The Meisenheimer Reaction in the 1,5-Naphthyridine Series. II[1a]

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The action of phosphorus oxychloride on 1,5-naphthyridine 1,5-dioxide yields a mixture of isomeric dichloro-1,5-naphthyridines. The presence of 2,4-dichloro-1,5-naphthyridine and 3,8-dichloro-1,5-naphthyridine was verified by comparison with synthetic samples prepared *via* known procedures. 2,6-Dichloro-1,5-anphthyridine and 2,8-dichloro-1,5-naphthyridine were prepared by new unambiguous synthetic routes and also found to be present among the reaction products. The mass and nmr spectra indicate that the fifth major product of the mixture is 2,7-dichloro-1,5-naphthyridine. The expected 4,8-dichloro-1,5-naphthyridine isomer was not detected anywhere in the reaction products. The independent synthesis of this isomer and comparison of it with all of the products isolated from the reaction mixture substantiate its absence. The nmr and mass spectra of the dichloronaphthyridines are discussed.

The Meisenheimer reaction is the action of phosphorus oxychloride or sulfuryl chloride on the *N*-oxide function of pyridine or a polycyclic azine resulting in nucleophilic substitution by the chloride ion at a ring carbon and loss of oxygen.[2] This reaction usually gives mixtures of isomers and an extensive review of the literature has been made by Ochiai.[3]

Previously we have shown[4] that 1,5-naphthyridine 1-oxide yields a mixture of 2- and 4-chloro-1,5-naphthyridines from the Meisenheimer reaction rather than just 2-chloro-1,5-naphthyridine as had been previously reported by Hart.[5] In the same paper, Hart reported 2,6-dichloro-1,5-naphthyridine as the only product isolated from the Meisenheimer reaction on 1,5-naphthyridine 1,5-dioxide.[5] This result has recently been questioned[6] and we now wish to report our investigations as to the identity of the reaction products.

We have now repeated Hart's work using the same conditions he described.[5] Analysis of the mixture by gas chromatography shows six distinct peaks with peak 5 having a definite shoulder indicating that the peak consists of two components. The assignment of structures to the compounds giving peaks 3, 4, 5, and 6 was made from interpretation of the nmr and mass spectra for each and the results are in Table I.

TABLE I

COMPONENTS OF MEISENHEIMER MIXTURE

Peak	Percentage[a]	Compd
1	1.1	
2	0.3	
3	9.4	2,7-Dichloro-1,5-naphthyridine
4	17.6	3,8-Dichloro-1,5-naphthyridine
5	46.1 (37%)[b]	2,6-Dichloro-1,5-naphthyridine
	(9%)[b]	2,4-Dichloro-1,5-naphthyridine
6	25.5	2,8-Dichloro-1,5-naphthyridine

[a] These percentages are an average of two runs and the maximum deviation is 0.36%. [b] This value was obtained as an approximation from fractional sublimation of peak 5.

In addition, the two components of peak 5 and the identity of the components in peaks 4 and 6 were confirmed by comparison of their nmr spectra with those of synthetic samples made by unambiguous routes. The infrared spectra of the four synthetic isomers were identical with the components of peaks 4, 5, and 6. Mixture melting points with three of the components further confirmed their identity.

The preparative gas chromatogram of peak 1 indicates that it is a mixture of two compounds. The mass spectrum of peak 1 shows the molecular ion as *m/e* 198 indicating that at least one and probably both of the components are dichloro-1,5-naphthyridine isomers. However, insufficient material was obtained for further analysis.

No data are available to identify peak 2 due to insufficient material. The material from peaks 1 and 2 amounts to less than 1.5% of the reaction products. The five dichloro-1,5-naphthyridine isomers which have been identified comprise over 98% of the products.

The mass spectrum of peak 3 shows a molecular ion at *m/e* 198. This indicates the material is a dichloro-1,5-naphthyridine. The nmr spectrum consists of two different AB systems with two protons overlapped, one from each AB system. The chemical shifts of the protons indicate that the position para to the nitrogen is unsubstituted in both rings. The chemical shifts of the other two protons that indicate one meta and one ortho position also have hydrogens. The coupling constant of 1.4 cps is typical of ortho–para coupling indicating substitution at the meta or 3 position. The coupling constant of 8.6 cps is typical of 3–4 coupling, meaning the 2 position is substituted in the other ring. The isomer with the chlorine substituted at the ortho position in one ring and the meta position in the other ring would be 2,7-dichloro-1,5-naphthyridine.

The mass spectrum of peak 4 shows *m/e* 198 as the molecular ion. The nmr spectrum clearly shows the presence of two different AB systems and integrates for four protons. The coupling constant 2.1 cps indicates the H_2 and H_4 protons are coupled, meaning the ring is substituted with a chlorine in the 3 position. The AB pattern for the other ring is indicative of chlorine substitution para to the nitrogen or in the 8 position. The coupling constant of 4.3 cps must come from hydrogens ortho and meta to the nitrogen. Thus, peak 4 then could only be 3,8-dichloro-1,5-naphthyridine. The chemical shifts of the four protons are in full agreement with this assigned structure as can be seen from Table II. McCaustland

(1) (a) Presented in part at the combined Southeast and Southwest Regional Meeting of the American Chemical Society, New Orleans, La., Dec 2–4, 1970. (b) Taken in part from the Ph.D. Dissertation of A. C. Plasz, University of Kentucky, 1970.

(2) J. Meisenheimer, *Ber.*, **59**, 1848 (1926).

(3) E. Ochiai, "Aromatic Amine Oxides," Elsevier, New York, N. Y., 1967, pp 259–269.

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

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

(6) W. W. Paudler and T. J. Kress, *Advan. Heterocycl. Chem.*, **11**, 168 (1970).

TABLE II

NMR SPECTRAL DATA OF SOME CHLORO-1,5-NAPHTHYRIDINES

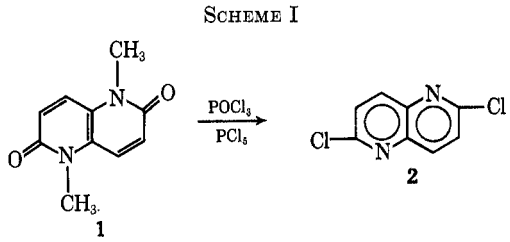
Compd	Solvent	Chemical shifts[a] H_2	H_3	H_4	H_6	H_7	H_8	Coupling constants[b] $J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$
2-Chloro-1,5-naphthyridine[c]	CCl_4		7.48	8.19	8.78	7.53	8.16			8.0	4.3	1.6	8.6
4-Chloro-1,5-naphthyridine[c]	CCl_4	8.66	7.45		8.89	7.41	8.27	4.5			4.0	1.5	8.4
2,4-Dichloro-1,5-naphthyridine	$CDCl_3$		7.75		8.99	7.71	8.30				4.1	1.9	8.4
2,6-Dichloro-1,5-naphthyridine	$CDCl_3$		7.62	8.23		7.62	8.23			8.4			8.4
2,7-Dichloro-1,5-naphthyridine	$CDCl_3$		7.62	8.35	8.92		8.32			8.6		1.4	
2,8-Dichloro-1,5-naphthyridine	$CDCl_3$		7.66	8.77	8.33	7.74				8.5	4.5		
3,8-Dichloro-1,5-naphthyridine	$CDCl_3$	8.98		8.44	8.66	7.74			2.1		4.3		
4,8-Dichloro-1,5-naphthyridine	$CDCl_3$	8.95	7.82		8.95	7.82		4.4			4.4		

[a] Chemical shifts (δ) are recorded as parts per million downfield from TMS. [b] Coupling constants (J) are in cycles per second. [c] E. V. Brown and A. C. Plasz, *J. Heterocycl. Chem.*, **7**, 593 (1970).

and Cheng[7] have recently reported the synthesis of 3,8-dichloro-1,5-naphthyridine from 3-amino-5-chloropyridine *via* the diethyl ethoxymethylenemalonate (EMME) route. The 3,8-dichloro-1,5-naphthyridine we prepared by their method was identical with the material from peak 4.

Almost one-half of the reaction products are found in peak 5. There are two components in this fraction and they have been identified as 2,6-dichloro-1,5-naphthyridine and 2,4-dichloro-1,5-naphthyridine and are present in an approximate 4:1 ratio. This was determined by fractional sublimation which separated the two isomers. 2,4-Dichloro-1,5-naphthyridine was prepared according to Oakes and Rydon.[8] The synthetic 2,4-dichloro-1,5-naphthyridine was identical with that of the more volatile fraction of peak 5. The nmr spectrum of 2,4-dichloro-1,5-naphthyridine had the expected AMX system for the unsubstituted ring with the singlet peak for the H_3 proton superimposed on the quartet from the X proton of the AMX system. Coupling constants for all protons were typical for this system. A modification of Fargher and Farness'[9] synthesis of 2-chloropyridine applied to 1,5-dimethyl-1,5-naphthyridine-2,6(1*H*,5*H*)-dione[10] (**1**) afforded 2,6-dichloro-1,5-naphthyridine (**2**) in 14.4% yield (Scheme I). The synthetic 2,6-dichloro-1,5-naphthyridine was

SCHEME I



1 2

identical with the fraction which sublimed above 95° from peak 5. The nmr spectrum of 2,6-dichloro-1,5-naphthyridine was characterized by the expected A_2B_2 pattern and typical coupling constant and chemical shifts (see Tables II and III).

The identity of peak 6 has been confirmed by the synthesis of 2,8-dichloro-1,5-naphthyridine. Diethyl ethoxymethylenemalonate (EMME) and 5-amino-2-hydroxypyridine were refluxed in phenyl ether at 250° to afford 7-carbethoxy-2,8-dihydroxy-1,5-naphthyridine (**3**). Saponification gave 7-carboxy-2,8-dihydroxy-1,5-naphthyridine (**4**) followed by decarboxylation in mineral oil at 300° to yield 2,8-dihydroxy-1,5-naphthyridine (**5**). The 2,8-dihydroxy-1,5-naphthyridine was converted to 2,8-dichloro-1,5-naphthyridine (**6**) by refluxing with a phosphorus oxychloride–phosphorus pentachloride mixture (Scheme II). The synthetic 2,8-dichloro-1,5-naphthyridine was identical with the material isolated from the peak 6 in the Meisenheimer mixture. The nmr spectrum of 2,8-dichloro-1,5-naphthyridine was characterized by two different AB systems. Typical chemical shifts and coupling constants were observed for the AB system of the H_3 and H_4 protons and the AB system of the H_6 and H_7 protons. As would be expected, the H_3 and H_7 protons have similar chemical shifts; however, the splitting and slight difference in chemical shifts allow both peaks

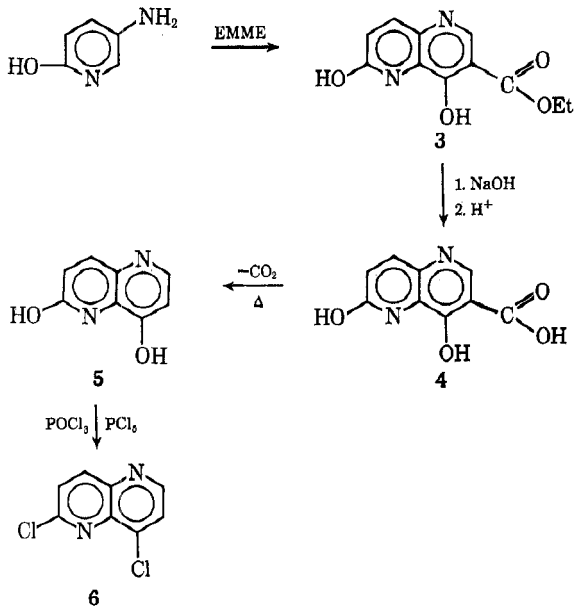
TABLE III

MASS SPECTRA OF DICHLORO-1,5-NAPHTHYRIDINE

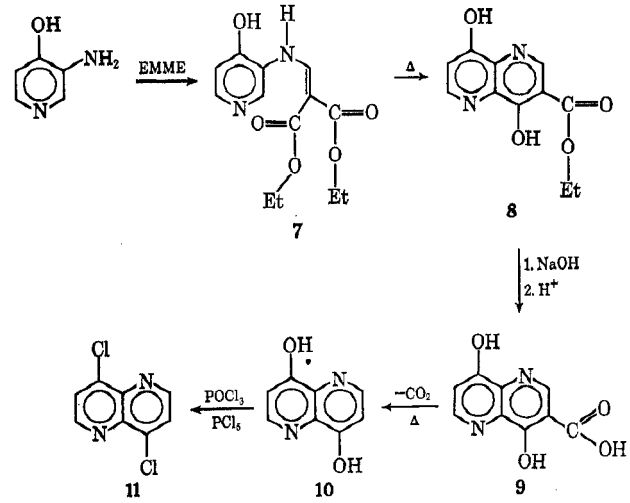
m/e	Relative abundances 2,4	2,6	2,7	2,8	3,8	4,8
202	11	10	10	10	10	11
200	64	64	60	60	56	62
199	10	10	9	9	9	10
198	100	100	100	100	100	100
165	28	25	29	30	18	24
164	8	7	9	9	5	8
163	85	75	94	97	54	73
138	2	2	4	4	7	5
137	2	4	7	9	4	5
136	7	5	14	11	20	17
127	14	56	12	16	5	8
112	12	2	3	3	2	2
103	10	2	3	1	1	1
102	9	3	2	2	1	1
101	10	13	8	10	7	8
100	25	28	25	33	33	38
99	13	11	10	10	12	15
85	5	8	7	11	7	9
81	5	14	7	2	1	3
76	23	23	17	23	17	19
75	32	27	23	30	19	19
74	15	11	12	17	18	21
73	4	12	17	16	16	18
64	8	24	20	22	22	21
63	8	9	16	8	8	7
62	9	8	9	9	7	7
52	13	16	11	15	8	7
51	37	17	11	14	11	10
50	37	36	7	39	28	27
49	10	10	7	11	10	11
Temp, °C	170	170	200	185	185	180
Trap	10	10	70	10	10	10

(7) D. J. McCaustland and C. C. Cheng, *J. Heterocycl. Chem.*, **7**, 467 (1970).
(8) V. Oakes and H. N. Rydon, *J. Chem. Soc.*, 204 (1958).
(9) R. G. Farcher and R. Farness, *ibid.*, **107**, 688 (1915).
(10) H. Rapoport and A. D. Batcho, *J. Org. Chem.*, **28**, 1753 (1963).

SCHEME II



SCHEME III



of each doublet to be distinctly clear in the nmr spectrum.

One surprising feature in the analysis of the reaction products was the fact that no 4,8-dichloro-1,5-naphthyridine was formed. In all of the fractions of the Meisenheimer mixture analyzed by nmr, there was no indication that 4,8-dichloro-1,5-naphthyridine was present. The independent synthesis of 4,8-dichloro-1,5-naphthyridine was achieved using the diethyl ethoxymethylenemalonate route. Condensation of 4-hydroxy-3-aminopyridine with EMME in refluxing toluene gave the uncyclized ester **7**. An attempt to condense and cyclize in one step with phenyl ether was accompanied by vigorous frothing and foaming upon formation of the condensation product at 110–130°. Cyclization of purified **7** to 3-carbethoxy-4,8-dihydroxy-1,5-naphthyridine (**8**) in refluxing phenyl ether proceeded smoothly. Saponification of **8** gave crude 3-carboxy-4,8-dihydroxy-1,5-naphthyridine (**9**) which was directly decarboxylated and sublimed under vacuum at 250–300° to give 4,8-dihydroxy-1,5-naphthyridine (**10**). The conversion of **10** to 4,8-dichloro-1,5-naphthyridine (**11**) was done with a refluxing mixture of phosphorus oxychloride and phosphorus pentachloride (Scheme III). When this compound was injected into the gas chromatograph, its retention time was higher than any of the other isomers under exactly the same conditions. The nmr spectrum of 4,8-dichloro-1,5-naphthyridine had the expected A_2B_2 pattern and $J_{2,3}$ coupling constant.

The mass spectra for the dichloro-1,5-naphthyridines are shown in Table III. The major fragmentation from the molecular ion of the dichloro-1,5-naphthyridines is the loss of a chlorine atom to give the expected isotopic cluster at *m/e* 163 and 165 in a 3:1 ratio due to the one chlorine atom still attached (spectra in which metastables are observed which support these transitions are in Table IV). Metastable evidence (Table IV) supports two different fragmentations from the *m/e* 163 and 165 peaks. The loss of HCl as a neutral fragment gives rise to the peak *m/e* 127. The loss of HCN from *m/e* 163 and 165 to give the fragments at *m/e* 136 and 138 still in the approximate 3:1 ratio indicating the chlorine atom has not been lost yet. The fragments at *m/e* 138 and 136 expel HCl to give rise to a *m/e* 100 moiety. This *m/e* 100 moiety also results from the loss of HCN from the *m/e* 127 peak. Metastable evidence supports both fragmentations. Contributions to the peaks at *m/e* 101, 100, and 99 could also come from doubly charged ions.

TABLE IV
METASTABLES

Parent ion	Daughter ion	Neutral fragment	Calcd met	Obsd 2,4	2,6	2,7	2,8	3,8	4,8
200 →	165	35	136.13	√	√	√	√	√	√
200 →	163	37	132.84	√	√	√	√	√	√
198 →	163	35	134.19	√	√	√	√	√	√
163 →	136	27	113.47	√		√	√	√	√
165 →	138	27	115.42				√	√	√
163 →	127	36	98.95	√	√	√	√	√	√
165 →	127	38	97.75	√	√		√	√	√
127 →	100	27	78.74	√	√		√		
138 →	100	38	72.83	√			√		
136 →	100	36	73.53	√	√		√	√	√
100 →	73	27	53.29						

Further fragmentation is quite similar to other naphthyridines recorded in the literature.[11,12] The peaks at *m/e* 76, 75, 74, 64, 63, 52, 51, and 50 are characteristic in naphthyridine spectra,[11,12] and the peaks at *m/e* 52, 51, 50, and 49 are characteristic of pyridine systems.[13]

Experimental Section

Melting points were taken on a Fisher-Johns block and are corrected unless otherwise stated. Melting points of compounds which sublime easily were taken in a sealed tube and are uncorrected and noted in the text. Infrared spectra were taken on a Beckman IR-8 spectrometer using potassium bromide pellets. Nuclear magnetic resonance spectra were obtained with a Varian T-60 spectrometer using 25 mg of sample and 0.5 ml of solvent except for the 2,7-dichloro-1,5-naphthyridine where only 3 mg of compound was obtained pure. The internal standard was TMS (4%) and deuteriochloroform was the solvent unless otherwise

(11) E. V. Brown, A. C. Plasz, and S. R. Mitchell, *J. Heterocycl. Chem.*, **7**, 661 (1970).
(12) W. W. Paudler and T. J. Kress, *ibid.*, **4**, 547 (1967).
(13) American Petroleum Institute, Research Project 44, "Mass Spectral Data," Thermodynamics Research Center Publications, College Station, Texas, 1966, Spectra No. 617.

indicated. Mass spectra were obtained with either a Hitachi Perkin-Elmer RMU-6E or RMU-7 mass spectrometer with an ionizing potential of 70 eV. The direct inlet was used and the temperature and trap current for each compound are in Table III.

3,8-Dichloro-1,5-naphthyridine was prepared by the method of McCaustland and Cheng,[7] mp 176.5–177.5° (lit.[7] mp 176–179°).

2,4-Dichloro-1,5-naphthyridine was prepared by the method of Oakes and Rydon,[8] mp 138–139° (lit.[8] 140°).

2,6-Dichloro-1,5-naphthyridine (2).—1,5-Dimethyl-1,5-naphthryidine-2,6(1*H*,5*H*)-dione (1)[10] (1.20 g, 0.0063 mol), phosphorus pentachloride (2 g, 0.0096 mol), and phosphorus oxychloride (10 ml) were refluxed for 9 hr. The excess phosphorus oxychloride was removed under vacuum and ice was added. The mixture was basified with concentrated ammonium hydroxide and a solid precipitated. The purple solid was removed by filtration to yield 0.18 g (14.4%). This was sublimed twice under vacuum to give 0.11 g of yellow powder, mp 258–260° uncor (sealed tube), (lit.[5] 236°).

Anal. Calcd for $C_8H_4N_2Cl_2$: C, 48.24; H, 2.01; N, 14.07. Found: C, 48.40; H, 1.86; N, 14.22.

7-Carbethoxy-2,8-dihydroxy-1,5-naphthyridine (3).—2-Hydroxy-5-nitropyridine (20.0 g, 0.143 mol) was reduced with 10% palladium on carbon in ethanol on the low-pressure (3 atm) Parr apparatus. The catalyst was removed by filtration and the ethanol was evaporated. The 5-amino-2-hydroxypyridiue (15.0 g, 0.108 mol) was added to 475 ml of phenyl ether containing (31 g, 0.14 mol) of diethyl ethoxymethylenemalonate and refluxed at 250° for 1 hr. The solution was cooled, and the solids were removed by filtration and then slurried in hot Skellysolve B. Filtration gave 19.6 g of brown crude ester. The brown solid (18.95 g) was vacuum sublimed at 250–300° for 1 hr to give 5.1 g (20.2%) of yellow solid. This yellow solid was recrystallized twice from methanol to give a white fluffy solid, mp 293–295°.

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.27; N, 11.97. Found: C, 56.32; H, 4.48; N, 11.73.

7-Carboxy-2,8-dihydroxy-1,5-naphthyridine (4).—7-Carbethoxy-2,8-dihydroxy-1,5-naphthyridine (48 g, 0.21 mol) was refluxed in 400 ml of 6% sodium hydroxide for 15 hr. The mixture was treated with charcoal while hot and was filtered through a Celite bed. The cooled solution was neutralized with 50% hydrochloric acid added dropwise to pH 7. The solid was filtered and dried at 110° overnight. The yield was 34 g (80.5%), mp >350°.

2,8-Dihydroxy-1,5-naphthyridine (5).—7-Carboxy-2,8-dihydroxy-1,5-naphthyridine (11.6 g, 0.0565 mol) was slowly added to stirring mineral oil (500 ml) at 300°. After addition the mixture was kept at 300–310° for 45 min, and the mixture was cooled and filtered. The solids were washed with Skellysolve B to remove the mineral oil and dried overnight at 120°. The solid was then extracted with 500 ml of boiling water and the solution was filtered. The solution was concentrated to give a solid which was removed by filtration yielding 2.67 g (29.2%). Sublimation under vacuum at 280° separated the dihydroxy compound from the residue. The material was resublimed at 280° under vacuum and recrystallized from ethanol; another sublimation and final recrystallization from methanol gave a white powder, mp >360° (sublimes).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.70; N, 17.28. Found: C, 59.02; H, 3.94; N, 17.09.

2,8-Dichloro-1,5-naphthyridine (6).—2,8-Dihydroxy-1,5-naphthyridine (2 g, 0.012 mol), phosphorus oxychloride (50 ml), and phosphorus pentachloride (10 g, 0.048 mol) were refluxed for 4 hr. The excess phosphorus oxychloride was removed *in vacuo* and the residue dissolved in 200 ml of ice water. Ammonium hydroxide was added and the yellow precipitate was removed by filtration. The yield, after drying, was 1.15 g, recrystallized from Skellysolve B, 1.06 g (43.4%). The material was sublimed at 120–155° at atmospheric pressure to give the analytical sample as white needles, mp 153.5–156° (sealed tube).

Anal. Calcd for $C_8H_4N_2Cl_2$: C, 48.24; H, 2.01; N, 14.07. Found: C, 48.43; H, 1.79; N, 14.03.

Ethyl β-(4-Hydroxy-3-pyridylamino)-α-carbethoxyacrylate (7).—3-Nitro-4-hydroxypyridine[14] was reduced with 10% palladium on carbon in ethanol on the low-pressure Parr apparatus (3 atm). The catalyst was removed by filtration and the ethanol was evaporated to give the crude amine which was used without further purification for the next step. To a 1-l. three-necked round-bottomed flask, fitted with a stirrer and condenser, was added 400 ml of toluene. Diethyl ethoxymethylenemalonate (20 g, 0.093 mol) and 3-amino-4-hydroxypyridine (5 g, 0.047 mol) were added, and the mixture was heated to reflux and kept there 8 hr. The solution was cooled, and the product was removed with suction filtration and recrystallized from methanol (charcoal) to give 7.7 g. (58.3%) of white plates, mp 243.5°–245.5°.

Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.01; H, 5.72; N, 10.00. Found: C, 55.21; H, 5.72; N, 9.85.

3-Carbethoxy-4,8-dihydroxy-1,5-naphthyridine (8).—Ethyl β-(4-hydroxy-3-pyridylamino)-α-carbethoxyacrylate (15 g, 0.054 mol) was added to 450 ml of phenyl ether and refluxed (250–255°) for 1 hr. The mixture was cooled and filtered. The solid was washed with large volumes of Skellysolve B until the washings were colorless and was then refluxed 1 hr in boiling benzene to remove the remaining phenyl ether, cooled, removed by filtration from the benzene, and dried to give 6.3 g (50.2%) of dirt-brown solid. This was sublimed under vacuum at 280° in 1-g amounts for 3 hr. The sublimer was rinsed clean with hot ethanol and the ethanol was evaporated to give a total yield of 0.44 g (3.5%) of yellow solid, mp >300° (sublimes). An additional sublimation and recrystallization from ethanol gave the analytical sample.

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.27. Found: C, 56.28; H, 4.26.

3-Carboxy-4,8-dihydroxy-1,5-naphthyridine (9).—3-Carbethoxy-4,8-dihydroxy-1,5-naphthyridine (1.0 g, 0.0043 mol) was refluxed with 50 ml of 4% sodium hydroxide for 4 hr. The solution was cooled overnight and then acidified with 3 *M* hydrochloric acid at pH 7. The precipitate was collected in a sintered glass funnel and the precipitation process repeated on the mother liquor three more times. The four crops were dried at 110° for 1 hr and gave 0.68 g (77.3%) of acid which decarboxylates and sublimes at >320°.

4,8-Dihydroxy-1,5-naphthyridine (10).—3-Carboxy-4,8-dihydroxy-1,5-naphthyridine (0.68 g, 0.0033 mol) was decarboxylated and sublimed under vacuum at 250–300° and the yellow solid was removed from the sublimer with boiling ethanol–water. The process was repeated two additional times and the solids were dried at 110° for 1 hr. The yield of yellow solids was 0.33 g (61.7%), mp >300° (sublimes).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.70; N, 17.28. Found: C, 58.79; H, 3.77; N, 17.18.

4,8-Dichloro-1,5-naphthyridine (11).—4,8-Dihydroxy-1,5-naphthyridine (0.20 g, 0.0012 mol), phosphorus oxychloride (50 ml), and phosphorus pentachloride (5 g, 0.024 mol) were refluxed for 1 hr, after which time all of the solid dissolved. After an additional hour of reflux, the mixture was cooled and excess phosphorus oxychloride was removed under vacuum. The resulting purple, syrupy liquid was cooled in an ice bath and ice-cold dilute ammonium hydroxide was added with vigorous stirring until the syrup had dissolved and formed a gray suspension. The mixture was made strongly basic with additional ammonium hydroxide and filtered through a sintered-glass funnel, and the precipitate was washed with 10 ml of 1:1 ice-cold ethanol–water and air-dried overnight. The crude dichloro compound (0.22 g) was sublimed under vacuum at 150° to give 0.15 g (61.5%) of grayish white powder. Recrystallization from Skellysolve B and then benzene, followed by two sublimations at 200–220° and atmospheric pressure, gave white needles, mp 278–279°.

Anal. Calcd for $C_8H_4N_2Cl_2$: C, 48.24; H, 2.01; N, 14.07. Found: C, 48.38; H, 1.99; N, 14.14.

1,5-Naphthyridine 1,5-Dioxide.[5]—1,5-Naphthyridine (4.1 g, 0.032 mol), peracetic acid (15 ml), and glacial acetic acid (40 ml) were heated in a 100-ml round-bottomed flask in an oil bath. The temperature initially rose to 75° and dropped to 50° where it was kept for 20 hr. The mixture was cooled in ice, basified with solid potassium hydroxide, and extracted with 500 ml of chloroform, and the chloroform was evaporated. The solids were extracted with boiling ethanol. Upon cooling, 1.22 g (24.9%) of yellow needles were collected, mp 298–301° (lit.[5] 301°).

Meisenheimer Reaction.—1,5-Naphthyridine 1,5-dioxide (1.24 g, 0.00766 mol) and phosphorus oxychloride (40 ml) were mixed together while cooling in an ice bath. The mixture was brought to reflux and the dioxide went into solution and then was refluxed for 30 min. The excess phosphorus oxychloride was removed *in vacuo*, 100 ml of ice water and 20 ml of ammonium hydroxide were added, and the black gum turned into a gray-white solid. The solid was removed by filtration and air-dried to give 1.17 g of crude material which softened at 135°, darkened at 175°, and

(14) E. Koenigs and K. Freter, *Ber.*, **57**, 1187 (1924).

melted from 205 to 240° where some sublimation was noted. The mixture was dissolved in acetone and analyzed with a Hewlett-Packard Model 5750 gas chromatograph and Infotronics Digital Readout CRS-108 integrator using a 6 ft × 0.125 in. Carbowax 20M column at 180°. Six distinct peaks were obtained and the fifth peak had a definite shoulder indicating two components for that peak. The area percentages calculated for each peak appear in Table I.

Separation and Identification of Isomers.—The crude mixture from the Meisenheimer reaction was separated with a Hewlett-Packard Model 5750 gas chromatograph using a 20 ft × 0.375 in. o.d. aluminum column filled with 20% Carbowax 20M on Chromosorb W. The sample was dissolved in acetone and injected into the column at 230°. The components of the six individual peaks were collected and the two components of peak 5 were separated by fractional sublimation. The components were identified by their mass, infrared, and nmr spectra and by comparison with spectra of synthetic isomers where possible. Mixture melting points were used in three cases as additional proof of structure. In the cases where infrared and nmr spectra of synthetic isomers and separated isomers could be obtained, they were identical in all respects leaving no doubt as to the identity of the compound. The melting point of 3,8-dichloro-1,5-naphthyridine separated from the mixture was 177.5–178.5° and the mixture melting point with the synthetic sample occurred at 177–178.5°. The melting point of separated 2,4-dichloro-1,5-naphthyridine from peak 5 was 124.5–130°. The melting point of separated 2,6-dichloro-1,5-naphthyridine from peak 5 was 257–260° and the mixture melting point with synthetic 2,6-dichloro-1,5-naphthyridine occurred at 257–259°. The melting point of 2,8-dichloro-1,5-naphthyridine, separated as peak 6 from the Meisenheimer mixture, was 154.5–156° and the mixture melting point with synthetic 2,8-dichloro-1,5-naphthyridine occurred at 154–157°. All of these melting points in this section were taken in a sealed tube and are uncorrected.

Registry No.—**2**, 27017-66-9; **3**, 28252-73-5; **4**, 28252-74-6; **5**, 28252-75-7; **6**, 28252-76-8; **7**, 28252-77-9; **8**, 28252-78-0; **9**, 28252-79-1; **10**, 28312-61-0; **11**, 28252-80-4; 3,8-dichloro-1,5-naphthyridine, 28252-81-5; 2,4-dichloro-1,5-naphthyridine, 28252-82-6; 2-chloro-1,5-naphthyridine, 7689-62-5; 4-chloro-1,5-naphthyridine, 7689-63-6; 2,7-dichloro-1,5-naphthyridine, 28252-85-9.

Permanganate Ion Oxidations. VI. Kinetics and Mechanism of the Oxidation of Alkanenitronate Anions[1]

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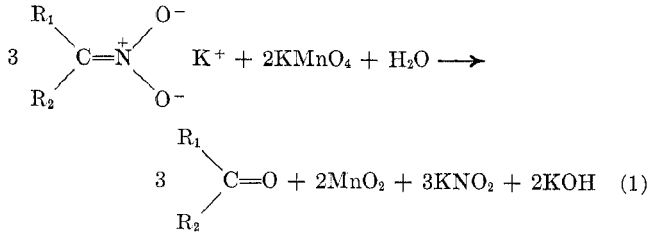
The kinetics of the permanganate ion oxidation of the alkanenitronate anions from nitromethane, nitroethane, 1- and 2-nitropropane, and 1- and 2-nitrobutane have been studied by spectrophotometric stopped-flow techniques. Between pH 11.6 and 13.7 the reaction follows the rate law $v = k$[alkanenitronate anion][MnO_4^-]. The reactions are characterized by low enthalpies of activation ($\Delta H^{\ddagger}$ = 6.00 to 8.84 kcal/mol) and large negative entropies of activation ($\Delta S^{\ddagger}$ = −16.0 to −23.0 eu). A positive salt effect is observed, and correlation of σ^* substituent values and second-order rate constants gives a ρ of 0.53 at 10°. The kinetic data suggest that the rate-determining step involves a stepwise addition of permanganate ion to the carbon of the carbon–nitrogen double bond in the alkanenitronate anion. Possible activated complexes for the permanganate ion oxidation of cyclohexanenitronate anion and phenylmethanenitronate anions are also discussed.

Although kinetic and mechanistic studies of the alkaline permanganate ion oxidation of the potassium salts of phenylmethanenitronate anions,[2,3] cyclopentanenitronate anion,[4] and cyclohexanenitronate anion[4] have been reported in recent years, not one of them has been concerned with the permanganate ion oxidation of simple alkanenitronate anions.[5] The permanganate ion oxidation of the potassium salts of aliphatic nitro compounds is an excellent preparative method[6,7] for the synthesis of aldehydes and ketones (eq 1).[6-10] These reactions are also of interest because of their extremely rapid rates of oxidation (k_2 larger than 100 l. mol^{-1} sec^{-1}). It is the purpose of this work to point out some pertinent features of a reasonable mechanism proposed herein for the permanganate ion oxidation of alkanenitronate anions.



$$3\ \mathrm{R_1R_2C{=}\overset{+}{N}(O^-)_2} + K^+ + 2KMnO_4 + H_2O \longrightarrow 3\ \mathrm{R_1R_2C{=}O} + 2MnO_2 + 3KNO_2 + 2KOH \quad (1)$$

R_1 = H; R_2 = $(CH_3)_3C$ (69%)[7]
R_1 = H; R_2 = $(CH_3)_2CH$ (73%)[7]
R_1 = H; R_2 = $CH_3(CH_2)_2$ (97%)[7]
R_1 = CH_3; R_2 = $(CH_3)_3C$ (94%)[7]
R_1 = R_2 = CH_3 (96%)[7]

Experimental Section

Reagents.—2-Nitropropane,[11,12] 1-nitropropane,[12] 1-nitrobutane,[13,14] 2-nitrobutane,[13,14] nitromethane,[12] and nitroethane[11] were distilled immediately before use. Distilled water, which was passed through an ion-exchange cartridge (Type R-2, Illinois Water Treatment Co., Rockford, Ill.), was used to prepare all solutions. Potassium chloride (Malinckrodt) was used to maintain 1.0 *M* ionic strength. Potassium permanganate stock solutions were prepared from Acculute standard volumetric concentrates. The pH, which was measured potentiometrically, was adjusted with Acculute standard volumetric potassium hydroxide (CO_2 free) concentrate.

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(12) Aldrich Chemical Co., Inc.
(13) Sample from Professor H. Feuer, Department of Chemistry, Purdue University, Lafayette, Ind.
(14) Sample from Dr. A. T. Nielsen, U. S. Naval Ordnance Test Station, China Lake, Calif.