these cases of substituted imines.[9,10] Even though rapid isomerization is operative, the assignment of product distribution by pmr chemical shifts is attainable since the minor isomer must subject the N–CH_3 protons to the strongly shielding effect of the aromatic ring,[11] whereas the chemical shift of the N–CH_3 for the major *E* isomer will closely resemble the unsubstituted case **1e**.

Previously, it has been established *via* ^{13}C carbonyl chemical shifts of substituted acetophenones that ortho substituents induce twisting of the acetyl group from the plane of the aromatic ring by steric inhibition of resonance.[12] Since this deviation from coplanarity exists in the parent ortho-substituted ketones, the corresponding *N,N*-dimethylhydrazones (**1a–d**) should also deviate from planarity by a comparable degree, thus minimizing the proximate steric crowding caused by the ortho substituent. Removal of partial resonance stabilization associated with the aryl group allows the ketone derivatives to exist in both *E* and *Z* configurations, as in *N,N*-dimethylhydrazones of simple dialkyl ketones.[6b] Such steric interactions are not indicated for the 16 meta- and para-substituted acetophenone *N,N*-dimethylhydrazones which exist in the more stable *E* configuration, and in these cases neither heat nor treatment with acid gave evidence for the presence of the *Z* configuration.

The quaternization of **1a** with methyl iodide by standard procedures gave rise to an oil, which upon crystallization from ethanol–ethyl acetate yielded the (*E*)-2′-methoxyacetophenone *N,N,N*-trimethylhydrazonium iodide. The mother liquor was subsequently concentrated and the residue was recrystallized several times from enthanol at −70° giving the corresponding (*Z*)-methiodide. The nmr spectra are again useful in verifying both the structure and purity; the *Z* and *E* $-N^+(CH_3)_3$ moieties are evidenced by singlets at 3.29 and 3.61 ppm, which can easily be assigned to the *Z* and *E* isomers, respectively. The abnormally high field resonance is assigned to the nearly orthogonal group *Z* to the aromatic ring, while the more downfield absorption is assigned to the (*E*)-trimethylamine moiety. Neither of these methiodides isomerize upon heating at moderate temperatures but do hydrolyze slowly in aqueous media; thus the covalent bonding of the dimethylamino unshared electrons prevented their assistance in the geometrical isomerization.

The rapid geometric isomerization of these hydrazones adequately explains the fact that the *o*-haloacetophenone *N,N*-dimethylhydrazones give quantitatively 1,3-dimethyl-1*H*-indazole[2,13] after standing for several days at room temperature or heating in a sealed tube at 120° for several hours. The irreversible internal nucleophilic displacement possible only through the *Z* orientation would easily deplete the *E* isomer in this equilibrium mixture by converting it to the cyclized product, followed then by the elimination of methyl halide.[14]

(9) A. Mannschreck and U. Koelle [*Tetrahedron Lett.*, 963 (1967)] have recently suggested that the dipolar resonance structure a contributes to the ground state of dimethylhydrazones.

$$>C{=}NN(CH_3)_2 \longleftrightarrow >\bar{C}N{=}\overset{+}{N}(CH_3)_2$$
a

(10) The lateral-shift (inversion) mechanism *vs.* the rotational mechanism has been recently reviewed by Kessler [*Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970)].

(11) L. M. Jackman and S. Sternhall, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, pp 94–98.

(12) K. S. Dhami and J. B. Stothers, *Tetrahedron Lett.*, 631 (1964); *Can. J. Chem.*, **43**, 479 (1965).

(13) (a) E. Fischer and J. Tafel, *Justus Liebigs Ann. Chem.*, **227**, 303 (1885); (b) K. V. Auwers and M. Duesberg, *Ber.*, **53**, 1179 (1920).

Experimental Section[15]

The ortho-substituted acetophenone *N,N*-dimethylhydrazones were prepared according to the procedure described previously.[2] All spectral properties and microanalyses of the compounds were consistent with the assigned structures.[2]

(*Z*)- and (*E*)-2′-Methoxyacetophenone *N,N,N*-Trimethylhydrazonium Iodide.—A solution of 2′-methoxyacetophenone *N,N*-dimethylhydrazone [10 g, 52 mmol, bp 65–66° (0.1 mm)] and methyl iodide (20 g) in absolute ethanol (100 ml) was stirred under nitrogen for 2 days. The solvent was removed *in vacuo* affording a pale yellow semisolid which when washed with anhydrous ether gave the crude crystalline methiodide (14.2 g, 42.5 mmol) in 82% yield, mp 120–146°.

The crude methiodide was recrystallized twice from ethanol–ethyl acetate (2:1) yielding predominately the *E* isomer (4.2 g) as white needles: mp 158–159° dec; ir (KBr) 1628, 723 cm^{-1} (C=N); nmr (D_2O) δ 2.72 (s, CCH_3, 3 H), 3.61 (s, $N^+(CH_3)_3$, 9 H), 3.89 (s, $C_{arom}OCH_3$, 3 H), *ca.* 7.2 ppm (C_{arom}H, complex, 4 H).

Anal. Calcd for $C_{12}H_{19}N_2OI$: C, 43.12; H, 5.73; N, 8.38. Found: C, 43.06; H, 5.71; N, 8.18.

The mother liquor was concentrated *in vacuo* and recrystallized four times from absolute ethanol at −70° giving analytically pure the *Z* isomer: mp 140–141° dec; ir (KBr) 1640, 750 cm^{-1} (C=N); nmr (D_2O) δ 2.32 (s, CCH_3, 3 H), 3.29 (s, $N^+(CH_3)_3$, 9 H), 3.89 (s, $C_{arom}OCH_3$, 3 H), *ca.* 7.3 (C_{arom}H, 4 H).

Anal. Calcd for $C_{12}H_{19}N_2OI$: C, 43.12; H, 5.73; N, 8.38. Found: C, 43.10; H, 5.68; N, 8.43.

Registry No.—(*E*)-**1a**, 28541-35-7; (*Z*)-**1a**, 28541-36-8; (*E*)-**1b**, 28541-37-9; (*Z*)-**1b**, 28541-38-0; (*E*)-**1c**, 28541-39-1; (*Z*)-**1c**, 28541-40-4; (*E*)-**1d**, 28541-41-5; (*Z*)-**1d**, 28541-42-6; (*E*)-**1e**, 28541-43-7; (*Z*)-**1e**, 28541-44-8; (*Z*)-2′-methoxyacetophenone *N,N,N*-trimethylhydrazonium iodide, 28541-45-9; (*E*)-2′-methoxyacetophenone *N,N,N*-trimethoxyhydrazonium iodide, 28541-46-0.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(14) Other examples of similar geometrical isomerizations are known. See W. Borsche and W. Schriba, *Justus Liegibs Ann. Chem.*, **541**, 283 (1939), and W. Borsche and A. Herbert, *ibid.*, **546**, 293 (1941).

(15) Melting points were determined in sealed capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were measured in carbon tetrachloride solution with tetramethylsilane as the internal standard on a Varian A-60 instrument. Microanalyses were performed by Spang Microanalytic Laboratory, Ann Arbor, Mich.

Naphthyridine Chemistry. XIII. The Meisenheimer Reaction of the 1,5- and 1,6-Naphthyridine 1-Oxides

WILLIAM W. PAUDLER* AND DAVID J. POKORNY

Clippinger Laboratories, Department of Chemistry, Ohio University, Athens, Ohio 45701

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The Meisenheimer reaction of the 1,5-naphthyridine mono- and di-*N*-oxides has been reported[1,2] to afford

(1) E. V. Brown and A. C. Plasz, *J. Org. Chem.*, **32**, 241 (1967).

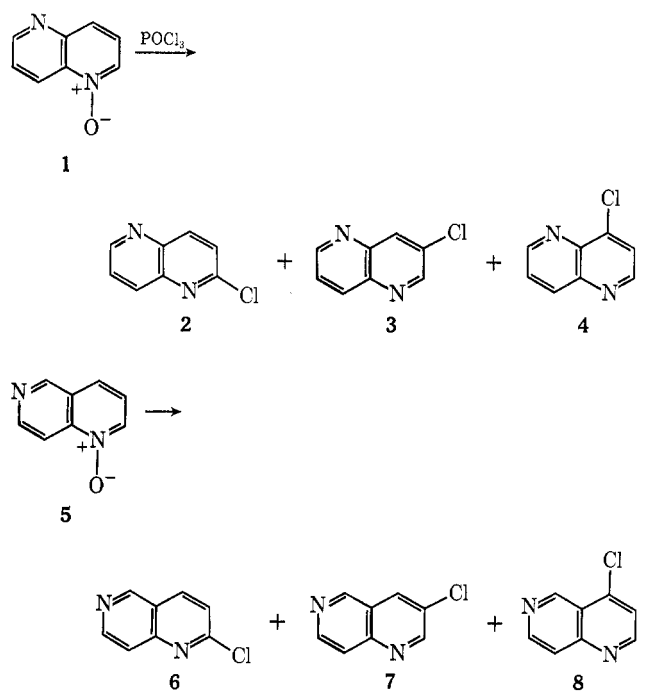
(2) E. P. Hart, *J. Chem. Soc.*, 1879 (1954).

the 2- (2) and 4-chloro-1,5-naphthyridine (4) from the mono-*N*-oxides 1 and the 2,6-dichloro-1,5-naphthyridine from the di-*N*-oxide.

Kobayashi, Kumadaki, and Sato[3] have described the formation of 5-chloro-1,6-naphthyridine as the lone product from the reaction of phosphoryl chloride with 1,6-naphthyridine 6-oxide, while, without isolation because of the reported lability, the 2-chloro-1,6-naphthyridine (6) has been described as the sole chloro isomer obtained when 1,6-naphthyridine 1-oxide (5) was subjected to the Meisenheimer reaction. When the Meisenheimer reaction was tried with 1,6-naphthyridine 1,6-dioxide, the 2,8-dichloro- and the 2,5-dichloro-1,6-naphthyridines were the only observed products.

In view of the fact that 5-nitroquinoline 1-oxide affords the 2-, 3-, and 4-chloro-5-nitroquinolines in the relative proportions 35:20:10 and the 6-nitroquinoline 1-oxide yields the three isomers in the ratio 16:35:56 when these *N*-oxides are treated with phosphoryl chloride,[4] it became of some interest to reexamine the Meisenheimer reaction of the 1-oxides of 1,5- and 1,6-naphthyridine.[5] We now wish to report the results of this study (*cf.* Scheme I).

SCHEME I



1,5-Naphthyridine 1-Oxide.—Reaction of 1,5-naphthyridine 1-oxide (1) with phosphoryl chloride results in a four-component mixture of bases, as shown by thin layer chromatography and gas chromatography. Quantitative gas chromatographic separation of this reaction mixture affords the two components with the longest retention time in their pure states. These compounds in the order of increasing retention time were identified respectively as 2-chloro- (2) and 4-chloro-1,5-naphthyridine (4). The other two components are present in the reaction mixture at too low a percentage to permit their direct isolation by preparative gas chromatography. Nevertheless, they were identified as 1,5-naphthyridine and 3-chloro-1,5-naphthyridine (3) by a comparison of their retention time, by behavior on tlc, and, in the case of the 3-chloro-1,5-naphthyridine (3), by the following procedure.

When the basic four-component mixture is treated with base, the 2- and the 4-chloro-1,5-naphthyridines (2 and 4, respectively) are hydrolyzed. To assure complete hydrolysis of the remaining small amount of the 4-chloro isomer 4, the chloroform extract of the aqueous base hydrolysis mixture [shown to contain 1,5-naphthyridine, traces of 4-chloro-1,5-naphthyridine (4), and the 3-chloro-1,5-naphthyridine (3)] was treated with sodium methoxide in methanol. The resulting mixture of 1,5-naphthyridine, 4-methoxy-1,5-naphthyridine, and 3-chloro-1,5-naphthyridine (3) was passed through an alumina column to afford pure 3-chloro-1,5-naphthyridine (3).

The latter compound was also prepared by the Eisch chlorination of 1,5-naphthyridine in a manner analogous to that described by us[6] for the bromination of 1,5-naphthyridine,

The 2-chloro- (2) and 4-chloro-1,5-naphthyridine (4) have been previously described,[2,7] and our compounds were shown to have properties identical with these chloro isomers.

The relative proportions of the four different components obtained by treatment of 1,5-naphthyridine 1-oxide with phosphoryl chloride were determined by gas chromatography.

Table I lists the average values of the relative proportions of these four compounds as obtained from five different experiments. The percentage composition is reproducible within 5% of the values given for each component.

Thus we find that the ratio of 4- to 2-chloro-1,5-naphthyridine obtained by us is 56:44 and is essentially identical with that reported by Brown (57:43).[1] The previously undetected 3-chloro isomer 3 is present to the extent of 3% of the total reaction products. The small amount (0.5%) of the parent compound is presumably formed by thermal deoxygenation of the *N*-oxide, since great care was taken to assure the absence of any 1,5-naphthyridine from the *N*-oxide reactant.

An interesting observation regarding the formation of the parent and the 3-chloro-1,5-naphthyridine (3) is the following: When the phosphoryl chloride is added *to* the 1,5-naphthyridine (1) without any cooling, the amounts of 3-chloro- (3) and parent 1,5-naphthyridines are about 7.5 and 3.5%, respectively. On the other hand, when the *N*-oxide is added slowly, and with cooling, to the phosphoryl chloride, the amount of 3-chloro- (3) product and parent 1,5-naphthyridine is decreased to 3.0 and 0.5%, respectively. The relative proportion of the 4-chloro- (4) and 2-chloro-1,5-naphthyridine (2) are, however, *unaffected* by this change

(3) Y. Kobayashi, I. Kumadaki, and H. Sato, *Chem. Pharm. Bull.*, **17**, 1045 (1969).

(4) (a) G. B. Bachmann and D. E. Coöper, *J. Org. Chem.*, **9**, 302 (1944); (b) R. W. Gouley, G. W. Moersch, and H. S. Mosher, *J. Amer. Chem. Soc.*, **69**, 303 (1947). (c) The formation of 3-chloro-6-nitroquinoline in this reaction has been questioned; *cf.* E. Ochiai, "Aromatic Amine Oxides," Elsevier, New York, N. Y., 1960, p 260.

(5) W. W. Paudler and T. J. Kress [*Advan. Heterocycl. Chem.*, **11**, 124 (1970)] have questioned the earlier results of the 1,5-naphthyridine 1-oxide products in the Meisenheimer reaction.

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

(7) J. T. Adams, C. K. Bradsher, D. S. Breshlow, S. T. Amore, and C. R. Hauser, *J. Amer. Chem. Soc.*, **68**, 1317 (1946).

TABLE I

RELATIVE PROPORTIONS OF THE MEISENHEIMER REACTION PRODUCTS OF THE 1-OXIDES OF 1,5- AND 1,6-NAPHTHYRIDINES

	Substituent					
Reactant	Nil	2-Chloro	3-Chloro	4-Chloro	2-Methoxy	4-Methoxy
1,5-Naphthyridine 1-oxide	0.5	42.3	3.0	54.2[a]		
1,6-Naphthyridine 1-oxide	2.0	12.0	20.0	66.0[a]		
1,6-Naphthyridine 1-oxide	4.0		21.0		11	64[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 are, of course, less accurate than the gc data.

in the mode of addition. The data reported in Table I represent the values obtained by the latter mode of addition.

The temptation thus may be great to suggest that the 3-chloro-1,5-naphthyridine (**3**) is formed by electrophilic chlorination of 1,5-naphthyridine. However, when 1,5-naphthyridine itself is treated with phosphoryl chloride, even under more severe conditions than were employed in the Meisenheimer reaction, *no* reaction takes place and the 1,5-naphthyridine is recovered quantitatively. Whether the 3-chloro group actually enters the nonoxidized ring (structure **1**, position 7) or the oxidized one (position 3) is, at present, a moot point. However, since the nitroquinoline 1-oxides also afford the 3-chloro isomer, one might suggest that it is, in fact, the 3 position of the 1,5-naphthyridine 1-oxide (**1**) that is involved.[4c]

1,6-Naphthyridine 1-Oxide.—The reaction of 1,6-naphthyridine 1-oxide (**5**) with phosphoryl chloride also affords four basic components, as established by gas chromatography. These components, in order of increasing retention times, are 1,6-naphthyridine, 3-chloro- (**7**), 4-chloro- (**8**), and 2-chloro-1,6-naphthyridine (**6**), respectively. The identity of these compounds was established by comparison with authentic samples.[3,8] Thus, contrary to the literature report[4] which claims the sole formation of the 2-chloro isomer, we find that in fact the 4-chloro and the 3-chloro isomers are formed as the major products in this reaction.

Since the possibility exists that the work-up might have caused the hydrolysis of substantial amounts of the 2- and 4-chloro-1,6-naphthyridines (**6** and **8**), we assured ourselves of the fact that this is not the case by modifying the work-up of the reaction mixture in such a manner so that no water was present. When this was done by adding methanol to the reaction mixture and the resulting solution was heated in the presence of sodium methoxide, there was isolated 2- and 4-methoxy-1,6-naphthyridine, along with the 3-chloro-1,6-naphthyridine (**7**), in essentially the same relative proportions observed for the corresponding chloro isomers (*cf.* Table I). It is of some interest to compare these results with those obtained from the Meisenheimer reaction of the 5- and the 6-nitroquinoline 1-oxides.

While the relative abundance of the three chloro isomers from the 5-nitroquinoline 1-oxide reaction is 2 > 3 > 4, we find that the related 1,5-naphthyridine 1-oxide generates the three isomers in the sequence 4 > 2 > 3. This can be readily explained by the substantial steric effect caused by the 5-nitro group toward nucleophilic chlorination at the 4 position of the quinoline nucleus. However, it is not yet clear why the amount of 3-chloro-1,5-naphthyridine (3%) is so much less than the 3-chloro-5-nitroquinoline 1-oxide (20%).

The lack of analogy between the results obtained from the 6-nitroquinoline 1-oxide (4 > 2 > 3) and the 1,6-naphthyridine 1-oxide (4 > 3 > 2) is also not at all obvious and this too must await the results of other experiments on related quinoline and naphthyridine *N*-oxides.

(8) W. W. Paudler and T. J. Kress, *J. Heterocycl. Chem.*, **2**, 393 (1965).

Experimental Section[9]

1,5-Naphthyridine 1-Oxide (**1**).—To 1,5-naphthyridine (5.2 g, 40 mol) dissolved in 15 ml of 30% H_2O_2 was added 0.4 g of $Na_2WO_4 \cdot 2H2O$ and the resulting solution was heated at 55° for 110 min. The reaction mixture was then cooled to 10° and 100 mg of activated MnO_2 was added in two portions within 30 min. The mixture was then stirred for an additional 30 min, after which time the solution no longer gave a positive test with starch–iodide paper. The solution was then made basic with Na_2CO_3 and extracted continuously with $CHCl_3$ for 12 hr. The dried (anhydrous $MgSO_4$) $CHCl_3$ extract was evaporated to dryness and the remaining pale-yellow residue was triturated with hot pentane (two 300-ml portions), followed by hot cyclohexane (two 500-ml portions). The remaining solid is essentially pure (tlc) 1,5-naphthyridine 1,5-dioxide (0.6 g, 10% of theory). The cyclohexane was twice clarified with activated charcoal and the filtrate was concentrated to 150 ml. Upon cooling, 2.3 g of 1,5-naphthyridine 1-oxide was collected. The filtrate afforded an additional 0.6 g of the mono-*N*-oxide upon further reduction of its volume to 40 ml [total yield 2.9 g, 67% of theory, mp 125–127° (lit.[1] 125–127°, prepared by preacetic acid oxidation of 1,5-naphthyridine)].

Meisenheimer Reaction of 1,5-Naphthyridine 1-Oxide (**1**).—The 1,5-naphthyridine 1-oxide (100 mg, 0.77 mol) was added to well-stirred, ice-cold, freshly distilled $POCl_3$ (8 ml). After being stirred for 5 min this mixture was heated in an oil bath (preheated to 120°) for 20 min. The excess $POCl_3$ was then removed under an aspirator vacuum. Traces of remaining $POCl_3$ were then removed by heating the reaction residue to 65° under an aspirator vacuum. To the remaining dark mass was then added a mixture of aqueous Na_2CO_3 and ice (10 ml and 10 g, respectively). After trituration of the material, the essentially clear, dark-brown solution was extracted with ice-cold $CHCl_3$ (five 50-ml portions). The twice dried (anhydrous $MgSO_4$) $CHCl_3$ extracts were then evaporated to dryness below 40° to afford a white crystalline residue (100 mg) of reaction products.

Tlc [alumina plates, ether–hexane (1:1)] of the reaction product showed four distinct spots (made visible by I_2 vapor). These spots in increasing order of their R_f values were identified as 1,5-naphthyridine and 4-chloro- (**4**), 2-chloro- (**2**), and 3-chloro-1,5-naphthyridine (**3**), respectively, by comparison with authentic samples. Gas chromatography (20 ft × 3/8 in. aluminum column, packed with 20% SE-30 on Chromosorb W, column temperature 220°, flow rate 150 ml/sec) also afforded four peaks identified as 1,5-naphthyridine (retention time 10 min), 3-chloronaphthyridine (15.1 min), 2-chloronaphthyridine (16.1 min), and 4-chloro-1,5-naphthyridine (18.1 min).

(9) The gas chromatograph used in these studies was an Aerograph Model A-90P-3 connected to a Sargent SRG recorder equipped with a Disc Integrator. The pmr spectra were obtained with a Varian HA-100 instrument and are dilute solutions in $CDCl_3$. The melting points were obtained with a Thomas-Hoover melting point apparatus and are corrected. The elemental analyses of the 3-chloronaphthyridines were done by Mrs. V. Gindlesberger of this department.

Preparative gc on the same column afforded the 4- and 2-chloro-1,5-naphthyridines as pure compounds, mp 102–103° (lit.[1] 102–103°), mp 114–116° (lit.[1] 114–116°), respectively.

The 3-chloro-1,5-naphthyridine was obtained pure by the following procedure. A suspension of 1.9 g of the reaction mixture from this reaction in 40 ml of 12% NaOH was heated under reflux for 3 hr, and the resulting solution was continuously extracted with $CHCl_3$. The dried (anhydrous $MgSO_4$) extracts were evaporated to dryness to yield 0.19 g of a white crystalline residue. This material was shown (tlc, gc) to contain 3-chloro-, 4-chloro-, and parent 1,5-naphthyridine. The 4-chloro-1,5-naphthyridine was removed by heating the reaction mixture in methanolic CH_3ONa (50 ml, 1.00 g of CH_3ONa) for 4 hr. After removal of the solvent, the residue was dissolved in 20 ml of water and the solution was continuously extracted with $CHCl_3$. The contents of the $CHCl_3$ extracts were then placed on an alumina column (neutral grade III, 30 g) and the 3-chloro-1,5-naphthyridine (**3**) was eluted with 12% ether–hexane. In this manner, 53 mg of compound **3** (mp 90.5–91°) was obtained. This compound is identical with the 3-chloro-1,5-naphthyridine obtained by the Eisch procedure (*vide infra*). The per cent yields of compounds **4**, **3**, **2**, and 1,5-naphthyridine are 42.8, 2.6, 33.8, and 0.04%, respectively. The relative percentages of the four compounds obtained are listed in Table I. Essentially the same amounts of all of these compounds are also obtained when Brown's procedure, utilizing PCl_5–$POCl_3$, is employed.

Meisenheimer Reaction of 1,6-Naphthyridine 1-Oxide (5).—The 1-oxide **5** was prepared by the method described in ref 3 except that the excess H_2O_2 was decomposed as described in our preparation of 1,5-naphthyridine 1-oxide. When 1,6-naphthyridine 1-oxide (100 mg, 0.77 mm) was treated with $POCl_3$ for 2 hr and the reaction mixture was worked up as described for the 1,5-naphthyridine 1-oxide reaction, 96 mg of reaction products was obtained.

Tlc and gc (same conditions as described above) showed the presence of 1,6-naphthyridine, 3-chloro- (**7**), 4-chloro- (**8**), and 2-chloro-1,6-naphthyridine (**6**) in the relative percentages listed in Table I. The retention times on gc and the melting points of the compounds in the order mentioned are 11.9 min, 16.7 min (103–103.5°), 17.6 min [90° (lit.[9] 90°)], and 19.4 min [88–89° (lit.[3] 88°)]. The per cent yields of the compounds, in the order parent, **7**, **8**, and **6**, are 1.9, 9.1, 15.2, and 50.2%, respectively.

Formation of 2- (9) and 4-Methoxy-1,6-naphthyridine (10).—In order to ascertain that hydrolysis of neither the 2- nor the 4-chloro-1,6-naphthyridine takes place during the work-up, the procedure was modified in one experiment by "decomposing" the reaction products with methanol in place of water. The resulting methanolic solution was then refluxed in the presence of 500 mg of CH_3ONa for 4 hr. Evaporation of the reaction mixture afforded a solid residue. This residue was dissolved in 20 ml of water and the resulting solution was continuously extracted with $CHCl_3$. The dried (anhydrous $MgSO_4$) extracts were evaporated to dryness to afford 80 mg of products. An nmr spectrum of a $CDCl_3$ solution of this mixture was a composite of 4-methoxy-, 2-methoxy-, and 3-chloro-1,6-naphthyridine, along with traces of the parent compound. This composite spectrum was analyzed by comparison with suitable authentic samples.[9] The relative proportions of the component thus obtained are listed in Table I.

3-Chloro-1,5- and -1,6-naphthyridine (3 and 7).—Into an efficiently stirred solution of 130 mg (1 mmol) of the appropriate naphthyridine in 30 ml of CCl_4 cooled to 5° was bubbled Cl_2 gas for 15 min. The resulting mixture containing a white precipitate was heated to reflux and 180 mg of pyridine dissolved in 5 ml of CCl_4 was added over a 15-min period. After heating for an additional 24 hr, the cooled reaction mixture was filtered and the collected solid was digested with 10% sodium hydroxide (25 ml) for 1 hr. The solution was then extracted with CH_2Cl_2 and the extract was combined with the $CHCl_3$ filtrate. The combined solutions were evaporated *in vacuo* affording a tan solid.

Gas chromatographic separation under the conditions described for the separation of the Meisenheimer reaction products afforded the following compounds.

3-Chloro-1,5-naphthyridine: 16 mg, 10% yield, mp 90.5–91°. *Anal.* Calcd for $C_8H_5N_2Cl$: C, 58.37; H, 3.06; N, 17.02. Found: C, 58.49; H, 3.20; N, 17.22.

3,7-Dichloro-1,5-naphthyridine: 8 mg, 4% yield, mp 150–52°. *Anal.* Calcd for $C_8H_4N_2Cl_2$: C, 48.03; H, 2.01; N, 14.01. Found: C, 47.89; H, 2.11; N, 14.20.

3-Chloro-1,6-naphthyridine: 24 mg, 15% yield, mp 103–103.6°. *Anal.* Calcd for $C_8H_5N_2Cl$: C, 58.37; H, 3.06; N, 17.02. Found: C, 58.26; H, 2.89; N, 16.93.

No attempt was made at this point to isolate two other chloro-1,6-naphthyridines, presumably the 8-chloro and the 3,8-dichloro derivatives. Detailed studies of the Eisch chlorination procedure on numerous naphthridines along with analyses of their pmr spectra will be the subject of a forthcoming publication.

Registry No.—**1**, 27305-48-2; **3**, 7689-63-6; **5**, 23616-39-9; **7**, 28795-77-9; 3,7-dichloro-1,5-naphthyridine, 28795-78-0.

Piperidinodechlorination of Chloronitronaphthalenes. A Further Comparison between Nitro-Group and Aza-Group Activation[1]

GABRIELLO ILLUMINATI,* GIANCARLO SLEITER,* AND MAURIZIO SPERANZA

Department of Chemistry, The University of Rome, 00185 Rome, Italy, and Centro C.N.R. dei Meccanismi di Reazione, Rome, Italy

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The importance of specific solvation (H bonding) in the nucleophilic reactions of N-heteroaromatic substrates has been stressed in recent studies[2–5] and was suggested[3,5] to be a major differential feature between aza- and nitro-group activation, on the basis of the solvent effects observed in the reaction of 2- and 4-chloroquinoline with piperidine. The most appropriate comparison with the latter reaction requires the investigation of the nitronaphthalene analogs, which is the object of the present note.

The kinetics of the piperidinodechlorination of 2- and 4-chloro-1-nitronaphthalene have been studied in toluene, ethyl acetate, piperidine, methanol, and dimethyl sulfoxide. The reactions in ethyl acetate were followed as long as the piperidinolysis of the solvent[3,6] remained kinetically unimportant. Possible solvolysis in methanol solution[7] could be excluded either by product analysis or by an indirect method.[8] The reactions of the compounds investigated yielded the expected products and followed regular second-order or pseudo-first-order kinetics, in agreement with previous studies.[9] With the reaction of 4-chloro-1-nitronaphthalene in toluene, initially linear kinetic plots eventually became erratic after some 50–60% reaction, probably because thermal decomposition of the substrate occurred.[10] The second-order rate constants at varying temperatures and the activation parameters for 2- and 4-chloro-1-nitronaphthalene are collected in Table I.

(1) Nucleophilic Heteroaromatic Substitution. XXXV.
(2) G. Illuminati and G. Marino, *Chem. Ind. (London)*, 1287 (1963).
(3) G. Illuminati, G. Marino, and G. Sleiter, *J. Amer. Chem. Soc.*, **89**, 3501 (1967).
(4) F. Genel, G. Illuminati, and G. Marino, *ibid.*, **89**, 3516 (1967).
(5) G. B. Bressan, I. Giardi, G. Illuminati, P. Linda, and G. Sleiter, *J. Chem. Soc. B*, 225 (1971).
(6) E. M. Arnett, J. G. Miller, and A. R. Day, *J. Amer. Chem. Soc.*, **72**, 5635 (1950).
(7) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951); H. Suhr, *Tetrahedron Lett.*, 5871 (1966).
(8) E. A. S. Cavell and N. B. Chapman, *J. Chem. Soc.*, 3392 (1953).
(9) M. Simonetta and P. Beltrame, *Gazz. Chim Ital.*, **88**, 769 (1958).
(10) E. Berliner, M. J. Quinn, and P. J. Edgerton, *J. Amer. Chem. Soc.*, **72**, 5305 (1950).