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Studies on Tertiary Amine Oxides. LXXVII.[1] The Pseudo-Gomberg Reaction of 4- and 2-Aminopyridine 1-Oxides

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The 1-oxido-4-pyridyl radical generated by the reaction of 4-aminopyridine 1-oxide with amyl nitrite reacted smoothly with aromatic hydrocarbons, including five-membered heterocycles, *i.e.* thiophene, furan and pyrrole, to give the arylated products when acetic acid was used as the solvent.

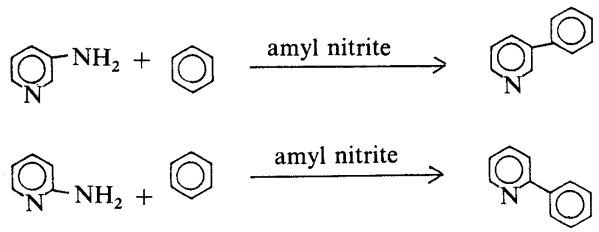
The relative rates of reaction with the 1-oxido-4-pyridyl radical indicated that this radical is electrophilic, and this finding was supported by a comparison of molecular orbital energy levels.

2-Aminopyridine 1-oxide also undergoes a similar reaction.

Keywords——pyridine *N*-oxide; Gomberg reaction; phenylpyridine; thienylpyridine; furylpyridine; 1-methanesulfonyl-pyrrolylpyridine; 1-oxido-4-pyridyl radical; molecular orbital; high-performance liquid chromatography

As an extension of our study on displacement reactions with carbon substituents at the 4-position of pyridine and quinoline 1-oxides, we examined the pseudo-Gomberg reaction of 4-aminopyridine 1-oxide with benzene derivatives and found that 4-arylpyridine 1-oxides were successfully formed in good yields. The same reaction of 2-aminopyridine 1-oxide was also attempted. Furthermore, on the basis of the relative rates of reaction of benzene and its substituted derivatives with the 1-oxido-4-pyridyl radical, this radical was concluded to be electrophilic.

A considerable number of reports has appeared on the pseudo-Gomberg reaction of heteroaromatic amines. Cadogan[2] showed that treatment of 3-aminopyridine in benzene with



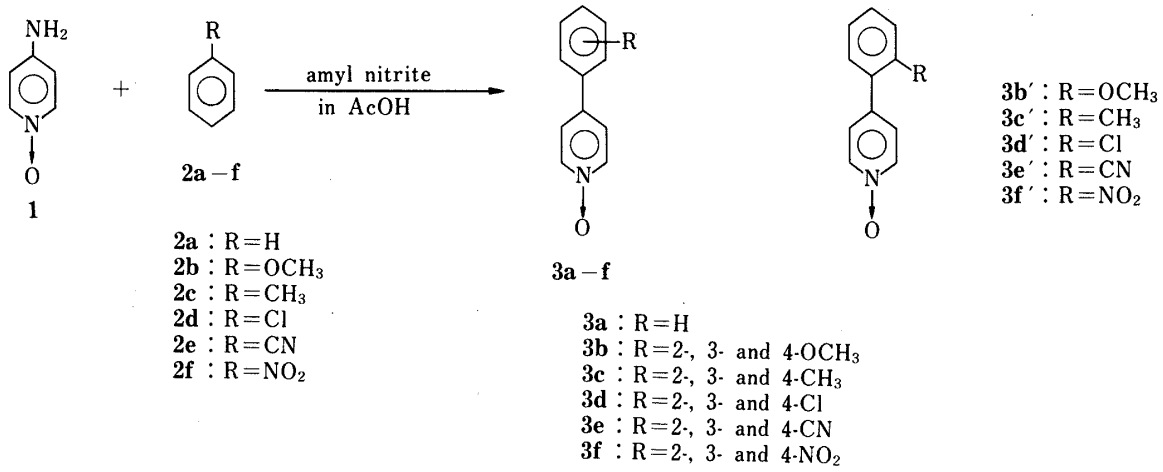
amyl nitrite afforded 3-phenylpyridine in 52% yield and Vernin *et al.*[3] reported that a similar reaction of 2-aminopyridine gave 2-phenylpyridine in 30—35% yield. However, there have been no reports on the pseudo-Gomberg reaction of 4-aminopyridine and aminopyridine 1-oxides. First, the reaction of 4-aminopyridine in benzene with amyl nitrite was attempted according to the procedure reported by Vernin *et al.*,[3] and it was found that this afforded 4-phenylpyridine in 41.3% yield. In order to examine the effect of a 1-oxide group on this reaction, the reaction of 4-aminopyridine 1-oxide (**1**) was carried out.

A mixture of 4-aminopyridine 1-oxide (1 mmol) and 1 ml of benzene in acetic acid was treated with 1.1 mmol of amyl nitrite under ice-cooling. The whole was stirred overnight at

room temperature, then the product was purified by chromatography on silica gel to afford 4-phenylpyridine 1-oxide (**3a**), mp 151—152 °C, as colorless needles in 73% yield. Its analytical values agreed with the empirical formula $C_{11}H_9NO$ and its infrared (IR), ^1H nuclear magnetic resonance (NMR) and mass spectra (MS) were consistent with the assigned structure.

When benzene alone was used as the solvent, the reaction did not proceed because of the complete insolubility of **1**. In ethanol or in dimethylformamide, the 1-oxido-4-pyridyl radical generated from **1** abstracted hydrogen from the solvent to form pyridine 1-oxide, so the yield of **3a** was very small. Thus, acetic acid was found to be the best solvent in this reaction.

Reaction of **1** with the benzene derivatives (**2b—f**) (R = OCH_3, CH_3, Cl, CN, NO_2) gave the corresponding arylation products (**3b—f**) in 39—85% yields as shown in Table II.



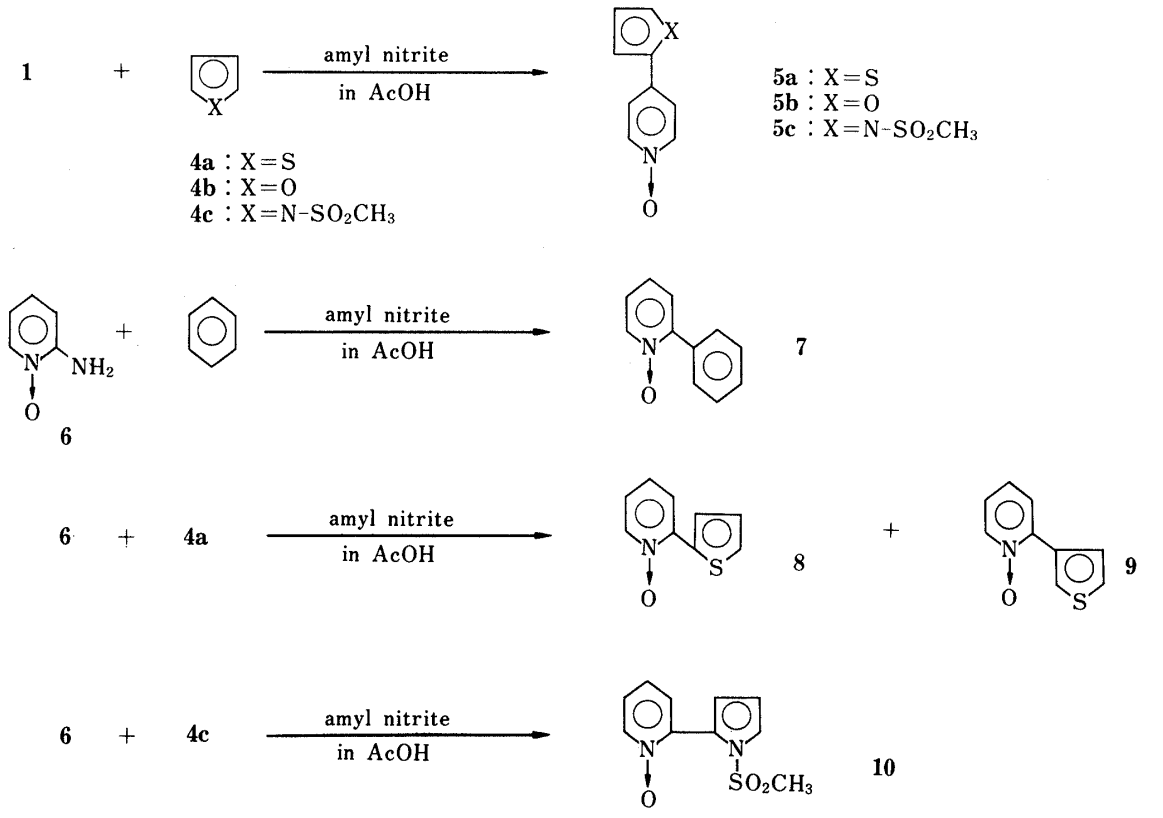
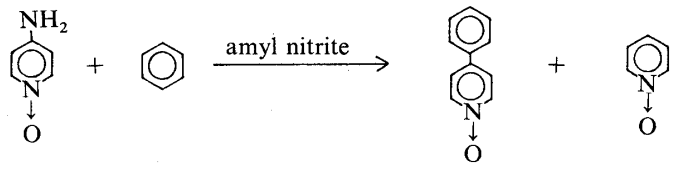


Chart 1

TABLE I. The Reaction of 4-Aminopyridine 1-Oxide with Benzene in Several Solvents



1 **3a**

Solvent	Reaction conditions	Yield (%)	
		3a	Pyridine *N*-oxide
AcOH	r.t., overnight	73.0	Trace
Benzene	r.t., overnight	Trace	—
EtOH	75 °C, 3 h	11.7	15.8
DMF	75 °C, 3 h	Trace	64.2

r.t.: room temperature.

TABLE II. The Yields of Products

Products	Yield (%)	Relative ratio			Isolated product and its yield (%)
		ortho	*meta*	*para*	
3a	73				
3b	85.3	77.0	11.3	11.7	**3b′** 62.1
3c	73	57.4	25.4	17.2	**3c′** 32.9
3d	52.3	59.3	20.9	19.8	**3d′** 29
3e	44.9	77.3	22.7		**3e′** 31.4
3f	39.3	38.2	18.6	43.2	**3f′** 13.2
5a	93.5				
5b	39.3				
5c	50				
7	20.9				

TABLE III. Relative Rates and Partial Rate Factors

Substances	Relative rate		Partial rate factors		
			K_o/K	K_m/K	K_p/K
2b	Ph-OCH_3 / Ph-H	$K=2.57$	5.94	0.87	1.80
2c	Ph-CH_3 / Ph-H	$K=1.42$	2.45	1.08	1.47
2d	Ph-Cl / Ph-H	$K=0.84$	1.49	0.53	1.00
2f	Ph-NO_2 / Ph-H	$K=0.11$	0.13	0.06	0.29

In the case of substituted benzene derivatives, as expected, formation of *ortho*, *meta*, and *para* isomers was observed. Attempts to separate the isomers completely did not succeed, but the *ortho* isomers (**3b′**—**f′**) were isolated in the pure state. The last column in Table II indicates

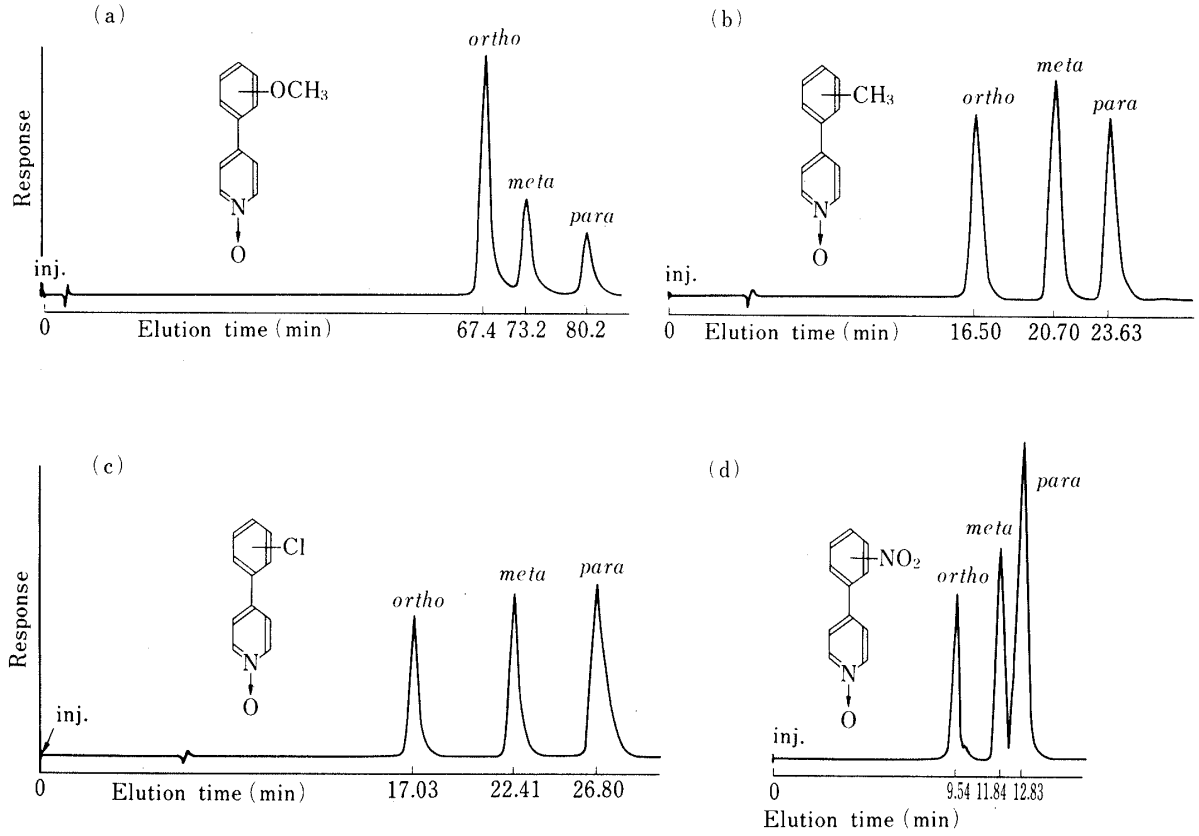


Fig. 1. HPLC Chromatogram of the Reaction Products of **1** with Substituted Benzene Derivatives

(a): column, TSK GEL LS-410 ODS SIL; flow rate, 0.83 ml/min; column size, 4 mm i.d. × 30 cm; pressure, 120 kg/cm^2; mobile phase, 3% THF–0.025 M PB (pH 2.2) +0.02 M HS; detector, UV 290 nm.

(b): column, TSK GEL LS-410 ODS SIL; flow rate, 0.5 ml/min; column size, 4 mm i.d. × 30 cm; pressure, 126 kg/cm^2; mobile phase, 30% CH_3CN–0.025 M Na_2HPO_4 +conc. H_3PO_4 (pH 2.2); detector, UV 310 nm.

(c): column, TSK GEL LS-410 ODS SIL; flow rate, 0.5 ml/min; column size, 4 mm i.d. × 30 cm; pressure, 126 kg/cm^2; mobile phase, 30% CH_3CN–0.025 M Na_2HPO_4 +conc. H_3PO_4 (pH 2.2); detector, UV 310 nm.

(d): column, TSK GEL LS-410 ODS SIL; flow rate, 0.7 ml/min; column size, 4 mm i.d. × 30 cm; pressure, 70 kg/cm^2; mobile phase, 25% CH_3CN–0.025 M Na_2HPO_4 +conc. H_3PO_4 (pH 2.2); detector, UV 300 nm.

the yields of the isolated *ortho* isomers.

Next, we tried to determine the ratio of *ortho*, *meta*, and *para* isomers formed in the reaction with substituted benzene derivatives by using gas chromatography (GC), but failed. Finally, separation by high-performance liquid chromatography (HPLC) (Fig. 1) was successful; the data are given as relative ratios in Table II. In order to explore the character of the 1-oxido-4-pyridyl radical **A**, the relative rates ($^{Ph-X}_{Ph-H}K$, X=OCH_3, CH_3, Cl, NO_2) of reaction with the 1-oxido-4-pyridyl radical **A** with benzene and four substituted benzene derivatives were determined according to a modification of the competitive technique described by Hey *et al.*[4,5] The experimental results are listed in Table III, and it is clear that the relative rates decrease with increasing electron-attracting effect. These results indicate that **A** has electrophilic character. A comparison of the orbital energies of the 1-oxido-4-pyridyl radical **A** and those of the substituted benzene derivatives (**2b—d, f**) (obtained by an INDO method) was in satisfactory agreement with the above conclusion. As demonstrated in Fig. 2, the HOMO of the 1-oxido-4-pyridyl radical **A** can interact more favorably with the HOMO of substituted benzene derivatives than with the LUMO.

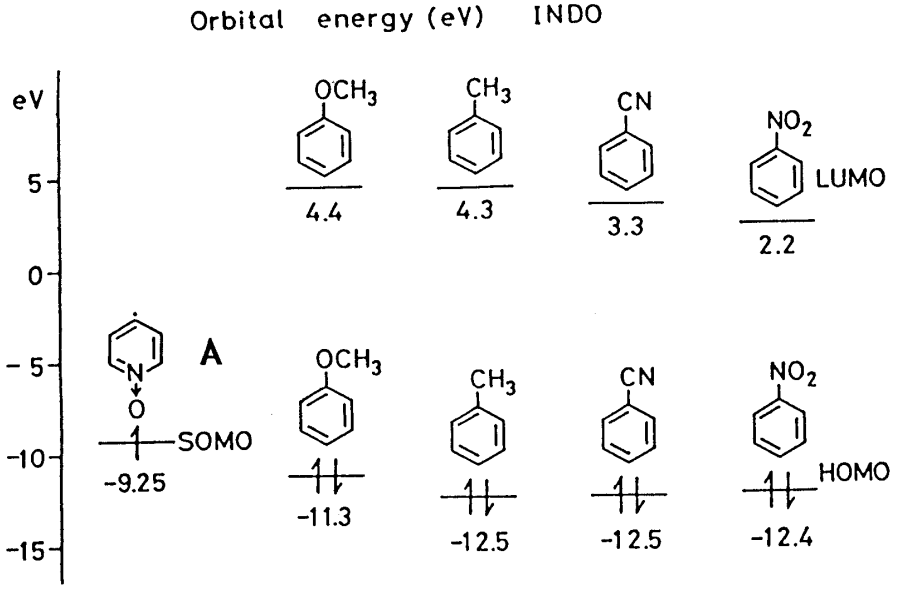


Fig. 2. Energies of the Frontier Orbitals of the 1-Oxido-4-pyridyl Radical A and Various Substituted Benzene Derivatives

TABLE IV. Spectral Data for the Products

Compounds	MS (M^+)	IR (cm^{-1}, Nujol)	NMR (δ, CF_3COOH)
3a	171	1240 (N→O)	8.77 (2H, d, J=7.0 Hz, Py-H_2, H_6) 8.23 (2H, d, J=7.0 Hz, Py-H_3, H_5) 7.88—7.62 (5H, m, Ph-H)
3b′	201	1250 (–OCH_3) 1225 (N→O) 1025 (–OCH_3)	8.67 (2H, d, J=7.0 Hz, Py-H_2, H_6) 8.28 (2H, d, J=7.0 Hz, Py-H_3, H_5) 7.69—7.48 (2H, m, Ph-H_3, H_6) 7.25—7.10 (2H, m, Ph-H_4, H_5) 3.96 (3H, s, –OCH_3)
3c′	185	1235 (N→O)	8.80 (2H, d, J=7.0 Hz, Py-H_2, H_6) 8.03 (2H, d, J=7.0 Hz, Py-H_3, H_5) 7.50—7.34 (4H, m, Ph-H) 2.43 (3H, s, –CH_3)
3d′	205 207	1230 (N→O)	8.83 (2H, d, J=7.0 Hz, Py-H_2, H_6) 8.17 (2H, d, J=7.0 Hz, Py-H_3, H_5) 7.64—7.24 (4H, m, Ph-H)
3e′	196	2283 (CN) 1241 (N→O)	8.96 (2H, d, J=7.0 Hz, Py-H_2, H_6) 8.28 (2H, d, J=7.0 Hz, Py-H_3, H_5) 7.74—8.10 (4H, m, Ph-H)
3f′	216	1524 (NO_2) 1358 (NO_2) 1245 (N→O)	8.86 (2H, d, J=7.0 Hz, Py-H_2, H_6) 8.37 (1H, dd, J=7.0 Hz, 2.0 Hz, Ph-H_3) 7.99 (2H, d, J=7.0 Hz, Py-H_3, H_5) 7.92—7.82 (2H, m, Ph-H_4, H_5) 7.52 (1H, dd, J=7.0 Hz, 2.0 Hz, Ph-H_6)
5a	177	1525 (C=C) 1240 (N→O) 705 (C–S–C)	8.18 (2H, d, J=7.3 Hz, Py-H_2, H_6) 7.47 (2H, d, J=7.3 Hz, Py-H_3, H_5) 7.45—7.38 (2H, m, thiophene-H_3, H_5) 7.13 (1H, dd, $J_{3,4}$=4.5 Hz, $J_{4,5}$=4.0 Hz, thiophene-H_4) (in $CDCl_3$)
5b	161	1233 (C–O–C or N→O) 1010 (C–O–C)	8.18 (2H, d, J=7.0 Hz, Py-H_2, H_6) 7.50 (2H, d, J=7.0 Hz, Py-H_3, H_5) 7.57—7.46 (1H, m, furan-H_5) 6.80 (1H, dd, $J_{3,4}$=4.0 Hz, J=1.0 Hz, furan-H_3)

TABLE IV. (continued)

Compounds	MS (M^+)	IR (cm^{-1}, Nujol)	NMR (δ, CF_3COOH)
			6.54 (1H, dd, $J_{4,3}=4.0$ Hz, $J_{4,5}=2.0$ Hz, furan-H_4) (in $CDCl_3$)
5c	238	1610 (C=N)	8.18 (2H, d, $J=7.3$ Hz, Py-H_2, H_6)
		1560 (C=C)	7.42 (2H, d, $J=7.3$ Hz, Py-H_3, H_5)
		1250 (N→O)	7.34 (1H, dd, $J_{3,5}=1.9$ Hz, $J_{4,5}=3.1$ Hz, Pyrr-H_5)
			6.49 (1H, dd, $J_{3,5}=1.9$ Hz, $J_{3,4}=3.2$ Hz, Pyrr-H_3)
			6.44 (1H, t, $J_{3,4}=3.2$ Hz, $J_{4,5}=3.1$ Hz, Pyrr-H_4) (in $CDCl_3$)
7	171	1245 (N→O)	8.82 (1H, d, $J=7.0$ Hz, Py-H_6)
			8.46 (1H, t, $J_{3,4}=8.0$ Hz, $J_{4,5}=8.0$ Hz, Py-H_4)
			8.08 (1H, dd, $J_{3,4}=8.0$ Hz, $J_{3,5}=2.0$ Hz, Py-H_3)
			7.96 (1H, t, $J_{4,5}=8.0$ Hz, $J_{5,6}=7.0$ Hz, Py-H_5)
			7.68—7.80 (5H, m, Ph-H)
8	177	1254 (N→O)	8.30 (1H, dd, $J_{5,6}=6.5$ Hz, $J_{4,6}=1.5$ Hz, Py-H_6)
		745 (C–S–C)	7.80—7.96 (2H, m, Py-H_4, H_5)
			7.54 (1H, dd, $J_{3,4}=5.0$ Hz, $J_{3,5}=1.3$ Hz, Py-H_3)
			7.02—7.38 (3H, m, thiophene-H) (in $CDCl_3$)
9	177	1280 (N→O)	8.83 (1H, dd, $J_{2,5}=3.1$ Hz, $J_{2,4}=1.3$ Hz, thiophene-H_2)
		760 (C–S–C)	8.29 (1H, dd, $J_{5,6}=6.2$ Hz, $J_{4,6}=1.8$ Hz, Py-H_6)
			7.58—7.70 (2H, m, Py-H_4, H_5)
			7.36 (1H, dd, $J_{4,5}=5.5$ Hz, $J_{2,5}=3.1$ Hz, thiophene-H_5)
			7.22 (1H, dd, $J_{3,4}=7.8$ Hz, $J_{3,5}=1.7$ Hz, Py-H_3)
			7.14 (1H, dd, $J_{4,5}=5.5$ Hz, $J_{2,4}=1.8$ Hz, thiophene-H_4) (in $CDCl_3$)
10	238	1604 (C=N)	8.22 (1H, m, Py-H_6)
		1567 (C=C)	7.22—7.40 (4H, m, Py-H_3, H_4, H_5, Pyrr-H_5)
		1245 (N→O)	6.36—6.44 (2H, m, Pyrr-H_3, H_4)

Partial rate factors derived from the ratios of isomers and relative rates are listed in Table III. Except in the case of nitrobenzene, the arylation rate factors appeared to increase in the order *meta*<*para*<*ortho*, as is the case with other aryl radicals.[6]

In view of the evidence that the 1-oxido-4-pyridyl radical is electrophilic, we examined its reaction with 5-membered heterocycles, so-called π-rich systems. Thiophene (**4a**), furan (**4b**) and 1-methanesulfonylpyrrole (**4c**) reacted smoothly to afford arylated products (**5a**—**c**) in 39.3—93.5% yields. It was noticeable that the reaction product with thiophene was obtained in a high yield 93.5% and substitution took place primarily at the 2-position of the heterocycles. The success in arylation of the pyrrole ring is very significant, because the intermolecular arylation of the pyrrole ring with aryl radicals derived from aromatic amines has not previously been reported. In the case of the reaction of pyrrole derivatives, 2- and 4-aminopyridine did not give good results.

2-Aminopyridine 1-oxide (**6**) also undergoes a similar reaction, although in a low yield. The reaction of **6** with benzene yielded 2-phenylpyridine 1-oxide (**7**) in 20.9% yield and that with **4a** gave two isomers, in contrast to the cases of 4-aminopyridine 1-oxide, 2-(2-thienyl)pyridine 1-oxide (**8**) and 2-(3-thienyl)pyridine 1-oxide (**9**), in 22.2 and 5.85% yields, respectively. 1-Methanesulfonylpyrrole was found to react to give 2-(1-methanesulfonyl-2-pyrrolyl)pyridine 1-oxide (**10**) in 34.9% yield.

In conclusion, the reaction of aminopyridine 1-oxide was found to proceed in higher yield than that of aminopyridine, especially in the reaction with 1-methanesulfonylpyrrole. The 1-

oxido-4-pyridyl radical is electrophilic and hence reacted smoothly with benzene derivatives having electron-donating groups and also with π-rich heterocycles.

The IR, ^{1}H-NMR and mass spectral data (Table IV) of the products were consistent with the proposed structures. Elemental analysis data were also satisfactory.

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO IR-E spectrometer. NMR spectra were measured with a JEOL PS-100 spectrometer at 100 MHz using tetramethylsilane (TMS) as an internal reference. MS were obtained on a JMS 01SG spectrometer. The preparative thin-layer chromatography (TLC) was performed on Kieselgel 60 PF_{245} (Merck, 20 × 20 cm).

General Procedure for Reaction of Aminopyridine 1-Oxide with Aromatic Hydrocarbons——A solution of 1.1 mol eq of amyl nitrite in an aromatic hydrocarbon (one volume) was added to a mixture of 1 mol eq of aminopyridine 1-oxide and hydrocarbon (10-fold excess by weight) and the whole was stirred overnight at room temperature. The solvent was distilled off under reduced pressure, 10% K_2CO_3 solution was added, and the mixture was extracted with CH_2Cl_2. The methylene dichloride was distilled off and the residue obtained was purified by chromatography.

Reaction of 4-Aminopyridine 1-Oxide (1) with Benzene in AcOH——A solution of 130 mg (1.1 mmol) of amyl nitrite in 1 ml of AcOH was added to a mixture of 110 mg (1 mmol) of **1** and 1.1 g of benzene in 20 ml of AcOH, and the whole was stirred overnight at room temperature. Evaporation of the solvent and extraction of the residue with CH_2Cl_2 gave the crude product, which was chromatographed on silica gel. 4-Phenylpyridine 1-oxide (**3a**) (125 mg) was obtained from the fraction eluted with CH_2Cl_2–MeOH (9 : 1). Recrystallization from diisopropyl ether gave colorless needles, mp 151—152 °C.

Reaction of 1 in a Large Excess of Benzene——A suspension of 110 mg of **1** in 3 ml of benzene was treated with 130 mg of amyl nitrite in 0.1 ml of benzene and the mixture was stirred overnight. After usual treatment, chromatography on silica gel gave 5 mg of **1** from the fraction eluted with CH_2Cl_2–MeOH (95 : 5).

Reaction of 1 with Benzene in EtOH——A mixture of 110 mg of **1**, 2 ml of EtOH and 2 ml of benzene was heated at 50 °C. To this solution, 130 mg of amyl nitrite in 0.1 ml of benzene was added, and stirring was continued for 3 h at the same temperature. After the reaction, the solvent was distilled off under reduced pressure. The residue was purified by preparative TLC. On development with the solvent system CH_2Cl_2–Me_2CO–MeOH (7 : 2 : 1), 20 mg (11.7%) of **1** was isolated from the fraction with Rf=0.40, and 15 mg (15.8%) of pyridine 1-oxide was isolated from the fraction with Rf=0.23.

Reaction of 1 with Benzene in DMF——Compound **1** (110 mg) was dissolved in 15 ml of DMF with heating, and 2 ml of benzene was added. Then, 130 mg of amyl nitrite in 0.2 ml of benzene was added. The mixture was stirred at 75 °C for 3 h; nitrogen gas was generated and the solution turned red. After usual treatment of the reaction mixture, separation as above gave 61 mg (64.2%) of pyridine 1-oxide and 4 mg of **1**.

Reaction of 1 with Anisole (2b)——Treatment of 330 mg of **1** and 3 g of anisole (**2b**) with amyl nitrite in AcOH, followed by chromatography on silica gel with CH_2Cl_2–MeOH (98 : 2—95 : 5) gave 514 mg (85.3%) of methoxyphenylpyridine 1-oxide mixture (**3b**). When this mixture was allowed to stand, crystals separated out. Further purification of the crystals by preparative TLC gave 374 mg (62.1%) of 4-(2-methoxyphenyl)pyridine 1-oxide (**3b'**) from the fraction with Rf=0.44 (CH_2Cl_2 : Me_2CO : MeOH = 7 : 2 : 1) as colorless needles (diisopropyl ether), mp 138—139.5 °C.

Reaction of 1 with Toluene (2c)——The usual work-up of 440 mg of **1** and 4 g of toluene (**2c**) with amyl nitrite in AcOH was carried out. Chromatographic separation on silica gel eluted with CH_2Cl_2–MeOH (98 : 2—95 : 5) gave 540 mg (73.0%) of methylphenylpyridine 1-oxide mixture (**3c**). Crystals that separated from the mixture were purified by preparative TLC. The fraction with Rf=0.44 (CH_2Cl_2 : Me_2CO : MeOH = 7 : 2 : 1) afforded 243 mg of 4-(2-methylphenyl)pyridine 1-oxide (**3c'**) as colorless needles, mp 126—128 °C (diisopropyl ether).

Reaction of 1 with Chlorobenzene (2d)——The usual treatment of 440 mg of **1** and 4 g of chlorobenzene (**2d**) with amyl nitrite was carried out as above. Chromatographic purification on silica gel gave 430 mg (52.3%) of chlorophenylpyridine 1-oxide (**3d**) from the fraction eluted with CH_2Cl_2–MeOH (97 : 3—95 : 5). Crystals that separated from the mixture were further purified by preparative TLC. The fraction with Rf=0.40 (CH_2Cl_2 : Me_2CO : MeOH = 7 : 2 : 1) gave 238 mg (29.0%) of 4-(2-chlorophenyl)pyridine 1-oxide (**3d'**) as colorless needles, mp 122—123 °C (diisopropyl ether).

Reaction of 1 with Nitrobenzene (2f)——The usual treatment of 330 mg of **1** and 3 g of nitrobenzene (**2f**) with amyl nitrite as above, followed by chromatographic separation on silica gel gave 255 mg (39.3%) of the mixture (**3f**) from the fraction eluted with CH_2Cl_2–MeOH (95 : 5). The initially eluted fraction was further purified by preparative TLC. The fraction with Rf=0.39 (CH_2Cl_2 : Me_2CO : MeOH = 7 : 2 : 1) gave 86 mg (13.2%) of 4-(2-nitrophenyl)pyridine 1-oxide (**3f'**) as yellow needles, mp 155—157 °C (benzene).

Reaction of 1 with Benzonitrile (2e)——The usual treatment of 330 mg of **1** and 3 g of benzonitrile (**2e**) with amyl nitrite as above and chromatographic separation on silica gel afforded 264 mg (44.9%) of the mixture (**3e**) from the

fraction eluted with CH_2Cl_2–MeOH (95 : 5). The initially eluted fraction was further purified by preparative TLC. The fraction with $Rf=0.42$ (CH_2Cl_2 : Me_2CO : MeOH = 7 : 2 : 1) gave 185 mg (31.4%) of 4-(2-cyanophenyl)pyridine 1-oxide (**3e'**) as colorless needles, mp 173—175 °C (benzene).

Reaction of 1 with Thiophene (4a)——The usual treatment of 220 mg of **1** and 2 g of thiophene (**4a**) with amyl nitrite as above, followed by chromatography on silica gel gave 331 mg (93.5%) of 4-(2-thienyl)pyridine 1-oxide (**5a**) as pale yellow needles, mp 182—185 °C (benzene), from the fraction eluted with CH_2Cl_2–MeOH (98 : 2).

Reaction of 1 with Furan (4b)——The usual treatment of 220 mg of **1** and 3 g of (**4b**) with amyl nitrite as above, followed by chromatography on silica gel with CH_2Cl_2–MeOH (98 : 2) gave 127 mg (39.5%) of 4-(2-furyl)pyridine 1-oxide (**5b**), mp 153—154 °C (diisopropyl ether), as colorless needles.

Reaction of 1 with 1-Methanesulfonylpyrrole (4c)——Amyl nitrite (300 mg) was added to a solution of 220 mg of **1** and 2.9 g of **4c** in 40 ml of AcOH with heating at 75 °C. Stirring was continued at the same temperature for 1 h, followed by usual treatment of the reaction mixture, and the CH_2Cl_2 extract was chromatographed on silica gel. **4c** (2.38 g) was recovered from the mixture, and the fraction eluted with hexane–CH_2Cl_2 (42 : 1) afforded 238 mg (50%) of 4-(1-methanesulfonyl-2-pyrrolyl)pyridine 1-oxide (**5c**) as colorless needles, mp 132—133 °C (diisopropyl ether).

Separation and Quantitative Determination of *ortho*-, *meta*- and *para*-Substituted Phenylpyridines by HPLC——Chromatographic conditions. Apparatus; Toyo Soda HLC-803A high-speed liquid chromatograph equipped with a ultraviolet monitor and a column of TSK GEL LS-410, 4 mm i.d. × 30 cm. Mobile phase, flow rate and pressure were as shown in Fig. 1.

Preparation of *meta*- and *para*-Substituted Phenylpyridine 1-Oxides. 4-(3-Methoxyphenyl)pyridine 1-Oxide——The diazonium solution prepared from 5 g of *meta*-anisidine and 2.8 g of $NaNO_2$ in a solution of 14.5 ml of conc. HCl and 10 ml of H_2O was added to 42 ml of pyridine at 40 °C during 2 h under stirring. Heating was continued for 1 h at 80 °C. After aq. NH_3 has been added to make the mixture alkaline, steam distillation was carried out to remove pyridine. The aqueous solution was extracted with benzene and the extract was purified by chromatography on alumina. The fraction eluted with benzene–CH_2Cl_2–Me_2CO (7 : 2 : 1) was further purified by preparative TLC. The fraction with $Rf=0.22$ (benzene : CH_2Cl_2 : Me_2CO = 7 : 2 : 1) gave 134 mg of 4-(3-methoxyphenyl)pyridine, which was oxidized with *meta*-chloroperbenzoic acid (MCPBA) (188 mg) in 10 ml of $CHCl_3$ for 6 d. Chromatographic separation on alumina gave 124 mg of 4-(3-methoxyphenyl)pyridine 1-oxide as colorless needles, mp 134—135 °C (diisopropyl ether), fraction eluted with CH_2Cl_2. *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.28; H, 5.61; N, 6.84. MS *m/e*: 201 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.79 (2H, d, $J=7.0$ Hz, Py–H_2, H_6), 8.24 (2H, d, $J=7.0$ Hz, Py–H_3, H_5), 7.70—7.29 (4H, m, Ph–H), 4.07 (3H, s, OCH_3).

4-(4-Methoxyphenyl)pyridine 1-Oxide——The coupling reaction using pyridine (83 ml), *para*-anisidine (10 g) and $NaNO_2$ (5.6 g) was carried out as above. The reaction product was purified by chromatography on silica gel. The fraction eluted with benzene–CH_2Cl_2–Me_2CO (7 : 2 : 1) was further purified by preparative TLC. The fraction with $Rf=0.17$ (benzene : CH_2Cl_2 : Me_2CO = 7 : 2 : 1) gave 162 mg of 4-(4-methoxyphenyl)pyridine, mp 94 °C (H_2O), as colorless plates. This compound was oxidized with 277 mg of MCPBA in 10 ml of $CHCl_3$ for 6 d. Chromatographic separation on alumina eluted with CH_2Cl_2 gave 100 mg of 4-(4-methoxyphenyl)pyridine 1-oxide, mp 116—117 °C (benzene), as colorless needles. *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.32; H, 5.65; N, 7.04. MS *m/e*: 201 (M^+). ^{1}H-NMR (CF_3COOH) δ: 8.67 (2H, d, $J=7.0$ Hz, Py–H_2, H_6), 8.16 (2H, d, $J=7.0$ Hz, Py–H_3, H_5), 7.86 (2H, d, $J=8.0$ Hz, Ph–H_2, H_6), 7.23 (2H, d, $J=8.0$ Hz, Ph–H_3, H_5), 4.04 (3H, s, $-OCH_3$).

4-(3-Methylphenyl)pyridine 1-Oxide——The coupling reaction using pyridine (80 ml), *meta*-toluidine (10 g) and $NaNO_2$ (6.4 g) was carried out as described in the case of *meta*-anisidine. The reaction product was purified by chromatography on silica gel. The fraction eluted with benzene–CH_2Cl_2–Me_2CO (7 : 2 : 1) was further purified by preparative TLC. The fraction with $Rf=0.29$ (benzene : CH_2Cl_2 : Me_2CO = 7 : 2 : 1) gave 295 mg of 4-(3-methylphenyl)pyridine, which was oxidized with MCPBA. Chromatography of the product on alumina with CH_2Cl_2 gave 240 mg of 4-(3-methylphenyl)pyridine 1-oxide, mp 127—129 °C (diisopropyl ether), as colorless needles. MS *m/e*: 185 (M^+). ^{1}H-NMR (CF_3COOH) δ: 8.84 (2H, d, $J=7.0$ Hz, Py–H_2, H_6), 8.18 (2H, d, $J=7.0$ Hz, Py–H_3, H_5), 7.66—7.48 (4H, m, Ph–H), 2.52 (3H, s, CH_3).

4-(4-Methylphenyl)pyridine 1-Oxide——The coupling reaction using pyridine (80 ml), *para*-toluidine (10 g) and $NaNO_2$ (6.4 g) was carried out as described in the case of *meta*-anisidine. The reaction product was chromatographed on silica gel. The fraction eluted with benzene–CH_2Cl_2–Me_2CO (7 : 2 : 1) was further purified by preparative TLC. The fraction with $Rf=0.25$, when developed with the same solvent system, gave 190 mg of 4-(4-methylphenyl)pyridine, which was also oxidized with MCPBA and chromatographed on alumina. The fraction eluted with CH_2Cl_2 gave 150 mg of 4-(4-methylphenyl)pyridine 1-oxide, mp 181—182 °C (diisopropyl ether), as colorless needles. MS *m/e*: 185 (M^+). ^{1}H-NMR (CF_3COOH) δ: 8.70 (2H, d, $J=7.0$ Hz, Py–H_2, H_6), 8.19 (2H, d, $J=7.0$ Hz, Py–H_3, H_5), 7.74 (2H, d, $J=8.0$ Hz, Ph–H_2, H_6), 7.46 (2H, d, $J=8.0$ Hz, Ph–H_3, H_5), 2.50 (3H, s, CH_3).

4-(3-Chlorophenyl)pyridine 1-Oxide——The coupling reaction using pyridine (57 ml), *meta*-chloroaniline (5 g) and $NaNO_2$ (2.7 g) was carried out as described in the case of *meta*-anisidine. The reaction product was chromatographed on silica gel. The fraction eluted with benzene–CH_2Cl_2–Me_2CO (7 : 2 : 1) was further purified by preparative TLC. The fraction with $Rf=0.28$ (same solvent system) gave 164 mg of 4-(3-chlorophenyl)pyridine, which was oxidized with MCPBA and chromatographed on alumina. The fraction eluted with CH_2Cl_2 gave 151 mg of

Table V. Elemental Analysis Data for the Products

Compounds	Formula	Analysis (%) Calcd (Found)		
		C	H	N
3a	$C_{11}H_9NO$	77.17	5.30	8.18
		(77.42	5.47	8.01)
3b′	$C_{12}H_{11}NO_2$	71.62	5.51	6.96
		(71.55	5.53	6.96)
3c′	$C_{12}H_{11}NO$	77.81	5.99	7.56
		(77.88	6.07	7.42)
3d′	$C_{11}H_8ClNO$	64.24	3.92	6.81
		(64.01	4.09	6.78)
3e′	$C_{12}H_8N_2O$	73.46	4.11	14.28
		(73.64	4.09	14.05)
3f′	$C_{11}H_8N_2O_3$	61.11	3.73	12.96
		(60.92	3.67	12.91)
5a	C_9H_7NOS	60.99	3.98	7.90
		(60.92	3.97	7.83)
5b	$C_9H_7NO_2$	67.07	4.38	8.69
		(67.01	4.40	8.45)
5c	$C_{10}H_{10}N_2O_3S$	50.43	4.23	11.57
		(50.26	4.22	11.72)
7	$C_{11}H_9NO$	77.17	5.30	8.18
		(76.74	5.22	8.25)
8	C_9H_7NOS	61.01	3.98	7.91
		(60.95	3.93	7.75)
9	C_9H_7NOS	61.01	3.98	7.91
		(61.15	4.02	7.63)
10	$C_{10}H_{10}N_2O_3S$	50.55	4.27	11.78
		(50.26	4.22	11.72)

4-(3-chrolophenyl)pyridine 1-oxide, mp 145—147 °C (diisopropyl ether), as colorless needles. MS *m/e*: 207 ($M^+ + 2$), 205 (M^+). ^{1}H-NMR (CF_3COOH) δ: 8.82 (2H, d, $J = 7.0$ Hz, Py–H_2, H_6), 8.22 (2H, d, $J = 7.0$ Hz, Py–H_2, H_6), 8.22 (2H, d, $J = 7.0$ Hz, Py–H_3, H_5), 7.78 (1H, s, Ph–H_2), 7.75—7.56 (3H, m, Ph–H).

4-(4-Chlorophenyl)pyridine 1-Oxide——The coupling reaction using pyridine (113 ml), *para*-chloroaniline (10 g) and $NaNO_2$ (5.4 g) was carried out as described in the case of *meta*-anisidine. The reaction product was chromatographed on silica gel. The fraction eluted with benzene–CH_2Cl_2–Me_2CO (7 : 2 : 1) was further purified by preparative TLC. The fraction with $Rf = 0.22$ (same solvent system) gave 219 mg of 4-(4-chlorophenyl)pyridine which was oxidized with MCPBA and chromatographed on alumina. The fraction eluted with CH_2Cl_2 gave 123 mg of 4-(4-chlorophenyl)pyridine 1-oxide, mp 166—168 °C (diisopropyl ether), as colorless needles. MS *m/e*: 207 ($M^+ + 2$), 205 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.23 (2H, d, $J = 7.0$ Hz, Py–H_2, H_6), 7.46 (2H, d, $J = 7.0$ Hz, Py–H_3, H_5), 7.48—7.43 (4H, m, Ph–H).

4-(3-Nitrophenyl)pyridine 1-Oxide——4-(3-Nitrophenyl)pyridine was prepared *via* nitration of 4-phenylpyridine and followed by separation of isomers (*o*-, *m*-, *p*-) according to the procedure reported by Pyman and Forsyth.[7] 4-(3-Nitrophenyl)pyridine (170 mg) was oxidized with MCPBA in $CHCl_3$ and the product was purified by chromatography on alumina. The fraction eluted with CH_2Cl_2 gave 150 mg of 4-(3-nitrophenyl)pyridine 1-oxide, mp 209—211 °C (benzene), as pale yellow needles. MS *m/e*: 216 (M^+). ^{1}H-NMR (CF_3COOH) δ: 8.95 (2H, d, $J = 7.0$ Hz, Py–H_2, H_6), 8.78 (1H, s, Ph–H_2), 8.58 (1H, d, $J_{4,5} = 8.0$ Hz, Ph–H_4), 8.38 (2H, d, $J = 7.0$ Hz, Py–H_3, H_5), 8.26 (1H, d, $J_{5,6} = 8.0$ Hz, Ph–H_6), 7.92 (1H, t, $J_{5,4} = 8.0$ Hz, $J_{5,6} = 8.0$ Hz, Ph–H_5).

4-(4-Nitrophenyl)pyridine 1-Oxide——4-(4-Nitrophenyl)pyridine was also prepared as above according to the procedure reported by Pyman and Forsyth.[7] 4-(4-Nitrophenyl)pyridine (200 mg) was oxidized with MCPBA in $CHCl_3$ and the product obtained was purified by chromatography on alumina. The fraction eluted with CH_2Cl_2 gave 180 mg of 4-(4-nitrophenyl)pyridine 1-oxide, mp 225—227 °C (benzene), as pale yellow needles. MS *m/e*: 216 (M^+). ^{1}H-NMR (CF_3COOH) δ: 8.93 (2H, d, $J = 7.0$ Hz, Py–H_2, H_6), 8.55 (2H, d, $J = 8.0$ Hz, Ph–H_3, H_5), 8.32 (2H, d, $J = 7.0$ Hz, Py–H_3, H_5), 8.04 (2H, d, $J = 8.0$ Hz, Ph–H_2, H_6).

Reaction of 2-Aminopyridine 1-Oxide (6) with Benzene in AcOH——A solution of 390 mg of amyl nitrite in 0.3 ml

of benzene was added to a solution of 330 mg (3 mmol) of **6** and 3 g of benzene in 6 ml of AcOH under ice-cooling. The mixture was stirred for 1 h, and the solvent was distilled off. A 10% K_2CO_3 solution was added and extract with CH_2Cl_2 was chromatographed on silica gel. The fraction eluted with CH_2Cl_2–MeOH (98 : 2) afforded 107 mg (20.9%) of 2-phenylpyridine 1-oxide **7** as colorless needles, mp 154 °C (diisopropyl ether).

Reaction of 6 with Thiophene (4a)——A solution of 1.3 g of amyl nitrite in 1 ml of thiophene was added to a solution of 1.1 g (10 mmol) of **6** and 10 g of thiophene. The solvent was distilled off, 10% K_2CO_3 solution was added to the residue, and the mixture was extracted with CH_2Cl_2. After evaporation of CH_2Cl_2, the residue was chromatographed on silica gel. The fraction eluted with CH_2Cl_2–MeOH (98 : 2) was further purified by preparative TLC. 2-(3-Thienyl)pyridine 1-oxide (**9**) (103 mg, 5.84%) was obtained from the fraction with Rf=0.45 (CH_2Cl_2 : Me_2CO : MeOH = 8 : 2 : 1) as pale orange needles, mp 118—119 °C (diisopropyl ether). 2-(2-Thienyl)pyridine 1-oxide (**8**) (393 mg, 22.2%) was obtained from the fraction with Rf=0.54 (CH_2Cl_2 : Me_2CO : MeOH = 8 : 2 : 1) as pale orange needles, mp 136—137 °C (diisopropyl ether).

Reaction of 6 with 1-Methanesulfonylpyrrole (4c)——A mixture of 220 mg (2 mmol) of **6** and 2.9 g of **4c** in 40 ml of AcOH was treated with 300 mg of amyl nitrite, with heating at 75 °C. Stirring was continued for 1 h. After usual treatment of the reaction mixture, the CH_2Cl_2 extract was purified by chromatography on silica gel. The fraction eluted with hexane–CH_2Cl_2 (2 : 1) gave 2.36 g of **4c** and that eluted with CH_2Cl_2–MeOH (65 : 1) gave 166 mg of 2-(1-methanesulfonyl-2-pyrrolyl)pyridine 1-oxide (**10**) as colorless needles, mp 182—183 °C (diisopropyl ether). The yield was 34.9%.

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References and Notes

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