Synthesis of Oximes. IV. 2-Pyridinealdoxime Methiodides from 2-Picoline Methiodides

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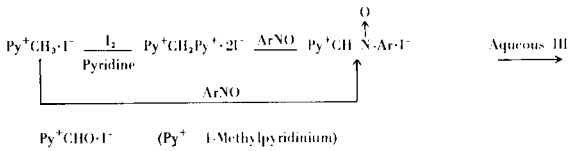
The Ortoleva-King-Krohnke sequence was used to prepare substituted 2-pyridinealdoxime methiodides. The methodology was extended to prepare three analogs in which two molecules of 5-hydroxy-2-pyridinealdoxime methiodide were coupled through the 5-position with dihalides.

J. Heterocyclic Chem., 14, 19 (1977).

In the three preceding papers of this series, various approaches to the synthesis of pyridine aldehydes and oximes have been described (1,2,3). The objective was to develop new methods to introduce the aldehyde group into nitrogen heterocycles, primarily pyridine, in order to make available additional analogs of 2-pyridinealdoxime methiodide (2-PAM) as therapeutic agents for organophosphorus poisoning (4). More importantly, the success of TMB-4, 1,1′-trimethylene-bis(4-hydroxyiminomethylpyridinium)dibromide, as an enzyme reactivator (4) comparable in efficacy to 2-PAM, led to an extension of the program to bis-quaternary analogs coupled in the 5-position of the pyridine ring. None of the methods developed to date (reference 3 and references therein) proved applicable and an alternative approach was required.

Our approach to the preparation of analogs of 2-PAM and TMB-4 is based, in part, on the treatment of 1-methyl-2-picolinium iodides with iodine and pyridine to form intermediate 1-methyl-2-(1-pyridiniummethyl)-pyridinium diiodides. This reaction was studied by Ortoleva (5), King (6), Berson and Cohen (7) and by Krohnke (8) who named the one-step procedure the Ortoleva-King reaction. The 1-methyl-2-(1-pyridiniummethyl)pyridinium diiodides were utilized by Krohnke (9) for the preparation of aldehydes by treatment with *p*-nitrosodimethylaniline or nitrosobenzene to form nitrones which were hydrolyzed readily to the 2-aldehydes with dilute acid. Krohnke noted that both reactions take place at room temperature under mild conditions and hence the method is particularly useful for sensitive aldehydes.

Krohnke (9) noted that nitrone-anil mixtures equally capable of hydrolysis to aldehydes could be obtained by direct nitrosation of 2-picoline methiodides, thus bypassing the Ortoleva-King reaction.



The same methodology is generally applicable to 2-picoline *N*-oxides as starting materials. Examples of this, as well as the direct nitrosation procedure, are reported herein.

Discussion

5-Substituted-2-pyridinealdoxime Methiodides. Ortoleva-King-Krohnke Sequence.

Four examples of 5-substituted 2-PAM's were prepared as shown schematically in Figure 1. The 1-methyl-2-picolinium iodides **1a**, **2a** and **3a** were treated with iodine and pyridine to yield the corresponding 1-methyl-2-(1-pyridiniummethyl)pyridinium diiodides **1b**, **2b** and **3b**. These were then treated with *p*-nitrosodimethylaniline to yield the nitrones **1d**, **2d** and **3d** in 71%, 84% and 80% yields, respectively; with nitrosobenzene, the yields of **1e** and **2e** were 75% and 80%, respectively.

Nitrone formation undoubtedly proceeds *via* the anhydro bases **1c**, **2c** and **3c** which were prepared independently in good yield by treating **1b**, **2b** and **3b** in chloroform with 20% sodium hydroxide. The anhydro

bases were sharp-melting red or orange solids, but they were too unstable to be analyzed. Their identity was confirmed by 1) treatment of **1c** with aqueous hydriodic acid to regenerate **1b**, 2) hydrolysis of **1c** to 1-methyl-2-pyridone with dilute base, as reported by Berson and Cohen (7), and 3) treatment of **1c** and **2c** with nitrosobenzene to yield the phenyl nitrones **1e** and **2e** in 81% and 94% yields, respectively.

The nitrones **1d**, **2d** and **3d** were hydrolyzed with 5% aqueous hydriodic acid at room temperature for 10 minutes, followed by treatment with hydroxylamine at *p*H 7 and at 100° (steam bath) for 30 minutes. The 2-PAM iodides **1**, **2** and **3** were obtained in 60%, 65% and 56% yields, respectively. Direct treatment of the nitrone **1d** with hydroxylamine at 100° was unsuccessful. At *p*H 7, starting material was recovered and at *p*H 8 or higher, 1-methyl-2-pyridone was obtained.

Direct Nitrosation.

Referring to Figure 1, compounds **1a**, **2a** and **4a** were

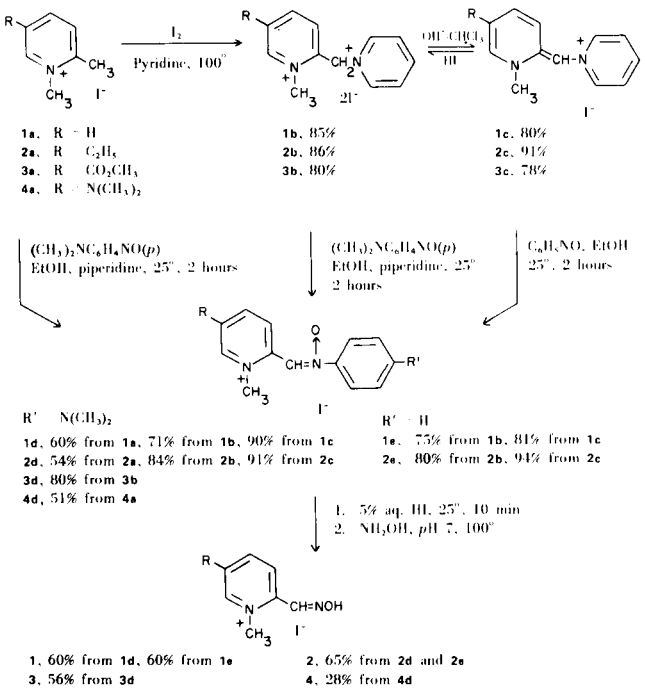


Figure 1. 2-Pyridinealdoxime Methoidides

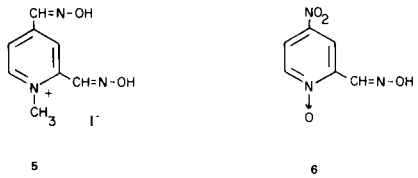
dissolved in ethanol and treated at room temperature for 2 hours with one equivalent of *p*-nitrosodimethylaniline in the presence of a small amount of piperidine. This procedure (7) yields the nitrones **1d**, **2d** and **4d** in 60%, 54% and 51% yields, respectively. In this case, anils are probably formed also. This was not investigated and the compounds were hydrolyzed and oximated directly to the corresponding 2-PAM's **1**, **2** and **4** in 60%, 65% and 28% yields, respectively.

2,4-Diformylpyridine Dioxime Methiodide (**5**).

2,4-Lutidine methiodide was converted to the dinitrone in 17% yield which was hydrolyzed and oximated to the title dioxime **5** in 15% yield. The product is identical with that prepared by treatment of 2,4-lutidine with iodine-DMSO to yield the aldehyde, followed by oximation and *N*-methylation (3).

4-Nitro-2-pyridinealdoxime *N*-Oxide (**6**).

The Ortoleva-King reaction is applicable also to pyridine *N*-oxides (9). 4-Nitro-2-picoline *N*-oxide was treated with iodine in pyridine to yield 4-nitro-2-(1-pyridiniummethyl)-pyridine *N*-oxide (**6a**), accompanied by a by-product identified as the 4-(1-pyridiniumiodide)-2-(1-pyridinium-methyl)pyridine *N*-oxide resulting from displacement of the 4-nitro group with pyridine. Treatment of the former with *p*-nitrosodimethylaniline gave the nitrone **6b** (85%) and hydrolysis and oximation gave the title oxime **6** (55%).



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Melting point and analytical data are shown in Tables I, II and III. Data for other compounds are included in the Experimental.

Bis-Quaternary 2-PAM Iodides.

The Ortoleva-King-Krohnke sequence was applied successfully to prepare two of the title compounds, **7** and **8**, as shown in Figure 2 (Method A). A third compound, **9**, was prepared as the monooxime resulting from the failure of one of the 2-methyl groups to react with iodine and pyridine.

For the dioxime **7**, the starting diiodide **7a** (39%) was prepared by coupling 1,4-dibromobutane with two moles of 5-hydroxy-2-picoline in aqueous DMF containing potassium carbonate, followed by quaternization with methyl iodide. The diiodide **7a** was treated with two moles of iodine in refluxing pyridine; the tetraiodide (78%, not shown) separated upon cooling. A suspension of the tetraiodide in ethanol was treated with *p*-nitroso-dimethylaniline to give the dinitrone **7b** (43%). In this case, heat was required to hydrolyze a suspension of the dinitrone **7b** in 50% acetic acid, followed by oximation to yield the bis-quaternary dioxime **7** in 37% yield, or 6% overall from 5-hydroxy-2-picoline.

For the dioxime **8**, the starting diiodide **8a** (31%) was prepared in the same manner from *p*-xylylene dibromide and 5-hydroxy-2-picoline, followed by quaternization with methyl iodide. In the next step, it was necessary to

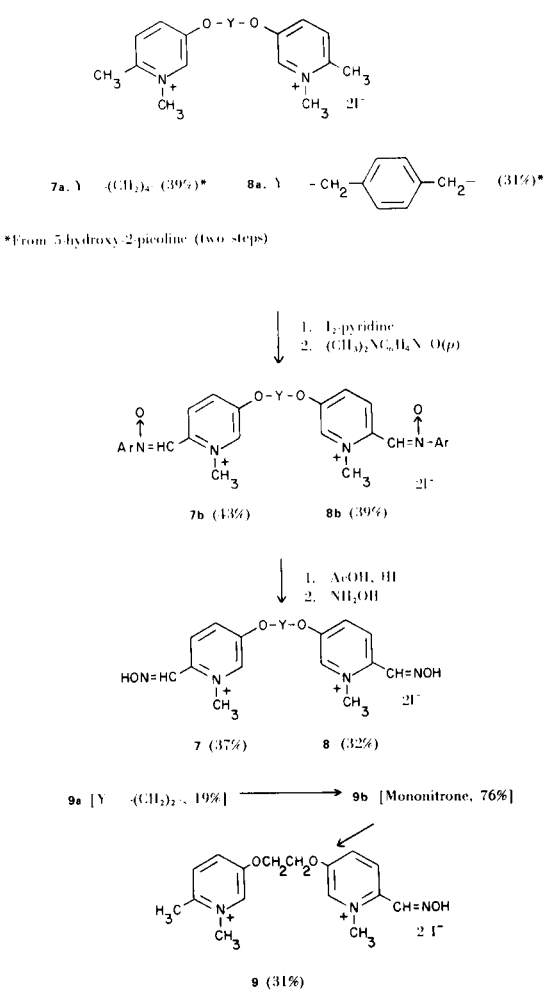


Figure 2. Bis-oximes by Method A.

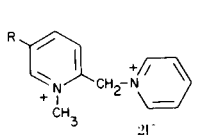
treat **8a** with iodine and pyridine under milder conditions, *i.e.*, heating the mixture at 70-80° for 2 hours (rather than at 95-100° for up to 12 hours) to minimize cleavage of the ether linkages by pyridine hydriodide (to form xylylene dipyridinium diiodide). Even so, the product was obtained as an oil which was nitrosated directly to solid, crude dinitrone **8b** (39% from **8a**, m.p. 189-192° dec.). The crude dinitrone **8b** was converted as above to the dioxime **8** in 32% yield, or 4% overall from 5-hydroxy-2-picoline.

In the third example (Figure 2), the starting diiodide **9a** was prepared by coupling 1,2-dibromoethane with 5-hydroxy-2-picoline, followed by quaternization with methyl iodide; in this case, the coupling step proceeded in but 19% yield and the quaternization in 75% yield (14% overall). Treatment with iodine and pyridine (steam bath, 2 hours) gave a semisolid triodide which was nitrosated directly to give the mononitrone **9b** (76% from **9a**). This was converted as above to the monooxime **9** in 31% yield.

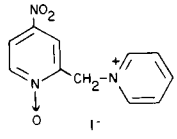
An alternative route to the bis-oximes was explored briefly and applied to the preparation of **7** and **8** as shown in Figure 3 (Method B).

5-Hydroxy-2-picoline was converted to the methiodide (**10**) in 89% yield. The methiodide **10** was treated with iodine and pyridine to give a mixture of 2-(1-pyridiniummethyl)mono- and diiodide salts **11a** and **11b** in approximately 58:42 ratio and in 23% yield calculated as mixed salts. The mixture was nitrosated directly to the nitrone inner salt **12** (95%). Conversion to the oxime in the usual manner, followed by basification, led to the oxime inner salt monoiodide **13** which is readily converted to the oxime diiodide **13a** by adjusting the *p*H to 4 with aqueous hydriodic acid. The oxime inner salt **13** was alkylated in low yields with 1,4-diiodobutane and *p*-xylylene dibromide in aqueous DMF to give compounds **7** (12%)

Table I



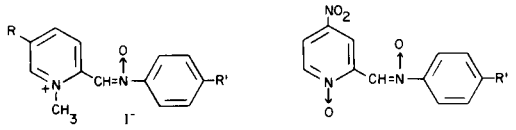
2I⁻



6a

No.	R	M.p. °	Formula	Anal. Calcd./Found C	H	I	N
1b (7)	H	187-188					
2b	C_2H_5	189-190	$C_{14}H_{18}I_2N_2$	35.92	3.87	54.23	5.96
				36.18	4.01	54.41	6.01
3b	CO_2CH_3	177-178	$C_{14}H_{16}I_2N_2O_2$	33.76	3.24	50.97	5.61
				33.79	3.49	50.74	5.91
6b		192-193	$C_{11}H_{10}IN_3O_3$	36.78	2.81	35.33	
				36.98	3.24	35.01	

Table II



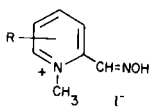
6b and 6c

No.	R	R'	M.p., °	Formula	Anal. Calcd./Found C	H	I	O
1d (10)	H	$N(CH_3)_2$	203-204 dec.	$C_{15}H_{18}IN_3O$	47.01	4.73	33.12	
					46.79	4.84	33.28	
1e	H	H	178-179 dec.	$C_{13}H_{13}IN_2O$	45.89	3.86	37.31	4.70
					45.81	3.79	37.81	4.59
2d	C_2H_5	$N(CH_3)_2$	210-212 dec.	$C_{17}H_{22}IN_3O$	49.65	5.39	30.82	3.89
					49.94	5.50	30.99	4.05
2c	C_2H_5	H	185-186 dec.	$C_{15}H_{17}IN_2O$	48.93	4.65	34.47	4.35
					49.01	4.78	34.63	4.62
3d	CO_2CH_3	$N(CH_3)_2$	217 dec.	$C_{17}H_{20}IN_3O_3$			28.76	
							28.38	
4d	$N(CH_3)_2$	$N(CH_3)_2$	220-223 dec.	$C_{17}H_{23}IN_4O$			29.77	
							29.58	
6b		$N(CH_3)_2$	205 dec.	$C_{14}H_{14}N_4O_4$	55.62	4.66	18.53 (a)	21.19
					55.16	4.98	18.58 (a)	21.12
6c		H	188-189			(b)		

(a) Nitrogen. (b) Not analyzed.

and **8** (11%), respectively. The conversion was low and further study is required to optimize the yields in this coupling procedure; admittedly the inner salt **13** is a poor nucleophile. Similarly, the iodine-pyridine reaction is capable of further improvement. Overall, Method B is a simpler procedure, but the overall yields of less than 1% are a distinct disadvantage relative to Method A.

Table III



No.	R	M.p., °	Footnote
1	H	224-226	(a)
2	5-C_2H_5	138-140	(a)
3	5-CO_2CH_3	164-166	(a)
4	5-$N(CH_3)_2$	203-205	(b)
5	4-CH=NOH	187-188	(a)
6	4-NO_2(*N*-oxide)	205-206	(b)

(a) Reference 3. (b) For anal., see Experimental.

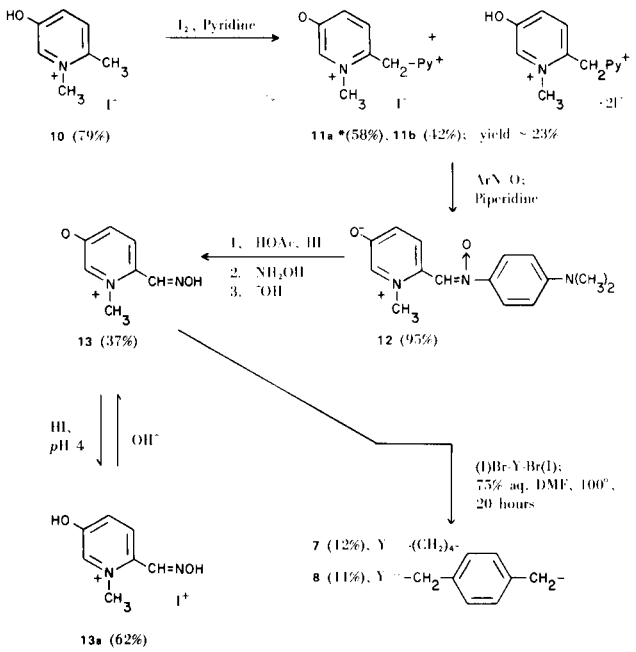


Figure 3. Bis-oximes by Method B.

EXPERIMENTAL

All melting points are uncorrected.

2-PAM Iodides **1**, **2** and **3**. Ortoleva-King-Krohnke Sequence.

Pyridinium diiodides **1b**, **2b** and **3b** were prepared by heating (steam bath) the 2-picolinium methiodides **1a**, **2a** and **3a** with I_2 in pyridine for 12, 12 and 3 hours, respectively. The precipitated products were collected and recrystallized from the following solvents: **1b**, 80% ethanol; **2b**, ethanol-water; and **3b**, 80% aqueous ethanol (Table I).

The anhydro bases, **1c**, **2c** and **3c**, were prepared by suspending the corresponding diiodides (1 g.) in chloroform (50 ml.) and shaking the suspension with 5 ml. of 20% aqueous sodium hydroxide. The resulting deep red chloroform layer was filtered and concentrated (aspirator) to one-third volume. Ether (10 ml.) was added with cooling and the anhydro bases were collected as orange to red crystals: **1c**, m.p. 144-146° dec.; **2c**, m.p. 145° dec.; and **3c**, m.p. 125-128° dec. The odor of pyridine was evident on standing and elemental analyses were not attempted.

Nitrones **1d**, **2d** and **3d** were prepared by dissolving the pyridinium diiodides **1b**, **2b** and **3b** in ethanol containing one equivalent of *p*-nitrosodimethylaniline and piperidine (2 ml./g. of diiodide). After standing at room temperature for 2 hours, ether was added to complete precipitation of the nitrones which were collected, washed with ether and recrystallized from ethanol-ether (Table II).

Nitrones **1e** and **2e** were prepared in the same manner from the anhydro bases **1c** and **2c** in ethanol containing nitrosobenzene, omitting the piperidine catalyst. Alternatively, **1e** and **2e** were prepared from **1b** and **2b** with catalyst.

All of the above nitrones were suspended in 5% hydriodic acid (*ca.* 1 g./10 ml.) for 10 minutes. Hydroxylamine (0.5 g./g. of nitrone) was added, the *p*H was adjusted to 7 and the resulting solution was heated (steam bath) for 30 minutes. The oximes were extracted with chloroform-ethanol (10:1). The solvents were removed (aspirator) and the resulting crude products were recrystallized from ethanol (**1** and **2**) or ethanol-ether (**3**).

2-PAM Iodides **1** and **2** by Direct Nitrosation.

2-Picoline methiodide (**1a**) and 5-ethyl-2-picoline methiodide (**2a**) were treated with *p*-nitrosodimethylaniline and piperidine catalyst in ethanol in the same manner as the corresponding pyridine diiodides to give the nitrones **1d** (60%), m.p. 203-204°, and **2d** (68%), m.p. 210-212°, respectively (the anil content was not determined). These nitrones were hydrolyzed and oximated, as described above, to give the 2-PAM iodides **1** (55%), m.p. 224-226°, and **2** (68%), m.p. 138-140°, identical in all respects to authentic samples.

5-Dimethylamino-2-PAM Iodide (**4**).

A mixture of 5-amino-2-picoline (5.0 g., 46 mmoles), 90% formic acid (15 ml.) and 36% formaldehyde (10 ml.) was heated (steam bath) for 16 hours. Aqueous hydrochloric acid (6 *N*, 20 ml.) was added and volatile materials were removed (aspirator). The solid residue was dissolved in minimum water, basified with sodium hydroxide and extracted with chloroform. The extract was dried (potassium carbonate) and distilled to give 5-dimethylamino-2-picoline, b.p. 42°/0.3 mm (5.04 g., 83%).

Anal. Calcd. for $C_8H_{12}N_2$: C, 70.56; H, 8.87; N, 20.57. Found: C, 70.86; H, 9.19; N, 20.31.

5-Dimethylamino-2-picoline (10 g.) and methyl iodide (15 ml.) in acetonitrile (50 ml.) were refluxed for 2 hours. The precipitated product was collected and recrystallized from methanol-ether to give 5-dimethylamino-2-picoline methiodide (**4a**), m.p. 173-175° (16.5 g., 78%).

Anal. Calcd. for I: 45.62. Found: I, 45.55.

The methiodide **4a** (8.34 g., 0.03 mole), *p*-nitrosodimethylaniline (6 g., 0.04 mole) and piperidine (2 ml.) in ethanol (20 ml.) were heated (steam bath) for 15 minutes, held at room temperature for 2 hours and refrigerated overnight. The red precipitate was collected, washed with ethanol-ether (1:1) and with ether and recrystallized from ethanol to give the nitrone **4d**, m.p. 220-223° dec., (6.3 g., 51%). For anal., see Table II.

The nitrone **4d** (4.26 g.) was suspended in 50% acetic acid (50 ml.) and refluxed 5 minutes. Aqueous hydriodic acid (2 ml., 47%, diluted with 10 ml. of water) was added and the solution was heated for 10 minutes (steam bath). Hydroxylamine, hydrochloride (2 g.), was neutralized with 10% sodium hydroxide and added to the solution which was heated 15 minutes (steam bath). The solution was adjusted to *p*H 6, clarified (Norit) and concentrated. Crude oxime was collected and recrystallized from acetonitrile to give product **4** (770 mg., 26%). The mother liquor was evaporated and extracted with acetonitrile to give additional product (65 mg.) after several recrystallizations. The combined products were recrystallized (x 2) from methanol containing a drop of 5% hydriodic acid) to give 5-di-methylamino-2-PAM iodide (**4**), m.p. 203-205°.

Anal. Calcd. for $C_9H_{14}IN_3O$: C, 35.19; H, 4.59; I, 41.32. Found: C, 35.52, H, 4.69; I, 40.94.

2,4-Diformylpyridine Dioxime Methiodide (**5**).

2,4-Lutidine methiodide (5 g.), *p*-nitrosodimethylaniline (7 g.) and piperidine (2 ml.) in ethanol (15 ml.) were allowed to stand at room temperature for 30 minutes. The precipitate was collected and recrystallized from ethanol to give a presumed nitrone-anil mixture (2.1 g.), m.p. 198-201°. The mixture was hydrolyzed and oximated, as described for **4d** above, to give the title oxime **5** (15%), m.p. 186-188° [lit (**3**) m.p. 186-188°]. The low yield is due, in part, to the difficulty in extracting the oxime from the reaction mixture.

4-Nitro-2-pyridinealdoxime *N*-Oxide (**6**).

A mixture of 4-nitro-2-picoline *N*-oxide (3 g.), iodine (5.4 g.) and pyridine (35 ml.) was heated for 16 hours (steam bath). The pyridine was evaporated under reduced pressure and the residue was dissolved in hot 90% ethanol and treated with Norit. After cooling to room temperature, a yellow product was collected, 2.2 g., m.p. 193-195° (Fraction A). Ether (10 ml.) was added to the mother liquor which was cooled in the refrigerator to yield a second crop. This was washed with ethanol-ether to give 1.5 g., m.p. 180-186° (Fraction B). The mother liquor, after removal of Fraction B, was evaporated to dryness and the residue was recrystallized from 80% ethanol to give 1.8 g. of a yellow product, m.p. 186-188° (Fraction C).

Fraction A, by ir spectra and tlc data, was largely a side product resulting from the displacement of the 4-nitro group by pyridine. Recrystallization of A from ethanol gave pure 4-(1-pyridinium)-2-(1-pyridiniummethyl)pyridine *N*-oxide diiodide, m.p. 210-212°.

Anal. Calcd. for $C_{16}H_{16}I_2N_3O$: I, 48.29; N, 8.05. Found: I, 48.06; N, 8.05.

Fraction B (tlc) was a mixture of the target intermediate, 4-nitro-2-(1-pyridiniummethyl iodide)pyridine *N*-oxide (**6a**), and the by-product containing 60% of **6a**. This mixture was recrystallized from 80% ethanol. The product was combined with Fraction C above and recrystallized from ethanol to give pure

intermediate **6a** (1.8 g., 25%), m.p. 192-193°.

Anal. Calcd. for $C_{11}H_{10}IN_3O_3$: C, 36.78; H, 2.81. Found: C, 36.98; H, 3.24.

Tlc analysis of all solids indicates that 40% of **6a** and 28% of by-product were formed in the reaction.

The pyridinium iodide **6a** (500 mg.) was dissolved in hot ethanol (10 ml.) to which *p*-nitrosodimethylaniline (300 mg.) and piperidine (0.2 ml.) were added. After standing at room temperature for 2 hours, ether (5 ml.) was added to the solution to complete precipitation of the product. The solid was collected, washed with ether and recrystallized from a mixture of chloroform-ethanol to give 2-formyl-4-nitropyridine *N*-oxide *p*-dimethylaminophenylnitrone (**6b**), 340 mg., m.p. 205° dec.

Anal. Calcd. for $C_{14}H_{14}N_4O_4$: C, 55.62; H, 4.66; N, 18.53; O, 21.19. Found: C, 55.10; H, 4.98; N, 18.58; O, 21.12.

2-Formyl-4-nitropyridine *N*-oxide phenylnitrone (**6c**) was prepared in the same way and recrystallized from ethanol to give product (70%), m.p. 188-189°.

The *p*-dimethylaminophenylnitrone **6b** (150 mg.) was dissolved in 35% aqueous hydrochloric acid (3 ml.). After a few minutes, *p*-dimethylaminophenyl hydroxylamine hydrochloride separated and was removed by filtration. The yellow filtrate was treated with hydroxylamine hydrochloride solution prepared from 100 mg. of the hydrochloride and 0.5 ml. of water. The *p*H was adjusted to 7 with 10% sodium hydroxide. The reaction mixture was kept on a steam bath for 30 minutes and then cooled overnight in the refrigerator. Colorless crystals were formed which were recrystallized from hot water to yield 4-nitro-2-pyridinealdoxime methiodide (**6**) (51 mg., 58%), m.p. 203-204°. Similarly, the phenylnitrone **6c** was converted to **6** (57%), m.p. 205-206°; mixture melting points of the two products were undepressed.

Anal. Calcd. for $C_6H_5N_3O_4$: C, 39.35; H, 2.75; N, 22.95; O, 34.98. Found: C, 39.17; H, 2.85; N, 22.78; O, 34.93.

Bis-Quaternary Dioximes **7** and **8** and Monooxime **9** by Method A.

The sequence for Method A is shown in Figure 2.

1,4-Bis(1′-methyl-2′-formyl-5′-pyridyloxy)butane Dioxime Diiodide (**7**).

A mixture of 5-hydroxy-2-picoline (109 g., 1.00 mole), 1,4-dibromobutane (108 g., 0.50 mole) and potassium carbonate (138 g., 1.00 mole) in 750 ml. of 67% aqueous dimethyl formamide was heated under reflux for 16 hours. After cooling to 10°, the crystalline product was collected and recrystallized from ethanol-water to give 55.4 g. (42%) of 1,4-bis(2′-methyl-5′-pyridyloxy)-butane, m.p. 91.5-93°.

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.60; H, 7.35; N, 10.28. Found: C, 70.51; H, 7.26; N, 10.44.

The above product (4.0 g., 0.0147 mole) and methyl iodide (16.7 g., 0.118 mole) in ethanol (25 ml.) and acetonitrile (50 ml.) were heated under reflux overnight. The crystalline solid was collected, washed with ether and dried to give 7.5 g. (92%) of 1,4-bis(1′,2′-dimethyl-5′-pyridyloxy)butane diiodide (**7a**).

Anal. Calcd. for I: 45.6. Found: I, 44.8.

A hot suspension of the bis-methiodide **7a** (550 mg.) in pyridine (10 ml.) containing iodine (520 mg.) was heated (steam bath) for 12 hours. After cooling, the crystalline product (750 mg., m.p. 204-206°) was collected and washed with cold pyridine and with ethanol. Recrystallization from ethanol-water gave 650 mg. (65%) of 1,4-bis[1′-methyl-2′-(pyridiniummethyl)-5′-pyridyloxy]butane tetraiodide, m.p. 213-215° dec.

Anal. Calcd. for $C_{28}H_{34}I_4N_4O_2$: C, 34.76; H, 3.52; I, 52.48; N, 5.79. Found: C, 34.57; H, 3.73; I, 52.20; N, 5.78.

Piperidine (0.5 ml.) was added to a hot suspension of the above tetraiodide (500 mg.) and *p*-nitrosodimethylaniline in 90% ethanol. The mixture was allowed to cool to room temperature and stirred for 4 hours. The resulting dark red precipitate was filtered and washed with ethanol and with ether to give 300 mg. (66%) of 1,4-bis[1′-methyl-2′-formyl-(*p*-dimethylaminophenylnitrone)-5′-pyridyloxy]butane diiodide (**7b**), m.p. 203-205°. An analytical sample was obtained by recrystallization from ethanol-water, m.p. 208° dec.

Anal. Calcd. for $C_{34}H_{42}I_2N_6O_4$: I, 29.75; N, 9.83. Found: I, 30.00; N, 10.09.

The bis-nitrone **7b** (2.55 g., 3.07 mmoles) was suspended in 50 ml. of 50% aqueous acetic acid, refluxed for 5 minutes and then heated on a steam bath for 30 minutes. Hydriodic acid (1.2 ml. of 47% hydriodic acid in 5 ml. of water) was added to the cooled mixture, followed immediately by a neutral (*p*H 7.0) solution of hydroxylamine (prepared from 1.2 g. of hydroxylamine hydrochloride and 10 ml. of water). The red solution was heated (steam bath) for one hour and filtered. The filtrate was decolorized (Norit), concentrated to one-half volume, adjusted to *p*H 6 and heated (steam bath) for 30 minutes. The mixture was concentrated under reduced pressure and cooled. The resulting semi-crystalline crude product was collected, dissolved in hot water and extracted with chloroform (discarded). The aqueous layer was concentrated and decolorized (x 2). On cooling, there was obtained 690 mg. (37%) of 1,4-bis(1′-methyl-2′-formyl-5′-pyridyloxy)butane dioxime diiodie (**7**), m.p. 202-204° dec. An analytical sample was prepared by recrystallization from ethanol-water (x 3), m.p. 206-207° dec.

Anal. Calcd. for $C_{18}H_{24}I_2N_4O_4$: C, 35.19; H, 3.93; I, 41.33. Found: C, 35.56; H, 4.20; I, 41.64.

1,4-Bis(1′-methyl-2′-formyl-5′-pyridyloxy)*p*-xylylene Dioxime Diiodide (**8**) by Method A.

A mixture of 5-hydroxy-2-picoline (10.9 g., 0.10 mole), α,α′-dibromo-*p*-xylene (13.2 g., 0.05 mole) and potassium carbonate (13.8 g., 0.10 mole) was refluxed overnight in dimethyl formamide (90 ml.) and water (30 ml.). After cooling, water (100 ml.) was added. The precipitate was collected and recrystallized from ethanol to give 5.0 g. (31%) of 1,4-bis(2′-methyl-5′-pyridyloxy)-*p*-xylylene, m.p. 140-141°.

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 75.00; H, 6.25; N, 8.75. Found: C, 74.89; H, 6.51; N, 8.93.

A solution of 1,4-bis(2′-methyl-5′-pyridyloxy)*p*-xylylene (5.0 g., 0.0156 mole) and methyl iodide (17.7 g., 0.125 mole) in acetonitrile (50 ml.) was heated to reflux; a solid separated and ethanol (25 ml.) was added to effect solution. The solution was refluxed for 18 hours. On cooling, the product separated and was collected to give 9.5 g. (100%) of 1,4-bis(1′,2′-dimethyl-5′-pyridyloxy)*p*-xylylene diiodide (**8a**), m.p. 220-222°.

A suspension of the above bis-methiodide (1.2 g.) in pyridine (20 ml.) containing iodine (1.1 g.) was stirred at 70-80° for 2 hours. Pyridine was decanted from the oily insoluble product which was washed with cold ethanol and with ether. The resulting material was dissolved in water, clarified (Norit) and evaporated (aspirator) to give 0.8 g. of 1,4-bis[1′-methyl-2′-(pyridiniummethyl)-5′-pyridyloxy]*p*-xylylene tetraiodide as a brown oily solid which was used in the next step without further purification.

In this case, the reaction was conducted at 70-80° (instead of 100°) and 2 hours (instead of 12 hours) as in the case of the 1,4-butane analog. Cleavage at the ether linkage resulted, forming $Py^+CH_2C_6H_4CH_2Py^+ \cdot 2I^-$, identified as terephthaldehyde by con-

version to the dinitrone, followed by hydrolysis. The other cleavage product was identified as 5-hydroxy-2-(1-pyridiniummethyl)-1-methylpyridinium diiodide.

The oily tetraiodide (0.8 g.) in hot ethanol (15 ml.) was treated with *p*-nitrosodimethylaniline (0.8 g.), followed by piperidine (0.6 ml.). The mixture was stirred at room temperature for 4 hours and cooled (refrigerator). The dark red precipitate was filtered and washed with ethanol and with ether to give 0.7 g. (39% from **8a**) of 1,4-bis[1'-methyl-2'-formyl-(*p*-dimethylaminophenylnitrone)-5'-pyridyloxy]*p*-xylylene diiodide (**8b**), m.p. 189-192° (vigorous dec.).

The bis-nitrone **8b** (1.1 g.) was suspended in 50% acetic acid (25 ml.) and heated (steam bath) for 30 minutes. The dark solution was treated with dilute hydriodic acid (0.6 ml. of 47% hydriodic acid in 5 ml. of water), followed immediately by a neutral solution (*p*H 7) of hydroxylamine (prepared from 1 g. of hydroxylamine hydrochloride and 8 ml. of water). The solution was heated (steam bath) for one hour and treated with Norit. The resulting clear light red solution was concentrated under reduced pressure to one-half volume, adjusted to *p*H 6 with sodium carbonate and heated (steam bath) for 30 minutes. The solution was concentrated under reduced pressure. The light yellow precipitate was collected, washed with cold water and with ethanol and recrystallized from hot water to give 250 mg. (32%) of 1,4-bis(1'-methyl-2'-formyl-5'-pyridyloxy)*p*-xylylene dioxime diiodide (**8**), m.p. 214-216°. An analytical sample was prepared by crystallization (x 3) from aqueous ethanol, m.p. 215-217° dec.

Anal. Calcd. for $C_{22}H_{24}I_2N_4O_4$: C, 39.90; H, 3.65; I, 38.33. Found: C, 40.10; H, 3.95; I, 38.56.

5-(1',2'-Dimethyl-5'-pyridyloxyethoxy)-1-methyl-2-formylpyridinium Oxime Diiodide (**9**) by Method A.

A mixture of 5-hydroxy-2-picoline (21.8 g., 0.20 mole), 1,2-dibromoethane (19.8 g., 0.10 mole) and potassium carbonate (27.6 g., 0.2 mole) in water (50 ml.) and dimethyl formamide (100 ml.) was heated with stirring under reflux for 16 hours. Upon cooling to 4°, the product crystallized and was collected by filtration. Recrystallization from ethanol-water gave 4.5 g. (19%) of 1,2-bis(2'-methyl-5'-pyridyloxy)ethane, m.p. 118-120°.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11,47. Found: C, 69.06; H, 6.59; N, 11.60.

A solution of the above compound (4.0 g., 0.016 mole) and methyl iodide (7 ml.) in acetonitrile (50 ml.) and ethanol (10 ml.) was heated under reflux for 18 hours. On cooling, the product crystallized and was collected by filtration. Recrystallization from 2-propanol-ether gave 6.5 g. (75%) of 1,2-bis(1',2'-dimethyl-5'-pyridyloxy)ethane diiodide (**9a**), m.p. 227-228°.

Anal. Calcd. for $C_{16}H_{22}I_2N_2O_2$: C, 36.38; H, 4.20; N, 5.31. Found: C, 36.46; H, 4.27; N, 5.55.

To a hot suspension of **9a** (2.2 g.) in pyridine (20 ml.), iodine (2.2 g.) was added and the solution was stirred on a steam bath for 2 hours. Pyridine was decanted and the oily product was washed with cold ethanol and with ether. The crude pyridinium salt, *p*-nitrosodimethylaniline (3 g.) and piperidine (1 ml.) in ethanol (20 ml.) were heated at 50-60° for 15 minutes and then stirred at room temperature for 3 hours. After cooling, the dark red nitrone was separated and washed with cold ethanol-ether to give 2.0 g. (76% based on **9a**) of the mononitrone iodide (**9b**), m.p. 205-208°. The product was essentially insoluble in organic solvents and was used for the hydrolysis without purification. A sample for analysis was prepared by dissolving the product in a large amount of hot ethanol, followed by precipitation with ether, m.p. 210-212°.

Anal. Calcd. for N: 8.32. Found: N, 8.25.

The mononitrone **9b** (1.3 g.) was suspended in 50% acetic acid (20 ml.) and held on a steam bath for one hour. Hydriodic acid (1.2 ml. of 47% hydriodic acid diluted with 7 ml. of water) was added, followed by a neutral solution (*p*H 7) of hydroxylamine (prepared from 2 g. of hydrochloride salt and aqueous sodium carbonate). The solution was held on a steam bath for one hour, treated with charcoal and concentrated under reduced pressure. The mixture was refrigerated overnight and the resulting precipitate was collected by filtration. The crude oxime **9** was washed with a small amount of cold water and recrystallized from 50 % aqueous ethanol to give 320 mg. (31%) of pure 5-(1',2'-dimethyl-5'-pyridyloxyethoxy)-1-methyl-2-formylpyridinium oxime diiodide (**9**), m.p. 120-123°. An analytical sample was prepared by recrystallization from 50% aqueous ethanol and had m.p. 123-125°.

Anal. Calcd. for $C_{16}H_{21}I_2N_3O_3 \cdot H_2O$: C, 33.40; H, 4.03; I, 44.13; N, 7.31; O, 11.12. Found: C, 33.10; H, 3.97; I, 43.81; N, 7.47; O, 11.04.

Bis-Quaternary Dioximes **7** and **8** by Method B.

The reaction sequence is shown in Figure 3.

5-Hydroxy-2-picoline (6 g.) and methyl iodide (10 ml.) in methanol (25 ml.) were allowed to stand at room temperature overnight. After cooling, the solid was collected. Ether was added to the mother liquor which was cooled and filtered. The combined crops (12 g., m.p. 256-258° dec.) were recrystallized from methanol-ether to give 9.8 g. (79%) of 5-hydroxy-2-picoline methiodide (**10**), m.p. 257-258° dec.

Anal. Calcd. for I: 50.54. Found: I, 50.33.

A mixture of methiodide **10** (5 g.), pyridine (25 ml.) and iodine (5.1 g.) was heated (steam bath) for 6 hours. After cooling, the brown product was collected to give a first crop (5.5 g.). The mother liquor was heated (steam bath) for another 10 hours. The dark suspension was cooled and a second crop was filtered and washed with cold pyridine to give a second crop (4 g.). The two crops were combined and recrystallized from a mixture of ethanol-water to yield a mixture of the 5-oxo (**11a**) and 5-hydroxy (**11b**) pyridiniummethyl diiodides, 3.5 g., m.p. 196-199°. Iodide analysis, 47.8%, corresponds to a ratio of **11a**:**11b** of 58:42, corresponding to a 23% yield as the mixed salts.

The mixed pyridiniummethyl diiodides were suspended in 90% ethanol (15 ml.) containing *p*-nitrosodimethylaniline (4 g.) and piperidine (2 ml.). The mixture was stirred and held at 50-62° for 30 minutes and at room temperature for 2 hours. Ether (20 ml.). was added and the mixture was refrigerated, filtered and washed with a cold ethanol-ether solution to yield 3.5 g. (95%) of 5-oxo-2-formyl-(*p*-dimethylaminophenylnitrone)-1-methylpyridine (**12**), m.p. 213-215° dec.

Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32. Found: C, 66.15; H, 6.19.

5-Oxo-1-methyl-2-pyridinealdoxime (**13**).

The nitrone **12** (3.5 g.) was suspended in 50% acetic acid (35 ml.), refluxed for 5 minutes and heated with stirring (steam bath) for 30 minutes. Hydriodic acid (1.5 ml. of 47% hydriodic acid in 10 ml. of water) was added to the reaction mixture, followed by a neutral (*p*H 7) solution of hydroxylamine (prepared from 3.5 g. of hydroxylamine hydrochloride and 15 ml. of water). The red-brown solution was stirred and heated (steam bath) for one hour and treated with Norit and filtered. The light yellow filtrate was adjusted to *p*H 6, concentrated under reduced pressure and cooled. The crystalline product was collected, washed with

cold water and with ethanol and with ether. The yield was 850 mg., m.p. 256-258° dec., which was recrystallized from boiling water to give 800 gm. (36.6%) of colorless crystals of oxime **13**, m.p. 259-260°.

Anal. Calcd. for $C_7H_8N_2O_2 \cdot H_2O$: C, 49.40; H, 5.92. Found: C, 49.46; H, 6.02.

5-Hydroxy-2-PAM Iodide (**13a**).

The oxime inner salt **13** (200 mg.) was suspended in 5 ml. of ethanol and adjusted to *p*H 4 with dilute aqueous hydriodic acid. To the clear solution, ether was added to precipitate 226 mg. (62%) of the quaternary salt **13a**, m.p. 185-187°. The product was recrystallized from a mixture of ethanol-ether to give an analytical sample, m.p. 189-191°.

Anal. Calcd. for $C_7H_9IN_2O_2$: C, 30.02; H, 3.22; I, 45.32. Found: C, 29.74; H, 3.46; I, 45.21.

1,4-Bis(1'-methyl-2'-formyl-5'-pyridyloxy)butane Dioxime Diiodide (**7**).

The inner salt **13** (51 mg.) was dissolved in 75% aqueous dimethyl formamide (5 ml.) and treated with 1,4-diiodobutane (55 mg.). The solution was heated (steam bath) for 20 hours and evaporated to dryness. The residue was suspended in ethanol and adjusted to *p*H 4 with hydriodic acid. Unreacted **13** remained in the solution as the methiodide **13a**, and the less soluble dioxime **7** was collected by filtration. After crystallization from water, the product had m.p. 203-205° and was identical with the product prepared by Method A. The yield was 11 mg. (12%).

1,4-Bis(1'-methyl-2'-formyl-5'-pyridyloxy)*p*-xylylene Dioxime Diiodide (**8**).

The inner salt **13** (27 mg.), *p*-xylylene dibromide (21 mg.), potassium iodide (20 mg.) and 75% dimethyl formamide (5 ml.) were heated (steam bath) for 20 hours and worked up as described above. After crystallization from water, the product **8** had m.p. 214-216° and was identical in all respects with the one prepared by Method A. The yield was 5.8 mg. (11%).

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