The product mixture (4.40 g.), m.p. 227-234°, exhibited peaks in the mass spectrum at m/e 330 (**9a**, M^+, ^{202}Hg) and m/e 390 (**10a**, M^+, ^{202}Hg) as well as fragments at m/e 456. It could not be recrystallized or fractionated and was unaffected by heating with sodium iodide in ethanol or with mercuric chloride.

The mixture was suspended in water (30 ml.), heated to 50° and treated with a solution of sodium bromide in water (10 ml.) containing bromine (2.93 g., 0.0182 mole). After stirring for 30 minutes at 50° the reaction mixture was treated with 6*N* aqueous sodium hydroxide, filtered, and the filtrate extracted with chloroform. The chloroform extract was washed with 10% hydrochloric acid, water, and dried (sodium sulfate). It was decolorized with charcoal and evaporated to give 2,6-dibromopyridine 1-oxide (**1a**) (12% based on pyridine 1-oxide used), m.p. 188-190°. The aqueous acid extract was neutralized with 6*N* sodium hydroxide and extracted with chloroform, the extract dried (sodium sulfate) and concentrated to give 2-bromopyridine 1-oxide (**12a**) (13% yield), hydrochloride m.p. 133-135° [lit. (12) m.p. 135-136°].

B. 4-Picoline 1-Oxide.

The product mixture (5.25 g.), m.p. 247-260°, exhibited peaks in the mass spectrum at m/e 345 (**9b**, M^+, ^{202}Hg) and m/e 418 (**10b**, M^+, ^{202}Hg), as well as fragment ions at higher m/e values. Again it was not possible to resolve or recrystallize this mixture.

Bromination and workup as in (A) above in the case of pyridine 1-oxide gave 2,6-dibromo-4-picoline 1-oxide (**1b**) (29%), m.p. 155-156°, undepressed on admixture with a sample prepared as described earlier, and 2-bromo-4-picoline 1-oxide (**12b**) (14%), hydrochloride, m.p. 145-147° [lit. (12) m.p. 147-148°].

Reaction of Lithiopyridine 1-Oxides with Mercuric Chloride (2 equiv.).

n-Butyllithium (0.05 mole) was added to a stirred suspension of the *N*-oxide (0.025 mole) in anhydrous THF (150 ml.) under nitrogen at -65°. After stirring the solution for 1 hour at -65° it was added dropwise to a stirred solution of mercuric chloride (0.05 mole) in THF (50 ml.) at -65°. A pale yellow solid separated. The suspension was warmed to room temperature, water (100 ml.) was added and the yellow solid was filtered, washed with water and dried.

A. Pyridine 1-Oxide.

The yellow solid (8.43 g.), m.p. 210-215°, could not be obtained analytically pure. It was treated with bromine in aqueous sodium bromide as described above to give 2,6-dibromopyridine 1-oxide (**1a**) (17%), m.p. 188-190°. No monobromopyridine 1-oxide was isolated.

B. 4-Picoline 1-Oxide.

The yellow mixture (10.18 g.), m.p. 222-226°, gave on bromination only 2,6-dibromo-4-picoline 1-oxide (**1b**) (32%), m.p. 155-156°.

C. 3,4-Lutididine 1-Oxide.

This gave a yellow product (10.52 g.), m.p. 236-240°, which was brominated as usual to yield 2,6-dibromo-3,4-lutidine 1-oxide (**1c**) (36%), m.p. 141-142°, identical with the product obtained earlier.

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REFERENCES

(1) A preliminary account of some of this work has been published; R. A. Abramovitch and E. E. Knaus, *J. Heterocyclic Chem.*, **6**, 989 (1969).

(2) R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, **55**, (1967).

(3) R. A. Abramovitch, E. M. Smith, E. E. Knaus, and M. Saha, *J. Org. Chem.*, 37, 1690 (1972). R. A. Abramovitch, M. Saha, E. M. Smith, and R. T. Coutts, *J. Am. Chem. Soc.*, **89**, 1537 (1967).

(4) R. A. Abramovitch, E. M. Smith, and R. T. Coutts, *J. Org. Chem.*, in the press.

(5) R. F. Evans, M. van Ammers, and H. J. den Hertog, *Rec. Trav. Chim.*, 78, 408 (1959).

(6) R. A. Abramovitch and C. S. Giam, *Can. J. Chem.*, **40**, 213 (1962).

(7) H. Mosher and F. Welsh, *J. Am. Chem. Soc.*, 77, 2902 (1955).

(8) F. C. Whitmore and R. G. Sobatzki, *ibid.*, **55**, 1128 (1933).

(9) G. E. Coates, "Organometallic Compounds," Methuen and Co., Ltd., London, 1960, p. 83.

(10) M. van Ammers and H. J. den Hertog, *Rec. Trav. Chim.*, 77, 340 (1958); *ibid.*, **81**, 124 (1962).

(11) R. Rousseau and A. Robins, *J. Heterocyclic Chem.*, 2, 196 (1965).

(12) E. Shaw, J. Bernstein, K. Losee, and W. A. Lott, *J. Am. Chem. Soc.*, 72, 4362 (1950).