Naphthyridine Chemistry XV. The Meisenheimer Reaction of 1,6-Naphthyridine 1,6-Dioxide

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The reaction of 1,6-naphthyridine 1,6-dioxide (**1**) with phosphorus oxychloride has been reported to yield 2,5-dichloro-1,6-naphthyridine (**2**) (13.5%) and 2,8-dichloro-1,6-naphthyridine (**3**) (15%) (1). Our interest (2,3) in these reactions led us to question the validity of the structural assignment of the major compound **3**, in this reaction and prompted its reinvestigation.

Gas chromatographic analysis of the reaction mixture indicated the presence of at least four components. The four gas chromatographic "peaks" were collected by preparative gas chromatography and, in order of elution, after further purification were identified as 5-chloro- (**4**) (2.4%), 3,5-dichloro- (**5**) (42.1%), 2,5-dichloro- (**2**) (33.8%) and 4,5-dichloro-1,6-naphthyridine (**6**) (15%). These identifications rest upon the following evidence:

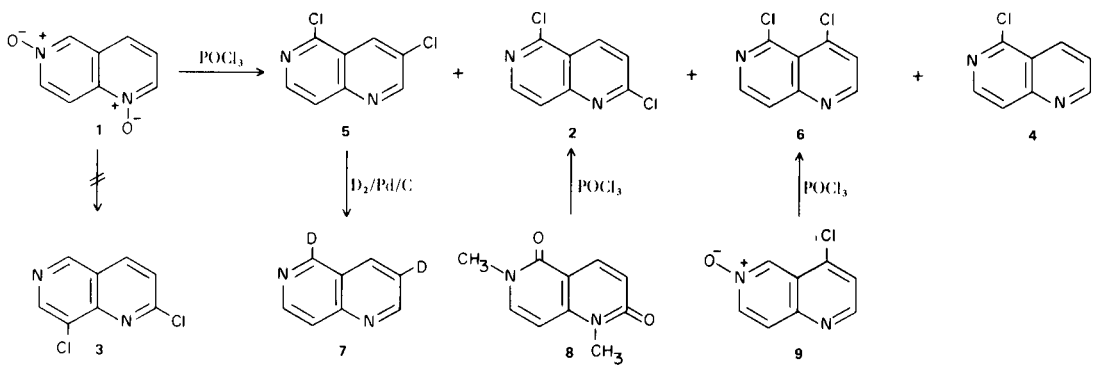
The major component, 3,5-dichloro-1,6-naphthyridine (**5**) was treated with deuterium in the presence of Pd/C catalyst to afford a dideuterio-1,6-naphthyridine which, by its pmr spectrum (see Experimental), is clearly 3,5-dideuterio-1,6-naphthyridine (**7**). Furthermore, the pmr spectrum of the dichloro compound in question is also clearly indicative of the positions of substitution. The physical properties of the 3,5-dichloro-1,6-naphthyridine (**5**) are identical to the properties that have been assigned to the "2,8-dichloro-1,6-naphthyridine" by earlier workers (1).

The second most abundant component was identified as the 2,5-dichloro-1,6-naphthyridine (**2**) by its unequivocal synthesis from 1,6-dimethyl-1,6-naphthyridine-2,6-(1*H*, 6*H*)dione (8) as shown in Scheme I.

The third "component" obtained from the gas chromotographic separation of the reaction mixture proved to be a mixture of at least three components as evidenced by its pmr spectrum. The major component (70%) of this minor fraction (21.7%) was identified as 4,5-dichloro-1,6-naphthyridine (**6**) by comparison with an authentic sample prepared as shown in Scheme I.

It has already been shown (1), that the treatment of 1,6-naphthyridine 6-oxide with phosphorus oxychloride affords the 5-chloro-1,6-naphthyridine as the, by far, major component. If we keep in mind that isoquinoline type *N*-oxides are more reactive than quinoline type *N*-oxides (4), we can anticipate the formation of 5-chloro-1,6-naphthyridine 1-oxide as the initial product. Once the 5-position is occupied by a chlorine atom, the second reaction sequence should give smaller amounts of the 4-chloro-derivative, because of the steric *peri* effect involved in this case, than is obtained from the reaction of 1,6-naphthyridine 1-oxide with phosphorus oxychloride. On the other hand, the formation of the 2,5- and the 3,5-dichloro derivatives should follow a pattern very similar to that observed in the 1,6-naphthyridine 1-oxide

SCHEME I



instance (2). These considerations are born out by the results obtained in this study.

The formation of 5-chloro-1,6-naphthyridine (**4**) can be accounted for by deoxygenation of the 1,6-naphthyridine 1,6-dioxide (**1**) at N-1, followed by subsequent reaction of the 6-oxide with phosphorus oxychloride. However, it also seems reasonable to suggest that the 5-chloro-1,6-naphthyridine generated from the 1,6-dioxide, is formed *via* deoxygenation of the potential intermediate 5-chloro-1,6-naphthyridine 1-oxide.

EXPERIMENTAL

Preparation of 6-Methyl-1,6-naphthyridin-5(6*H*)one Methiodide (**10**).

A solution of 6-methyl-1,6-naphthyridin-5(6*H*)one (5) (1g., 6.2 mmoles) in dry benzene (200 ml.) was refluxed for 3 days under a dry static nitrogen atmosphere. Filtration of the cooled mixture afforded the crude product (1.836 g., 0.16 mmoles, 97% m.p. 239-245°). A sample recrystallized from methanol-ether produced analytically pure material (m.p. 251-252°).

Anal. Calcd. for $C_{10}H_{11}IN_2O$: C, 39.75; H, 3.67; N, 9.27. Found: C, 40.01; H, 3.52; N, 9.30.

Preparation of 1,6-Dimethyl-1,6-naphthyridine-2,5(1*H*,6*H*)dione (**8**).

A sample of compound **10** (1.7 g., 5.6 mmoles) was treated according to the procedure of Rapoport and Batcho (6). The dried chloroform extracts were evaporated to afford product (0.927 g., 4.9 mmoles). This yellow material was twice sublimed to yield analytically pure compound **8** (0.8 g., 4.2 mmoles, m.p. 205-207° 75%); nmr (deuteriochloroform) τ 3.43 (H-3,d), 1.83 (H-4,d), 2.58 (H-7,d), 3.70 (H-8,d); J_{34} = 9.5 cps, J_{78} = 8.0 cps.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.24; H, 5.37; N, 14.52.

Preparation of 2,5-Dichloro-1,6-naphthyridine (**2**).

A mixture of the dione **8** (230 mg., 1.21 mmoles) and phosphorus oxychloride (25 ml.) in a sealed Carius tube was heated to 180° for 24 hours. The tube was cooled, opened and emptied into a 50 ml. flask. The excess phosphorus oxychloride was removed under aspirator vacuum to afford a residue which was treated with ice-cold sodium bicarbonate solution (50 ml.). The chloroform extracts (4 x 30 ml.) of the mixture were dried, filtered and evaporated to dryness yielding 207 mg. of material. An ether solution of this material was passed through an alumina column to afford cream-colored 2,5-dichloro-1,6-naphthyridine (**2**) (187 mg., 0.94 mmole) m.p. 175-176° (lit. 173-174° (1) 78%).

Preparation of 4-Chloro-1,6-naphthyridine 6-Oxide (**9**).

A solution of 4-chloro-1,6-naphthyridine (400 mg., 2.44 mmoles) and *m*-chloroperbenzoic acid (500 mg., 85%) in 30 ml. of chloroform was refluxed for 25 minutes. Tlc (alumina; chloroform) indicated that all of the starting material had been consumed. The solution was diluted to 125 ml. with ice-cold chloroform and extracted with cold, saturated sodium bicarbonate solution (3 x 25 ml.). The basic extracts were then reextracted with chloroform (3 x 50 ml.), and the combined chloroform extracts were dried with anhydrous magnesium sulfate and evaporated onto 5 g. of neutral alumina. This mixture was placed on an alumina column prepared with neutral alumina (Grade III) and anhydrous ether. The column was then successively eluted with 300 ml. of anhydrous ether to remove a small amount of starting material, 50 ml. of 50% chloroform-ether, and finally 300 ml. of chloroform. The desired material (compound **9**) (200 mg., 1.11 mmoles, 45%) was contained in the chloroform fraction. This material melted at 152-154° dec.; (nmr(deuteriochloroform) τ 1.18 (H-2,d) 2.39 (H-3,d) 0.96 (H-5,d) 1.60 (H-7,dd) 2.04 (H-8,d); J_{23} = 5 cps, J_{57} = 1.1 cps, J_{78} = 7 cps) and was used without further purification.

Preparation of 4,5-Dichloro-1,6-naphthyridine (**6**).

A sample of compound **9** (200 mg., 1.11 mmoles) was refluxed with phosphorus oxychloride (10 ml.) for 3 hours. The work-up was the same as that described for the preparation of 2,5-dichloro-1,6-naphthyridine. Removal of the chloroform gave the crude product (74 mg. 0.37 mmole, 33%). An analytical sample of 4,5-dichloro-1,6-naphthyridine (**6**) was obtained by preparative gas chromatography (m.p. 134-135°, nmr (deuteriochloroform) τ 1.16 (H-2,d), 2.40 (H-3,d), 1.52 (H-7,d), 2.15 (H-8,d); J_{23} = 4.8 cps, J_{78} = 5.8 cps).

Anal. Calcd. for $C_8H_4Cl_2N_2$: C, 48.27; H, 2.03; N, 14.08. Found: C, 48.49; H, 2.09; N, 14.34.

Formation of 3,5-Dideuterio-1,6-naphthyridine (**7**).

A sample (100 mg., 0.5 mmole) of the major component of the Meisenheimer reaction of compound **1** was dissolved in absolute methanol (20 ml.) containing fused potassium acetate (0.7 g.) and 10% Pd/C (50 mg.) (8). The reduction was conducted with deuterium gas until tlc (alumina:ether) revealed the presence of only 1,6-naphthyridine (approximately 30 ml. of deuterium gas (uncorrected) had been absorbed). The solution was filtered to remove catalyst and the filtrate was evaporated nearly to dryness. Water (15 ml.) and saturated sodium carbonate (3 ml.) was added and the resulting solution was continuously extracted (18 hours) with dichloromethane. The extract was dried with anhydrous magnesium sulfate, filtered and evaporated to an oil (50 mg., 77%). The nmr spectrum of this material indicated that H_3 and H_5 of 1,6-naphthyridine had been replaced by deuterium (nmr (deuteriochloroform) τ 0.95 (H-2,d), 1.17 (H-7,d), 1.75 (H-4,d), 2.08 (H-8,d); J_{24} = 1.9 cps, J_{78} = 6.0 cps).

The Meisenheimer Reaction of 1,6-Naphthyridine 1,6-Dioxide (**1**).

A sample of compound **1** (1.0 g., 6.1 mmoles) was refluxed for 1 hour with phosphorus oxychloride (50 ml.). The work-up included removal of excess phosphorus oxychloride under aspirator vacuum, treatment of the residue with ice-cold sodium bicarbonate solution (70 ml.), and extraction of the resulting mixture with dichloromethane (5 x 75 ml.). The extracts were dried with anhydrous sodium carbonate, filtered and evaporated to dryness to leave a solid (0.712 g.). This was dissolved in a small amount of chloroform and used for gas chromatographic analysis. The analytical and preparative chromatography were conducted with the same column utilizing the same conditions: 20 ft. x 3/8 inches aluminum column, packed with 20% SE-30 on Chromosorb W, column temperature 230°, flow rate 200 ml./min. The trace showed four peaks (compound, amount retention time) identified as the following: 5-chloro-1,6-naphthyridine, 2.4%, 12.4 minutes; 3,5-dichloro-1,6-naphthyridine, 42.1%, 16.9 minutes; 2,5-dichloro-1,6-naphthyridine, 33.8%, 18.4 minutes; the main component (70%) of peak 4 (21.7%) is 4,5-dichloro-1,6-naphthyridine, 21.5 minutes. The two minor components of peak 4 could be isolated but attempted separation of the components from 4,5-dichloro-1,6-naphthyridine by fractional recrystallization, fractional sublimation or micro-column chromatography led to

decomposition of these components, as evidenced by formation of orange solids. The mixture was analyzed by nmr spectroscopy, which showed the presence of three compounds, the major component being 4,5-dichloro-1,6-naphthyridine. The 3,5-dichloro-1,6-naphthyridine obtained by gc melted at 98-99° (lit. 93-94° (1); nmr (deuteriochloroform) τ 1.01 (H-2,d), 1.43 (H-4,dd), 1.52 (H-7,d), 2.16 (H-8,dd)).

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