mixed acetals were relatively unstable, isobutylene could be detected from its characteristic nmr signals, *i.e.*, δ 4.63 (septet, 1.1 Hz) and 1.64 (t, 1.1 Hz).

Diethyl Ether.—The reaction of ether under the same conditions as above gave a 43% yield of the mixed acetal MeCH(OEt)O-*t*-Bu. The crude product was short path distilled at 100° (bath) and 150-mm pressure and purified by preparative glc, δ (CCl_4) 1.11 (3 H, t, 7 Hz), 1.17 (3 H, d, 5 Hz), 1.19 (9 H, s), 3.43 (2 H, q, 7 Hz), and 4.84 (1 H, q, 5 Hz). Hydrolysis by dilute sulfuric acid gave acetaldehyde, ethanol, and *tert*-butyl alcohol.

Registry No.—3,4-Dichlorobenzyl phenyl ether, 33598-40-2; *tert*-butyl peroxide, 75-91-2.

Acknowledgments.—I thank Yap Chuan Hoe, Ong Lam Eng, and Miss Tan Chear Eng for some preliminary experiments.

Naphthyridine Chemistry. XIV. The Meisenheimer Reaction of the 1,X-Naphthyridine 1-Oxides

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The treatment of the 1,X-naphthyridine 1-oxides with phosphorus oxychloride affords the 2-, 3-, and 4-chloro-1,X-naphthyridines in varying amounts depending upon the position of the nonoxidized nitrogen atom. The 2-chloro compounds formed decrease from 0.60 to 0.13 mol ratio in the sequence 1,7-, 1,5-, 1,8-, 1,6-naphthyridine 1-oxide, while, in the same sequence, the 3-chloro isomers increases from 0.03 to 0.02 and the 4-chloro isomers from 0.37 to 0.67 mol ratio. Possible mechanisms to account for these changes are discussed.

Several recent papers[1-3] have described the results of studies of the Meisenheimer reaction on various naphthyridine *N*-oxides. In order to further delineate the effect that the position of the nonoxidized nitrogen atom has upon the product distribution in the naphthyridine 1-oxides when they are treated with phosphorus oxychloride, we have examined the behavior of the 1-oxides of 1,7- (**1**) and 1,8-naphthyridine (**2**).

When 1,7-naphthyridine 1-oxide (**1**) is treated with phosphorus oxychloride, a four-component mixture (as established by tlc and vpc) is obtained. Preparative scale vpc allows the separation of this mixture into three components. The compound with the shortest retention time is 1,7-naphthyridine (4% of the total reaction mixture); the second component (35% of the total reaction mixture) has a molecular formula of $C_8H_5N_2Cl$. The melting point of this material, as collected from the gas chromatograph, is 108–110°. Since the melting point for this compound, whose nmr spectrum is that expected for 4-chloro-1,7-naphthyridine, is 121–122°,[4] it appeared that we were dealing with a mixture. When this substance was twice sublimed and finally recrystallized from cyclohexane, its melting point was raised to that reported for the 4-chloro-1,7-naphthyridine (**3**). Thus, the material collected from the gas chromatograph is a mixture. In order to identify the component which "contaminated" the vpc peak, a sample of the crude reaction products was hydrolyzed with aqueous base in the anticipation that any 2- or 4-chloro-1,7-naphthyridine would be converted to the corresponding dihydro-oxo compounds, while any 3-chloro-1,7-naphthyridine that might be present would not be affected by these conditions.

In this fashion we obtained a two-component mixture consisting of 1,7-naphthyridine and 3-chloro-1,7-naphthyridine (**5**). The identity of these two products was established by comparison with authentic samples. It is of interest to note that the 3-chloro- and the 4-chloro-1,7-naphthyridines have the same retention times on several vpc columns and, consequently, the very minor amount of 3-chloro-1,7-naphthyridines formed in this reaction is not detectable in the presence of the substantial amounts of 4-chloro-1,7-naphthyridine formed. The amount of 3-chloro-1,7-naphthyridine obtained from this reaction could, consequently, not be directly calculated by an analysis of the vpc traces alone. The data presented in Table I are those obtained by taking this fact into account.

The third component (56% of the total reaction mixture) has a molecular formula of $C_8H_5N_2Cl$ and is identified as 2-chloro-1,7-naphthyridine (**4**) by an analysis of its nmr spectrum. This spectrum (Table II) shows the presence of one deshielded singlet (τ 0.61) and two AB patterns. The sizes of the coupling constants of the AB patterns (9.0 and 6.0 Hz, respectively) require that both of the systems involve coupling of protons on vicinal carbon atoms, thus establishing structure **4** as the correct one.

The fourth component, which appears as a very minor shoulder on the trailing edge of the peak due to the 2-chloro-1,7-naphthyridine, is estimated to correspond to 2% of the total reaction mixture. This material is neither 5-chloro-[5] nor 8-chloro-1,7-naphthyridine[6] by gc comparisons of these compounds with the unknown, and has not yet been identified.

In order to assure ourselves that neither the 2-chloro- (**4**) nor the 4-chloro-1,7-naphthyridine (**3**) is hydrolyzed during the aqueous work-up, we modified the usual procedure by utilizing methanol in place of water. When this was done, and the methanolic solution was heated with sodium methoxide until tlc no longer showed the presence of either the 2-chloro- or 4-chloro-1,7-naphthyridine (a total of 12 hr), we isolated a mixture of the 2- (**6**) and 4-methoxy-1,7-naphthyridines (**7**). An analysis of the nmr spectrum of this mixture showed that the ratio of 2- to 4-methoxy derivatives is

(1) W. W. Paudler and D. J. Pokorny, *J. Org. Chem.*, **36**, 1720 (1971).
(2) E. V. Brown and A. C. Plasz, *ibid.*, **32**, 241 (1967).
(3) Y. Kobayashi, I. Kumadaki, and M. Sata, *Chem. Pharm. Bull.*, **17**, 1045 (1969).
(4) J. G. Murray and C. R. Hauser, *J. Org. Chem.*, **19**, 2008 (1954).
(5) Prepared by Eisch chlorination of 1,7-naphthyridine: unpublished results.
(6) H. Rapoport and A. D. Batcho, *J. Org. Chem.*, **28**, 1753 (1963).

TABLE I

RELATIVE PROPORTIONS OF THE MEISENHEIMER REACTION PRODUCTS OF THE 1-OXIDES OF 1,7- AND 1,8-NAPHTHYRIDINES

	Substituent					
Reactant	Nil	2-Chloro	3-Chloro	4-Chloro	2-Methoxy	4-Methoxy
1,7-Naphthyridine 1-oxide (1)	4[a]	56[a]	3[a]	35[a]	63[b]	37[b]
1,8-Naphthyridine 1-oxide (2)		36	7	57	40[b]	60[b]

[a] These values were obtained by means of gc analysis. [b] These values were obtained from an analysis of the nmr spectrum of the reaction mixture and do not include the parent and 3-chloro isomers formed.

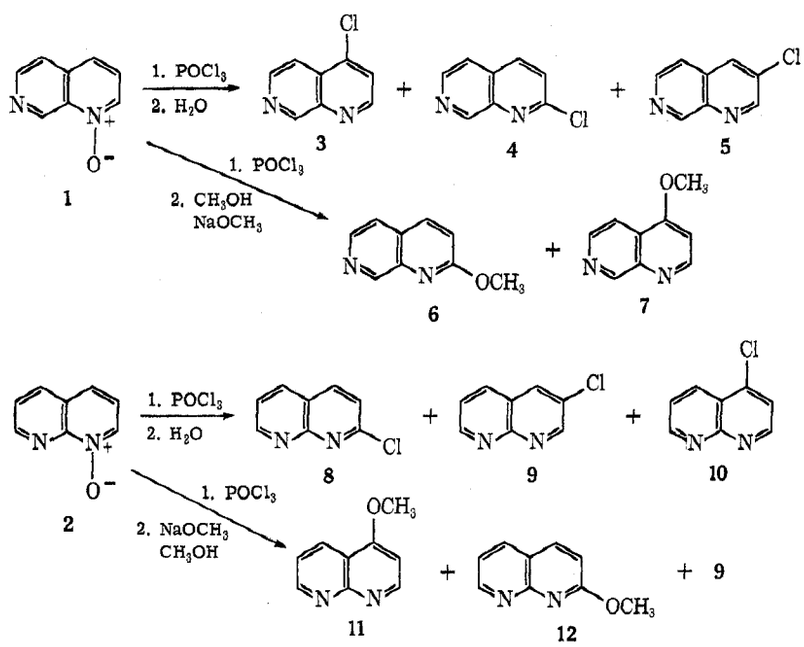
TABLE II

NMR SPECTRAL DATA OF SOME SUBSTITUTED 1,X-NAPHTHYRIDINES

	Chemical shifts, τ							Coupling constants, Hz					
Compound[a]	H_2	H_3	H_4	H_5	H_6	H_7	H_8	J_{23}	J_{24}	J_{34}	J_{56}	J_{57}	J_{67}
2-Chloro-1,7-naphthyridine (4)		2.48	1.94	2.40	1.39		0.61			9.0	6.0		
3-Chloro-1,7-naphthyridine (5)	1.14		1.93	2.46	1.41		0.56		2.0		5.5		
4-Chloro-1,7-naphthyridine (3)	1.12	2.34		2.02	1.28		0.46	5.0			6.0		
2-Methoxy-1,7-naphthyridine[b] (6)		2.98	2.11	2.51	1.55		0.78			8.8	5.5		
4-Methoxy-1,7-naphthyridine[c] (7)	1.21	3.17		2.11	1.44		0.57	5.0			6.0		
2-Chloro-1,8-naphthyridine (8)		2.53	1.84	1.78	2.49	0.89				8.5	8.0	2.0	4.4
3-Chloro-1,8-naphthyridine (9)	1.00		1.84	1.86	2.48	0.90			2.5		8.0	1.9	4.2
4-Chloro-1,8-naphthyridine (10)	0.98	2.42		1.41	2.40	0.82		4.8			8.5	2.0	4.2
2-Methoxy-1,8-naphthyridine[d] (11)		3.03	2.04	1.93	2.67	1.05				8.8	8.0	2.0	4.0
4-Methoxy-1,8-naphthyridine[e] (12)	1.10	3.24		1.48	2.59	0.95		5.0			8.0	2.0	4.0

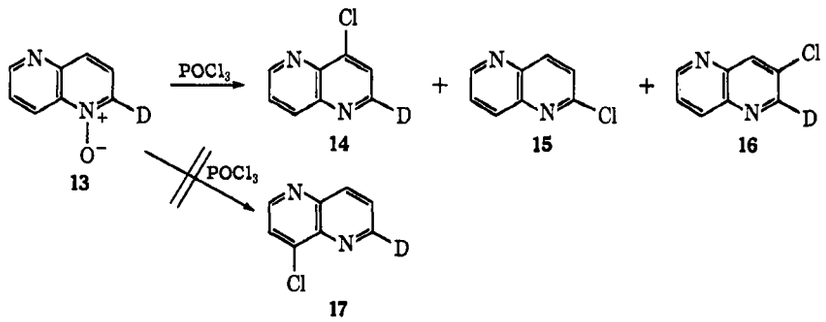
[a] Dilute solutions in $CDCl_3$. [b] $-OCH_3$, 5.96. [c] $-OCH_3$, 5.99. [d] $-OCH_3$, 6.01. [e] $-OCH_3$, 5.84.

SCHEME I



63:37%. Column chromatography afforded the 2-methoxy- (**6**) and the 4-methoxy-1,7-naphthyridines (**7**) in pure form. Thus, the results of the aqueous and the methanolic work-up procedures are identical, and none of the chloro compounds are hydrolyzed during the aqueous isolation procedure.

The treatment of 1,8-naphthyridine 1-oxide (**2**) and separation of the resulting mixture by column chromatography affords three pure components. In order of their elution they are 2-chloro- (**8**), 3-chloro- (**9**), and 4-chloro-1,8-naphthyridine (**10**) (36, 7, and 57%, respectively). The 2-chloro-1,8-naphthyridine (**8**) was identified by comparison with a sample obtained by an unequivocal synthesis (see Experimental Section). The 3-chloro-1,8-naphthyridine (**9**) was identified by its nmr spectrum (see Table I) and its stability to base. The 4-chloro-1,8-naphthyridine (**10**) was identified by an analysis of its nmr spectrum. The spectrum of the 4-chloro-1,8-naphthyridine (**10**) is typical of that expected for a 4-chloro-1,X-naphthyridine in that H_5 is considerably more deshielded (0.37 ppm) than the same proton in the corresponding naphthyridine itself. Furthermore, the 4-chloro- (**10**) as well as the 2-chloro-1,8-naphthyridine (**8**) are readily converted to their corresponding methoxy derivatives (**11** and **12**) by treatment with methanolic sodium methoxide (see Scheme I). In order to, again, make certain that none of the chloro compounds were hydrolyzed during the aqueous work-up, the isolation was modified, as described for the 1,7-naphthyridine instance, by replacing the water with methanol. Again, no change in the 2- (**8**) to 4-chloro-1,8-naphthyridine (**10**) product ratio was detected.



Discussion and Results

A comparison of the product distribution of the various 1,X-naphthyridine 1-oxides, upon treatment with phosphorus oxychloride, demonstrates that the location of the nonoxidized nitrogen atom has a ratio-reversing influence only in the case of the 1,7-naphthyridine, where the amount of 2 isomer (56%) formed predominates over that of the 4 isomer (35%).

The presence of a 6-nitrogen atom drastically increases the amount of 4-chloro (66%) with respect to the amount of 2-chloro (12%) isomer formed.[1] This decrease in the amount of 2-chloro isomer is counteracted by the formation of a substantial amount of 3-chloro-1,6-naphthyridine (20%). Since we have already shown[7] that electrophilic substitution of 1,6-naphthyridine affords 18% of the 3-substituted along with 23% of the 8-substituted isomer, and because no 8-chloro-1,6-naphthyridine is obtained in the Meisenheimer reaction of the 1,6-naphthyridine 1-oxide,[2] the generation of the 3-chloro-1,6-naphthyridine cannot be as a result of electrophilic substitution on some deoxygenated 1,6-naphthyridine 1-oxide in this reaction.

It is also highly improbable that electrophilic substitution would occur at the 3 position of 1,6-naphthyridine 1-oxide[8] or any phosphorylated derivative thereof. Thus, one is left with having to invoke either a free radical or a nucleophilic substitution process.[9]

In considering 1,5-naphthyridine 1-oxide, there exists the possibility that some of the 4-chloro-1,5-naphthyridine might be formed by substitution at C_8 in the 1,5-naphthyridine 1-oxide. In order to test this, we examined the Meisenheimer reaction on 2-deuterio-1,5-naphthyridine 1-oxide (**13**).

An analysis of the reaction products, in the manner described earlier,[1] established that the chlorine atoms in all of the monochloro-1,5-naphthyridines reside in the originally *N*-oxidized ring. Consequently, the 4:2 chloro-1,5-naphthyridine ratio is not artificially increased by halogenation at C_8 of the 1,5-naphthyridine 1-oxide (to form compound **17**).

A reasonable way to examine the various changes in isomer distribution is a comparison of the molar isomer ratios obtained in the different cases (see Table III).

(7) W. W. Paudler and T. J. Kress, *J. Org. Chem.*, **33**, 1384 (1968).

(8) In some, as yet unpublished work, we have found, for example, that bromination, under Eisch conditions, of 1,5-naphthyridine 1-oxide affords 7-bromo-1,5-naphthyridine 1-oxide.

(9) R. A. Abramovitch and G. M. Singer, *J. Amer. Chem. Soc.*, **91**, 5672 (1969), have suggested that the small amounts of 3-chloropyridine that are formed when pyridine *N*-oxide is treated with imidoyl chloride arise *via* the intermediacy of a 2,3-dihydropyridine derivative. This process cannot be significantly responsible for the differing amounts of 3-chloro-1,X-naphthyridines that are formed, since one would anticipate that the 3-chloro-1,5- and 3-chloro-1,7-naphthyridines should be formed in larger amounts than the 3-chloro isomers of the 1,6- and 1,8-naphthyridines.

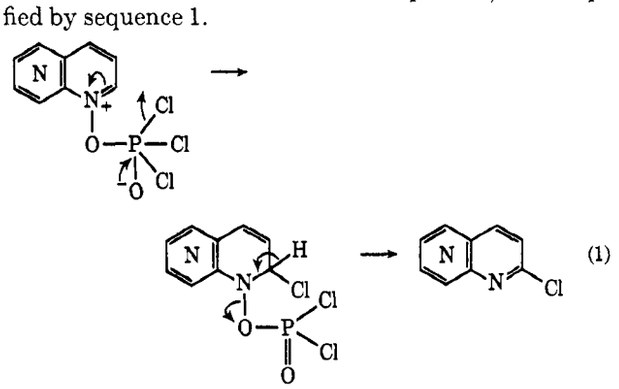
TABLE III
RELATIVE ISOMER RATIOS OF THE VARIOUS CHLORONAPHTHYRIDINES OBTAINED FROM THE MEISENHEIMER REACTION ON 1,X-NAPHTHYRIDINE 1-OXIDES

Compound	2-Chloro isomer	3-Chloro isomer	4-Chloro isomer
1,7-Naphthyridine	0.60	0.03	0.37
1,5-Naphthyridine[a,b]	0.42	0.03	0.55
1,8-Naphthyridine	0.36	0.07	0.57
1,6-Naphthyridine[a]	0.13	0.20	0.67

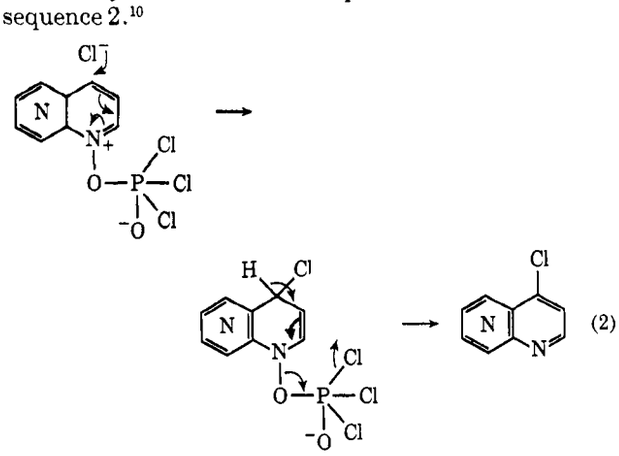
[a] See ref 1. [b] See ref 2.

These data clearly show that in the sequence 1,7-, 1,5-, 1,8-, 1,6-naphthyridine 1-oxides, decreasing amounts of the 2-chloro isomers are formed with concurrently increasing amounts of the 3-chloro and 4-chloro isomers.

The formation of the 2-chloro compounds is envisioned to occur *via* an *intramolecular* process, as exemplified by sequence 1.

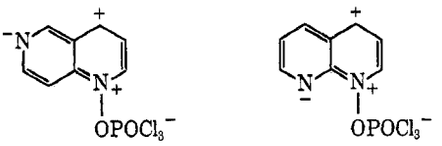


On the other hand, the 4-chloro isomers are probably formed by an *intermolecular* process as delineated in sequence 2.[10]



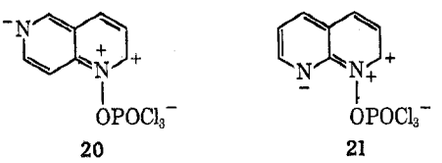
(10) Similar mechanisms have been proposed for the reaction of pyridine *N*-oxide with phosphorus pentachloride: J. Eisch and H. Gilman, *Chem. Rev.*, **57**, 561 (1957); R. A. Abramovitch and J. G. Saha, *Advan. Heterocycl. Chem.*, **6**, 229 (1966).

If we consider that the intermolecular process is readily facilitated by the presence of a nitrogen atom at either the 6 or 8 position because of some involvement of resonance contributors to the ground state such as **18** and **19**, we can account for the increased formation of



18 **19**

the 4-chloro isomers in these cases. The corresponding 2 isomer would not be formed by a similar involvement of the 2 position in light of the charge repulsions in the ground state resonance contributors such as exemplified by structures **20** and **21** that would be utilized in these instances.



20 **21**

The relatively high 4- to 2-chloro ratio in the 1,5-naphthyridine as compared to the 1,7-naphthyridine case may well be a matter of the inductive effect that the α-situated nonoxidized nitrogen atom has upon the C_4 position. This inductive effect certainly would be considerably less in evidence in the 1,7-naphthyridine, where the nonoxidized nitrogen atom is situated in a γ position with respect to C_4.

While these arguments, which involve the classical resonance and inductive considerations, account qualitatively for the observed changes in the isomer distribution in the Meisenheimer reaction of the 1,X-naphthyridine 1-oxides, it is not yet clear how these effects might be employed to explain the changes in the 3-chloro isomers that are formed. One is tempted, however, to suggest that, since the 3-chloro isomer amounts increase along with the 4-chloro isomers, there may well be a mechanistic relationship involved.

Experimental Section

The gas chromatograph used in these studies was an Aerograph Model A-90P-3 equipped with a Disc integrator. The pmr spectra were obtained with a Varian HA-100 instrument and are dilute (8%) solutions in $CDCl_3$ with TMS as internal standard. All column chromatography was done with Bio-Rad Laboratories neutral alumina grade III (Brockmann).

Preparation of 1,7-Naphthyridine 1,7-Dioxide.[11]—A solution containing 1,7-naphthyridine (1.3 g, 10 mmol), $NaWO_4 \cdot 2H_2O$ (0.1 g), and 30% H_2O_2 (10 ml) was heated at 55° for 6 hr. The excess peroxide was decomposed by the addition of activated MnO_2 (0.2 g) in portions to the ice-cold reaction mixture. After 2 hr the peroxide-free solution was filtered to remove MnO_2 and was evaporated to dryness under vacuum. The remaining solid was recrystallized, with clarification by charcoal, from absolute ethanol to afford yellow needles of 1,7-naphthyridine 1,7-dioxide: 1.3 g, 8.0 mmol, 80%; mp 273–275 dec, lit.[11] 275° dec.

Preparation of 1,7-Naphthyridine 1-Oxide from 1,7-Naphthyridine 1,7-Dioxide.[11]—A sample of 1,7-naphthyridine 1,7-dioxide (0.88 g, 5.4 mmol) was dissolved in hot methanol (400 ml). The cooled solution was transferred to a hydrogenation flask and nickel catalyst (0.9 g of Raney Nickel alloy treated with 50 ml of 20% NaOH for 2 hr at 100°) was added. The reduction was conducted at atmospheric pressure and was halted after an uptake of 160 ml (uncorrected) of hydrogen. The catalyst was removed by filtration and washed with methanol. The combined filtrate and washings were evaporated onto 5 g of alumina and placed on a chromatographic column (30 g of alumina) which had been prepared with anhydrous ether. The column was eluted with 700 ml of ether to afford 1,7-naphthyridine (0.18 g) followed by elution with 400 ml of chloroform to afford crude 1,7-naphthyridine 1-oxide (**1**), which was further purified by sublimation [100° (0.01 mm)] to give a white powder: 0.211 g, 1.4 mmol, 26%; mp 190–191°, lit.[11] 190–191°.

Meisenheimer Reaction of 1,7-Naphthyridine 1-Oxide (1).—The 1,7-naphthyridine 1-oxide (100 mg, 0.68 mmol) was added in portions to well-stirred, ice-cold, freshly distilled $POCl_3$ (10 ml). After 5 min at ice-bath temperature, the mixture was refluxed at 120° for 1 hr. The excess $POCl_3$ was removed *in vacuo*. A mixture of 20 g of ice and 20 ml of saturated $NaHCO_3$ solution was added to the ice-cold residue and the clear solution was extracted with 5 × 10 ml of cold methylene chloride. The dried (anhydrous Na_2CO_3) combined extracts were filtered and evaporated to dryness *in vacuo* to afford 38 mg of a pale yellow oil. Tlc (alumina–ether) revealed the presence of at least three components (visualized with I_2 vapor). Gas chromatography (20 ft × 3/8 in. aluminum column, packed with 20% SE-30 on Chromosorb W, column temperature 220°, flow rate 200 ml/min) showed the presence of 1,7-naphthyridine (10.2 min), 4-chloro- (13.6 min), 2-chloro- (15.1 min), and a shoulder (16.6 min). Preparative gc (same conditions as for analytical data) afforded samples of 4-chloro- (**3**) and 2-chloro-1,7-naphthyridine (**4**) as pure compounds, mp 122°, after two sublimations and a recrystallization from cyclohexane (lit.[4] 122°), mp 134–135°, respectively. The compounds in decreasing R_f value on neutral alumina with ether were **4**, **5**, **3**, and parent. The relative proportions of each compound as determined by integration of the gc traces and compared with artificial mixtures are shown in Table I.

Anal. Calcd for $C_8H_5N_2Cl$ (**4**): C, 58.37; H, 3.06; N, 17.02. Found: C, 58.22; H, 3.02; N, 16.93.

Identification of 3-Chloro-1,7-naphthyridine (5).—The Meisenheimer reaction of 1,7-naphthyridine 1-oxide (120 mg, 0.82 mmol) as described in the previous section was repeated and, after removal of the excess $POCl_3$, 20 ml of 10% NaOH solution was added to the residue and the mixture was refluxed for 12 hr. Continuous extraction of the resulting solution with CH_2Cl_2 for 12 hr and evaporation of the dried (anhydrous $MgSO_4$) extract afforded 3.3 mg of a mixture of 1,7-naphthyridine and 3-chloro-1,7-naphthyridine, as established by comparisons with authentic samples on tlc and vpc. Analysis of the vpc traces established that the mixture consisted of 61% 1,7-naphthyridine and 39% 3-chloro-1,7-naphthyridine, which corresponds to 4 and 3%, respectively.

Preparation of 4-Methoxy-1,7-naphthyridine (7).—A solution of 4-chloro-1,7-naphthyridine[4] (140 mg, 0.85 mmol) in 50 ml of methanol containing sodium methoxide (0.5 g) was refluxed for 8 hr. Evaporation of the methanol afforded a residue which was dissolved in water and continuously extracted with chloroform. The chloroform extract was dried (anhydrous $MgSO_4$), filtered, and evaporated to dryness. The remaining oil was sublimed [70° (0.1 mm)] to afford white crystalline **7** (34.2 mg, 0.21 mmol, 25%; mp 92–94°).

Anal. Calcd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.19; H, 5.28; N, 17.27.

Formation of 2-Methoxy- and 4-Methoxy-1,7-naphthyridine.—A sample of compound **1** (200 mg, 1.37 mmol) was treated with $POCl_3$ and worked up, as above, with the exception that sodium methoxide (0.1 g) in methanol (50 ml) was added to the residue in place of the ice and $NaHCO_3$ solution. The solution thus obtained was refluxed for 12 hr and evaporated to dryness. The residue was dissolved in water and continuously extracted with chloroform. The chloroform extract was dried with anhydrous $MgSO_4$, filtered, and evaporated to dryness to afford 132 mg of a pale orange oil. Tlc (alumina–ether) shows the presence of two components. Integration of the nmr spectrum of the oil as a solution in $CDCl_3$ revealed the composition of the mixture (Table I). The chloroform solution of the product mixture was evaporated onto 3 g of alumina and the residue was placed on top of an alumina-packed (60 g) chromatographic column using anhydrous distilled hexane. Elution with 1:1 ether–hex-

(11) This procedure affords higher yields than the previously reported one: W. W. Paudler, D. J. Pokorny, and S. J. Cornrich, *J. Heterocycl. Chem.*, **7**, 291 (1970).

ane (300 ml) afforded, after evaporation and sublimation of the residue [70° (0.1 mm)], 2-methoxy-1,7-naphthyridine (6): 42 mg; mp 52–54°. Further elution with pure ether gave 4-methoxy-1,7-naphthyridine (7) (28 mg; mp 92–94°) after evaporation and sublimation [70° (0.1 mm)] of the residue.

Anal. Calcd for $C_9H_8N_2O$ (6): C, 67.48; H, 5.03; N, 27.49. Found: C, 67.30; H, 5.17; N, 17.45.

Preparation of 2-Chloro-1,8-naphthyridine (8).—To a Carius tube was added 1-methyl-2-keto-1,2-dihydro-1,8-naphthyridine[12] (0.3 g, 1.87 mmol) and $POCl_3$ (25 ml). The tube was sealed and heated in an oven at 180° for 24 hr. The reaction mixture was treated in the same fashion as that described for the Meisenheimer reaction of 2. The solid (0.1 g) that was obtained was sublimed twice [85° (0.10 mm)], affording white crystals (86 mg, 28%, mp 135–136°).

Anal. Calcd for $C_8H_5N_2Cl$: C, 58.37; H, 3.06; N, 17.02. Found: C, 58.25; H, 3.17; N, 17.32.

Meisenheimer Reaction of 1,8-Naphthyridine 1-Oxide (2).—This reaction was carried out in the same manner as that of compound 1 with $POCl_3$. In this reaction 1,8-naphthyridine 1-oxide[1] (500 mg, 3.42 mmol) yielded a semisolid material (471 mg). Tlc (alumina–ether) indicates the presence of three components. The integration of the pmr spectrum of the crude reaction mixture permits the determination of the relative amounts of 2-chloro- (8) and 4-chloro-1,8-naphthyridine (10) (see Table I). The mixture of chloro compounds was evaporated onto alumina (5 g) and placed onto a chromatographic column (30 g of alumina) prepared with ether. Elution with ether afforded 2-chloro-1,8-naphthyridine (8) which melted at 135–136° after sublimation [85° (0.10 mm)]. Further elution with 1:1 chloroform–ether afforded a small amount of the 3-chloro isomer contaminated with the 4-chloro isomer. Finally, elution with chloroform afforded 4-chloro-1,8-naphthyridine (10). Recrystallization from cyclohexane gave white needles (mp 62–64°).

The amount of 3-chloro-1,8-naphthyridine (9) formed in the reaction was determined in the following manner. The reaction mixture from 500 mg of compound 2, after removal of excess $POCl_3$, was refluxed with 50 ml of 10% NaOH solution for 6 hr. The resulting solution was continuously extracted with chloroform and the chloroform extracts were dried with anhydrous $MgSO_4$, filtered, and evaporated to dryness affording crude 9. Sublimation [80° (0.10 mm)] afforded pure 3-chloro-1,8-naphthyridine (33 mg, mp 143–144°). This amount represents 7% of the total products formed.

Anal. Calcd for $C_8H_5N_2Cl$: C, 58.37; H, 3.06; N, 17.02. Found for 9: C, 58.35; H, 3.11; N, 17.27. Found for 8: C, 58.10; H, 3.27; N, 16.80.

Formation of 2-Methoxy- (12) and 4-Methoxy-1,8-naphthyridine (11).—In order to ascertain that hydrolysis of neither the 2-chloro- nor the 4-chloro-1,8-naphthyridine occurred during the work-up, the procedure was modified in the following manner. The crude product mixture from compound 2 obtained by removal of the excess $POCl_3$ was refluxed with 70 ml of methanol containing 1 g of CH_3ONa. After removal of the methanol and addition of water, the solution was continuously extracted with chloroform. The extracts were dried, filtered, and evaporated to dryness. The pmr spectrum of the product mixture was employed to obtain the relative percentages of the 2-methoxy and 4-methoxy isomers. Tlc (alumina, 7 drops; 3 ml of NeOH–EtOAc) shows three components. These compounds in order of their decreasing R_f values are 12, 9, and 11. Column chromatography of the mixture afforded 2-methoxy-1,8-naphthyridine (12) (53–55°, sublimed) and 4-methoxy-1,8-naphthyridine (11) (oil; picrate 183–185°).

Anal. Calcd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.40; H, 5.31; N, 17.69. Calcd for $C_{15}H_{11}N_5O_8$: C, 46.28; H, 2.85; N, 17.99. Found: C, 46.00; H, 3.08; N, 17.71.

Preparation of 2-Deuterio-1,5-naphthyridine 1-Oxide (13).—A sample of 1,5-naphthyridine 1-oxide[1] (0.5 g) was dissolved in 5 ml of 2.4 *N* NaOD in D_2O. After being stirred at room temperature for 12 hr, the solution was continuously extracted with chloroform, evaporated to dryness, and dried under vacuum, affording a sample (0.49 g) of compound 13. The nmr spectrum revealed that H_2 had been completely replaced by deuterium. This material was used without further purification in the Meisenheimer reaction.[1]

3-Chloro-4-hydroxy-1,7-naphthyridine Hydrochloride (22).—To a solution of 292 mg (2.0 mmol) of 4-hydroxy-1,7-naphthyridine[4] in 0.4 ml of acetic anhydride and 2.4 ml of acetic acid was added 0.2 ml of SO_2Cl_2.[13] The mixture containing a yellow precipitate was heated on a steam bath for 30 min. To the cooled solution was added 15 ml of dry ether and the precipitated solid was collected and washed with ether. The sample was dried under vacuum at 100° for 1 hr to afford the hydrochloride salt of 3-chloro-4-hydroxy-1,7-naphthyridine (400 mg, 1.85 mmol, 93%). A sample was recrystallized from acetic acid to afford the pure compound: mp 271–272 dec; nmr (in deuteriotrifluoroacetic acid) τ 1.32 (H_2, s), 1.27 (H_5, d), 1.05 (H_6, d), 0.20 (H_8, s, J_{56} = 6.0 Hz).

Anal. Calcd for $C_8H_6N_2OCl_2$: C, 44.24; H, 2.79; N, 12.91. Found: C, 43.97; H, 2.93; N, 13.20.

3,4-Dichloro-1,7-naphthyridine (23).—A solution of 375 mg (1.73 mmol) of compound 22 in 20 ml of freshly distilled $POCl_3$ was heated under reflux for 2 hr. The excess $POCl_3$ was removed *in vacuo* and an ice-cold saturated aqueous solution of $NaHCO_3$ (50 ml) was added to the chilled residue. The white precipitate that formed was extracted with $CHCl_3$ (3 × 75 ml). The dried combined extracts were evaporated to dryness to yield orange crystals (250 mg). A solution of this material in $CHCl_3$ was passed through a column of alumina and the eluate was evaporated to dryness. The remaining solid was sublimed to afford 23: 210 mg, 1.06 mmol, 61%; mp 125–127°; nmr ($CDCl_3$) τ 1.20 (H-2, s), 2.17 (H-5, d), 1.35 (H-6, d), 0.60 (H-8, s, J_{56} = 6.0 Hz).

Anal. Calcd for $C_8H_4N_2Cl_2$: C, 48.27; H, 2.03; N, 14.08. Found: C, 48.01; H, 2.27; N, 13.97.

3-Chloro-1,7-naphthyridine (45).—To a solution of 3,4-dichloro-1,7-naphthyridine (200 mg, 1.0 mmol) in 45 ml of ethanol was added 0.8 ml of 95% hydrazine and the solution was stirred for 18 hr. The precipitated analytically pure hydrochloride salt of 3-chloro-4-hydrazino-1,7-naphthyridine (80 mg, mp 200° dec) was removed by filtration and washed with a small amount of cold ethanol. Tlc (alumina; 1:1 hexane–ether) indicated that all of the starting material had been consumed. The filtrate was evaporated to dryness and the residue was dried under vacuum [100° (0.1 mm), 30 min], affording an additional sample of product: 125 mg, mp 190°, total yield 89%; nmr (in deuteriotrifluoroacetic acid) τ 1.20 (H_2, 5), −0.92 (H_2, d), 1.17 (H_6, d), 0.06 (H_8, s, J_{56} = 7 Hz).

Anal. Calcd for $C_8H_8N_4Cl_2$: C, 41.58; H, 3.49; N, 24.25. Found: C, 42.67; H, 3.30; N, 24.26.

The above sample (200 mg, 0.86 mmol) was dissolved in 40 ml of water containing 2 ml of acetic acid and heated to its boiling point. To this boiling solution was added in portions a hot solution of 1 g of $CuSO_4 \cdot 5H_2O$ in 10 ml of water. The resulting mixture was then heated at the boiling point for 5 min, cooled, and made basic with 50% aqueous NaOH. The mixture was then continuously extracted (8 hr) with $CHCl_3$ and the extracts were concentrated to a small volume (2 ml). This solution was used for preparative gas chromatography (some conditions as above) to separate the 3-chloro-1,7-naphthyridine from traces of 1,7-naphthyridine. In this fashion 38 mg of product was isolated and sublimed [100° (0.10 mm)] to afford pure 3-chloro-1,7-naphthyridine (35 mg, 24%, mp 88–89°).

Anal. Calcd for $C_8H_5N_2Cl$: C, 58.37; H, 3.06; N, 17.02. Found: C, 58.14; H, 2.95; N, 16.80.

Registry No.—1, 27305-52-8; 2, 27284-59-9; 3, 16287-97-1; 4, 35192-05-3; 5, 35170-89-9; 6, 35170-90-2; 7, 35170-91-3; 8, 15936-10-4; 9, 35170-93-5; 10, 35170-94-6; 11, 35171-00-7; 11 picrate, 35170-95-7; 12, 15936-12-6; 22, 35170-97-9; 23, 35170-98-0; 3-chloro-4-hydrazino-1,7-naphthyridine hydrochloride, 35170-99-1.

(12) W. W. Paudler and T. L. Kress, *J. Heterocycl. Chem.*, **5**, 561 (1968).

(13) A. R. Surrey and R. A. Cutler, *J. Amer. Chem. Soc.*, **68**, 2570 (1946).