(d) Establishment of the $1^+ + 1 \rightleftharpoons 2^+ \rightleftharpoons 2 + H^+$ Equilibrium (Scheme I). These sealed-tube reactions were similar to those of part a in scale and procedure. Compound **3** or a mixture of **2** and **3** was used instead of **1**; the mole ratio of water to the zinc chloride was 1. The reaction time was 1–8 h at 165 °C. When the tubes were opened, no internal standard was added. GLC column A was used to analyze for **1**, **4**, and **5**, and GLC column B was used to analyze for the dimers.

Preliminary Kinetic Experiment (Table III). This reaction was run in a vessel consisting of two separate compartments in the configuration of an inverted Y. One compartment was loaded with zinc chloride monohydrate and the other with **1** (zinc chloride monohydrate/**1** molar ratio of 1:10). The apparatus was swept with nitrogen, equilibrated to 165 ± 0.5 °C in a constant-temperature oil bath, and then tilted to allow the reactants to mix. The two-phase reaction mixture was magnetically stirred, and samples of the upper hydrocarbon phase were withdrawn with a syringe at predetermined times. The samples were mixed with a known amount of internal standard (2-methylnaphthalene in benzene) and analyzed on GLC columns A (for **1**, **4**, and **5**) and B (for dimers).

Acknowledgment. We thank Mr. John Elwell at Hill Air Force Base for taking mass spectra and Dr. Ronald J. Pugmire, who assisted in obtaining and interpreting ^{13}C NMR spectra. Financial support from the United States Department of Energy through Contracts E(49-18)-2006 and DE-AC02-79ER10510 is gratefully acknowledged. For assistance in the preparation of this manuscript, we thank the Northwest College and University Association for Science (University of Washington) under Contract DE-AMOL6-76-RL02225 with the U.S. Department of Energy.

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Occurrence of Even Telesubstitution in the Amination of Halogeno-2,6-naphthyridines[1-3]

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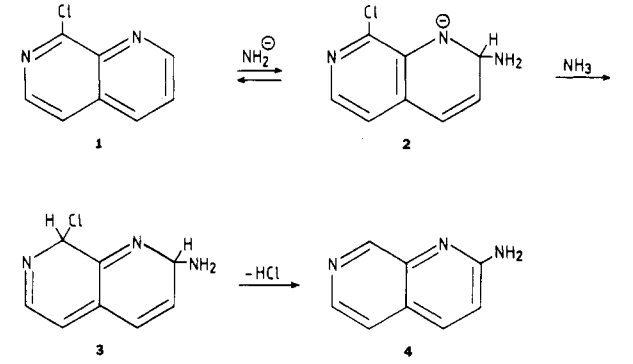
The conversion of 1-halogeno-2,6-naphthyridines into 1-amino-2,6-naphthyridine is shown to proceed via an even telesubstitution process [$S_N(AE)^{tele}$ process]. The amination of 2-bromo-1,5-naphthyridine into 2-amino-1,5-naphthyridine is shown to proceed via an $S_N(AE)^{ipso}$ substitution mechanism.

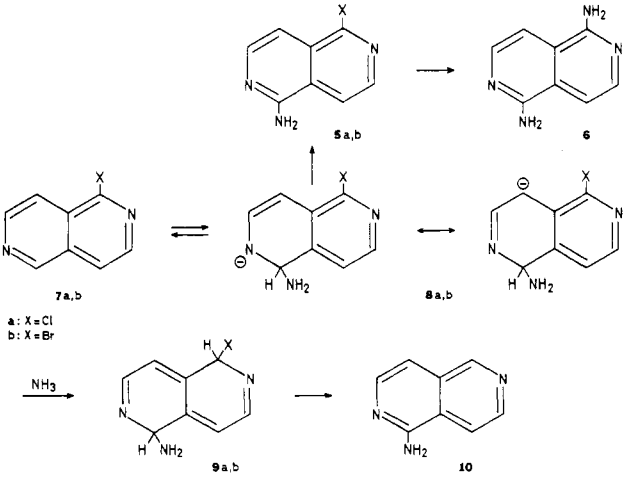
It has been reported[4,5] that 8-chloro-1,7-naphthyridine (**1**) when reacted with potassium amide in liquid ammonia (KNH_2/NH_3) undergoes a teleamination, leading to 2-amino-1,7-naphthyridine (**4**). As an even number of positions lies between the position of attack of the nucleophile and the position of departure of the leaving group, this reaction can be classified as an *even* telesubstitution. Odd telesubstitutions are also described, as exemplified by the amination of 7-chloro-2-deuterio-1,8-naphthyridine into 2-amino-1,8-naphthyridine.[4,5] The introductory step of the 1,4-teleamination of 8-chloro-1,7-naphthyridine (**1**) is the σ-adduct formation at position 2, yielding 2-amino-8-chloro-2,*X*-dihydro-1,7-naphthyridinide (**2**); its formation has been proved by NMR spectroscopy. Adduct **2** undergoes protonation at C-8 into **3** which by a base-catalyzed dehydrohalogenation gives product **4** ($S_N(AE)^{tele}$, Scheme I). This result induced us to study in more detail the generality of the phenomenon of even teleaminations in the naphthyridine series.

Recent investigations[3] have shown that 2,6-naphthyridine undergoes exclusively σ-adduct formation at C-1 (C-5) when dissolved in KNH_2/NH_3. This result induced our interest in the behavior of the 1-chloro(bromo)-2,6-naphthyridine (**7a,b**) toward potassium amide

Scheme I



Scheme II



since it is possible that also the 1-halogeno compounds **7a** and **7b** undergo addition at C-5, giving **8a** and **8b**, re-

(1) Part 32 on "NMR Investigations on σ Adducts of Heterocyclic Compound". See for part 31: Dlugosz, A.; van der Plas, H. C.; van Veldhuizen, A. *J. Heterocycl. Chem.*, in press.

(2) Part 17 on "Telesubstitutions in Heterocyclic Systems" from this laboratory. See for part 16: Kos, N. J.; van der Plas, H. C.; van Veldhuizen, A. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 267.

(3) Part 15 on "Naphthyridines". See for part 14: van den Haak, H. J. W.; van der Plas, H. C.; van Veldhuizen, A. *J. Heterocycl. Chem.* **1981**, *18*, 1349.

(4) van der Plas, H. C.; Wozniak, M.; van Veldhuizen, A. *Tetrahedron Lett.* **1976**, 2087.

(5) van der Plas, H. C.; Wozniak, M.; van Veldhuizen, A. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 151.

0022-3263/82/1947-1673$01.25/0

Table I. ^{1}H NMR Spectral Data of 1-Chloro- (7a) and 1-Bromo-2,6-naphthyridine (7b) and 2-Bromo-1,5-naphthyridine (19a) and Their σ Adducts in KNH_2/NH_3

compd	solvent	shift, δ H-3	H-4	H-5	H-6	H-7	H-8
7a	$CDCl_3$	8.40	7.57	9.28		8.75	7.93
8a	KNH_2/NH_3	7.42	6.84	5.01		7.21	4.74
		Δδ 0.98	0.73	4.27		1.54	3.19
7b	$CDCl_3$	8.39	7.68	9.23		8.73	7.91
8b	KNH_2/NH_3	7.44	6.90	5.01		7.27	4.75
		Δδ 0.95	0.78	4.22		1.46	3.16
19a	$CDCl_3$	7.74	8.25		8.99	7.64	8.25
20a	KNH_2/NH_3	*a*	*a*		4.94	5.34	*a*
					Δδ 4.05	2.30	

[a] These protons were detected as a broad multiplet at 6.2–7.3 ppm.

Table II. ^{13}C NMR Spectral Data of 1-Chloro- (7a) and 1-Bromo-2,6-naphthyridine (7b) and Their σ Adducts in KNH_2/NH_3

compd	solvent	shift, δ C-1	C-3	C-4	C-5	C-7	C-8	C-9	C-10
7a	$CDCl_3$	151.0	143.6	119.5	152.1	146.3	117.8	129.5	132.0
8a	KNH_2/NH_3		134.8	121.4	68.1	153.2	78.1	138.5	131.8
			Δδ 8.8	−1.9	84.0	−6.9	39.7	−9.0	0.2
7b	$CDCl_3$	144.5	144.1	120.0[a]	152.1	146.5	119.7[a]	131.7	131.7
8b	KNH_2/NH_3		135.3	121.8	68.5	153.2	80.1		
			Δδ 8.8	−1.8	83.6	−6.7	39.6		

[a] These signals may be interchanged.

spectively, which after protonation and a 1,6-dehydrohalogenation yield the teleamination product 5(1)-amino-2,6-naphthyridine (**10**, Scheme II).

NMR Spectroscopy of Solutions of 7a and 7b

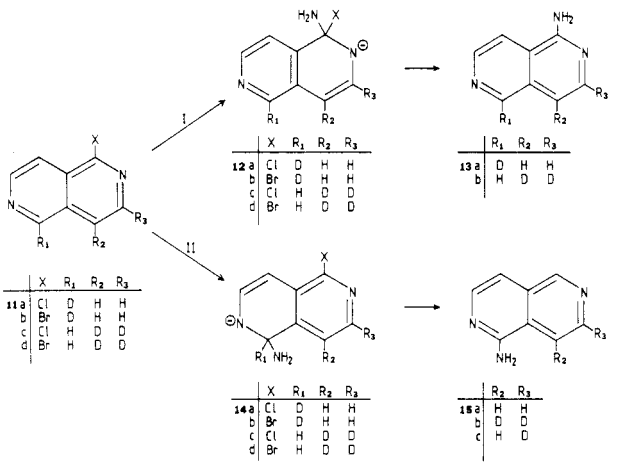
Compounds **7a,b** (being readily prepared from 2,6-naphthyridin-1(2*H*)-one[3]) when dissolved in liquid ammonia containing potassium amide indeed form the σ adducts **8a** and **8b**, as is shown by NMR spectroscopy (Table I). On comparison of the chemical shifts observed in solutions of **7a** and **7b** in KNH_2/NH_3 with those in solutions of **7a** and **7b** in $CDCl_3$, all hydrogens have undergone upfield shifts, but especially the shift of H-5 is considerable ($\Delta\delta$ = 4.27 and 4.22 ppm, respectively). This large upfield shift of H-5 can be explained by the fact that C-5 rehybridizes ($sp^2 \rightarrow sp^3$) due to σ-adduct formation at this position, leading to the 5-amino-5,*X*-dihydro-1-halogeno-2,6-naphthyridinides (**8a** and **8b**, respectively).[6]

Supporting evidence for the formation of a covalent amino adduct at position 5 has been provided by ^{13}C NMR spectroscopy, showing an upfield shift of about 84 ppm for C-5 (Table II). C-8 in **8a** and **8b** has also undergone a great upfield shift (about 40 ppm) due to the aza allylic resonance contribution which predicts a considerable negative charge at positions meta to the nitrogen atom (Scheme II). Aza allylic stabilization in dihydroazinides has been recognized before[3,7,8] as an important contribution to the stability of these anionic species.

Amination of 7a and 7b

Treatment of **7a** with KNH_2/NH_3 at −33 °C for 63 h yielded 5(1)-amino-2,6-naphthyridine (**10**, 20%), 1,5-diamino-2,6-naphthyridine (**6**, 17%), and 29% of the starting material **7a**. Amination of **7b** gave the products **10** and **6** in 28% and 14% yields, respectively, together with 36% of the starting material **7b**. The formation of σ adducts **8a** and **8b** in KNH_2/NH_3 suggests that the conversion of **7** into **10** may occur via **8**. To investigate this possible reaction pathway, we prepared 5-deuterio-1-halogeno-2,6-naphthyridines **11a** and **11b** by heating of 2,6-naphthyridin-1(2*H*)-one with D_2O and subsequent treatment of the product with POX_3.

Scheme III



From the two pathways[9] for amination, i.e., $S_N(AE)^{ipso}$ (route I, Scheme III), involving as an intermediate **12a,b**, and $S_N(AE)^{tele}$, involving as an intermediate **14a,b** (route II, Scheme III), it is evident that if the amination of **11a** or **11b** should occur via an $S_N(AE)^{ipso}$ process, the 1-amino compound **13a** still contains the same percentage of deuterium labeling at C-5 as was present in the starting material **11a** or **11b**, while in the case where substitution occurs via an $S_N(AE)^{tele}$ process involving the C-5 adduct **14a** or **14b**, no deuterium should be present in the amino compound formed, i.e. **15a**.

(6) Formally the correct nomenclature for **8a** and **8b** is 1-amino-5-halogeno-1,*X*-dihydro-2,6-naphthyridinide. For the sake of clarity, however, we prefered the nomenclature used here.

(7) van den Haak, H. J. W.; van der Plas, H. C.; van Veldhuizen, A. *J. Org. Chem.* **1981**, *46*, 2134.

(8) Zoltewicz, J. A.; Helmick, L. S.; Oestreich, T. M.; King, R. W.; Kandetzki, P. E. *J. Org. Chem.* **1973**, *38*, 1947.

(9) The term $S_N(AE)^{ipso}$ denotes a nucleophilic substitution in which the nucleophile attacks the same position that bears the leaving group. The term $S_N(AE)^{tele}$ denotes a nucleophilic substitution in which the nucleophile enters the molecule more than one position removed from the position from which the leaving group departs.

It was found that the amino compound obtained on amination of **11a** (18.6% undeuterated, 66.1% monodeuterated, and 15.3% dideuterated) and **11b** (19.2% undeuterated, 64.7% monodeuterated, and 16.1% dideuterated) showed a percentage of deuterium that was considerably lower than that present in the starting material **11a** and **11b** (the amino compound from **11a** was 73.9% undeuterated, 22.4% monodeuterated and 3.6% dideuterated; the amino compound from **11b** was 54.0% undeuterated, 37.8% monodeuterated, and 8.0% dideuterated).

From the mass spectroscopic data it was calculated that the *deuterated* compound **11a** reacts about 5 times faster in the $S_N(AE)^{tele}$ process than in the $S_N(AE)^{ipso}$ process (see Appendix). Moreover, it was found that the recovered starting material had a greater percentage of deuterium than that present in the original starting material (the **11a** recovered was 6.2% undeuterated, 82.0% monodeuterated, and 11.8% dideuterated; the **11b** recovered was 17.2% undeuterated, 66.9% monodeuterated, and 15.9% dideuterated). From this deuterium enrichment it was calculated that the $S_N(AE)^{tele}$ process has a kinetic isotope effect of about 2.5. This means that for the *undeuterated* compound **7a** the $S_N(AE)^{tele}$ substitution proceeds about 13 times faster than the $S_N(AE)^{ipso}$ process; in other words, on amination of **7a**, about 93% of product **10** is formed in an $S_N(AE)^{tele}$ process.

Similarly, it was found that the teleamination of **7b** has a kinetic isotope effect of 1.3 and that about 73% of product **10** is formed in a tele process. Confirmation of these results was obtained by a study of the amination of the 3,4-dideuterio-1-halogeno-2,6-naphthyridines **11c** and **11d**. These compounds were prepared by heating a basic solution of 2,6-naphthyridin-1(2*H*)-one in D_2O and subsequent treatment of the product obtained with POX_3.

Following the same lines as discussed above, it is evident that if **11c** and **11d** undergo amination according to an $S_N(AE)^{ipso}$ process (route I, Scheme III), 1-amino-3,4-dideuterio-2,6-naphthyridine (**13b**) is the expected product, whereas in an $S_N(AE)^{tele}$ process (route II, Scheme III), 5-amino-3,4-dideuterio-2,6-naphthyridine (**15b**) is obtained.

It was found that as the main product of the amination of both **11c** and **11d** neither **13b** nor **15b** but 5-amino-3-deuterio-2,6-naphthyridine (**15c**) was obtained. We assume that **15c** is formed from **15b** by an amide-catalyzed D/H exchange at position 4 in **15b**.

NMR spectroscopy showed that the product **15c** from **11c** contained 64% deuterium at position 3. No deuterium at other positions could be detected. Product **15c** from **11d** contained 46% deuterium at position 3. From these data it was calculated that the amination of **11c** proceeded for at least 92% via the $S_N(AE)^{tele}$ pathway. This result is in excellent agreement with the results obtained from amination of **11a**.

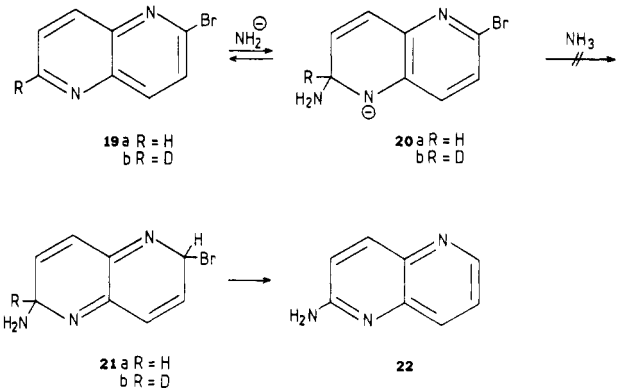
Amination of **11d** and investigation of the deuterium content of the product **15c** confirmed the results obtained from amination of **11b**.

Concerning the formation of the 1,5-diamino compound **6**, it is certain that this compound is not formed by subsequent amination of 1-amino-2,6-naphthyridine (**10**), since it has been reported[3] that Chichibabin amination of 2,6-naphthyridine at room temperature gave **10** and no trace of **6**. It seems more reasonable to explain the formation of **6** by a Chichibabin amination of **7a** and **7b** into 5-amino-1-halogeno-2,6-naphthyridine (**5a,b**) which reacts further to **6** (Scheme II).

Discussion

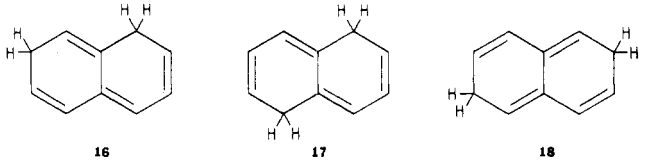
The conversion of the halogeno compounds **1**, **7a**, and **7b** into their corresponding amino compounds **4** and **10**, respectively, are both examples of even telesubstitutions. The amination of **7a** proceeds for 93% via the telemechanism, and the amination of **1** proceeds for 45% via a telepathway.[4,5]

Scheme IV



To understand why **1** is less inclined to telesubstitution than **7a**, one can make the suggestion that there is an energy difference between the nonaromatic dihydro intermediates **3** and **9**. Since the activation energy of the dehydrohalogenations of the dihydro intermediates is probably relatively small, the assumption seems justified that the different abilities of naphthyridines to undergo even telesubstitutions has some relation with the stabilities of the dihydro intermediates.

The linearly conjugated 1,5-dihydro system **9a** has probably somewhat more stability than the cross-conjugated 2,8-dihydro system **3**; therefore, its formation is favored. Some support for this statement can be taken from the fact that the estimated heat of formation of 1,7-(2,8)-dihydronaphthalene **16** is about 1.4 kJ/mol higher[10]



than that of its 1,5 isomer **17** at 240 K. The stability of 2,6-dihydronaphthalene (**18**) is estimated to be about 10 kJ/mol less than that of its 1,5 isomer **17**.[10] On the basis of these data we may expect that an even telesubstitution in which a 2,6-dihydronaphthyridine derivative is an intermediate is a very unfavorable process. In order to confirm this expectation, we investigated the occurrence of a teleamination with 2-bromo-1,5-naphthyridine (**19a**). This compound may give 2,6-dihydro intermediate **21a** (Scheme IV), which is considerably less stable than the dihydro compounds **3** and **9**.

There is convincing evidence for the formation of the 1:1 σ adduct **20a** when **19a** is dissolved in KNH_2/NH_3. The NMR spectrum of this solution, although not completely assigned due to its complexity, exhibits a double doublet at 5.34 ppm and a doublet at 4.94 ppm, which are ascribed to the signals derived from H-7 and H-6, respectively, of the 6-amino-2-bromo-6,*X*-dihydro-1,5-naphthyridinide (**20a**). The upfield shift of H-6 ($\Delta\delta$ = 4.05 ppm) is in good agreement with the reported value for σ-adduct formation in many naphthyridines[7,11] (see Table I). Moreover, in a solution of 2-bromo-6-deuterio-1,5-

(10) Shaw, K.; Golden, D. M.; Benson, S. W. *J. Phys. Chem.* **1977**, *81*, 1716.
(11) van der Plas, H. C.; van Veldhuizen, A.; Wozniak, M.; Smit, P. *J. Org. Chem.* **1978**, *43*, 1673.

naphthyridine (**19b**) in KNH_2/NH_3 no doublet at 4.94 ppm was present, and the double doublet at 5.34 ppm (due to H-7) was changed into a doublet. After reaction of **19b** with potassium amide in liquid ammonia we found that the isolated amino product had the same extent of deuteration as the starting compound. This means that the amination of **19** must proceed via an $S_N(AE)^{ipso}$ substitution process and not via an $S_N(AE)^{tele}$ substitution involving **20** and **21**.

The preparation of **19b** was accomplished by heating 1,5-naphthyridine in D_2O. The 2,6-dideuterio-1,5-naphthyridine obtained was oxidized with H_2O_2 to the *N*-oxide which on reaction with $POBr_3$ yielded 2-bromo-6-deuterio-1,5-naphthyridine **19b** (together with its 3-bromo isomer).

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were recorded on a Varian XL-100-15 spectrometer, a Varian EM 390 spectrometer, or a Hitachi Perkin-Elmer R-24B spectrometer. ^{13}C spectra were recorded on a Varian XL-100-15 spectrometer equipped with a Varian Fourier transform unit. The spectral width was 5000 Hz (1.25 Hz/point). Mass spectra were recorded on an AEI MS 902 instrument.

Starting Materials. The following compounds were prepared according to procedures described in the literature: 1-chloro-2,6-naphthyridine (**7a**),[12] 2,6-naphthyridin-1(2*H*)-one,[3] 2,6-dideuterio-1,5-naphthyridine,[11] 2-bromo-1,5-naphthyridine (**19a**).[4] 2,6-Dideuterio-1,5-naphthyridine *N*-oxide was prepared analogously to the procedure described for the undeuterated compound.[13]

1-Bromo-2,6-naphthyridine (7b). 2,6-Naphthyridin-1(2*H*)-one (0.49 g, 3.4 mmol) and 1.8 g (6.3 mmol) of $POBr_3$ were heated at 130–140 °C for 2 h in a stoppered flask. The reaction mixture was then cooled, carefully treated with ice and sodium bicarbonate, and extracted with ether. After the ethereal layer was dried on $MgSO_4$, the solvent was evaporated off, and the residue was purified by column chromatography on SiO_2 with $CHCl_3$ as the eluent, yielding **7b**: 0.50 g (71%); mp 94.5–95.5 °C. Anal. Calcd for $C_8H_5BrN_2$: C, 45.96; H, 2.41. Found: C, 46.25; H, 2.54.

1-Halogeno-5-deuterio-2,6-naphthyridine (11a,b). A 0.5-g (3.4 mmol) sample of 2,6-naphthyridin-1(2*H*)-one and 5 mL of D_2O were heated in a sealed tube at 155 °C for 12 h. After the mixture cooled, the solvent was evaporated off in vacuo and the residue treated with $POCl_3$ or $POBr_3$ as described above. NMR spectroscopy showed that the major part of the deuterium label (80%) in **11a,b** is present at position 5.

1-Halogeno-3,4-dideuterio-2,6-naphthyridine (11c,d). A 0.5-g (3.4 mmol) sample of 2,6-naphthyridin-1(2*H*)-one, 0.1 g of NaOH, and 5 mL of D_2O were heated in a sealed tube at 125 °C for 16 h. The mixture was neutralized with 1 N hydrochloric acid and continuously extracted with chloroform. Evaporation of the chloroform and treatment of the residue obtained with POX_3 (see above) gave **11c** and **11d**. NMR spectroscopy showed the following deuteration pattern: **11c**: position 3 has 77% D, position 4 has 74%, position 8 has 14% D. **11d**: position 3 has 74% D, position 4 has 73% D, position 8 has 21% D.

2-Bromo-6-deuterio-1,5-naphthyridine (19b). A 1.35-g (9.1 mmol) sample of 2,6-dideuterio-1,5-naphthyridine *N*-oxide was suspended in 30 mL of chloroform. The mixture was cooled in ice, and 3.67 g (12.7 mmol) of $POBr_3$ was added. After being stirred in ice for 15 min and subsequently at room temperature for an additional 15 min, the mixture was poured onto ice, basified with concentrated ammonia solution, and extracted with chloroform. The chloroform layer was dried on $MgSO_4$ and evaporated off in vacuo. The residue obtained was purified on a silica gel column with petroleum ether (bp 40–60 °C)/acetone (14:1) as the eluent. First 0.21 g (11%) of 3-bromo-2,6-dideuterio-1,5-naphthyridine was eluted and then 1.15 g (60%) of **19b**, followed by traces of 2,6-dideuterio-1,5-naphthyridine.

Amination of 1-Chloro-2,6-naphthyridine (7a). To a solution prepared by dissolving 0.20 g (5.1 mmol) of potassium in 30 mL of liquid ammonia containing a few crystals of ferric nitrate was added 0.20 g (1.2 mmol) of **7a**. After the mixture reacted at −33 °C for 63 h, 0.50 g of ammonium sulfate was added, and the ammonia was allowed to evaporate. Concentrated ammonia solution (25 mL) was added, and the mixture was continuously extracted with chloroform. The residue obtained on evaporation of the chloroform was dissolved in the minimum volume of methanol and placed on four plates (20 × 20 cm) covered with a 0.5-mm layer of silica GF 254. After the plates were developed 2 times in chloroform–ethanol (9:1), three bands were detected. Extraction of the upper band with methanol gave 14.2 mg (7%) of starting material, extraction of the middle band gave 35.8 mg (20%) of the 1-amino compound **10**, identical with an authentic specimen,[3] and extraction of the lower band gave 32.6 mg (17%) of 1,5-diamino-2,6-naphthyridine (**6**): mp >300 °C; ^1H NMR (Me_2SO) δ 6.51 (4 H, NH_2, br), 6.96 (2 H, H4, H8, d, J = 5.0 Hz), 7.67 (2 H, H3, H7, d, J = 5.0 Hz). It was analysed as its picrate (mp >300 °C). Anal. Calcd for $C_8H_8N_4 \cdot C_6H_3N_3O_7$: C, 43.19; H, 2.85. Found: C, 43.42; H, 2.93.

1-Bromo-2,6-naphthyridine (7b) was aminated in the same way as **7a**. The amination of 6-deuterio-2-bromo-1,5-naphthyridine (**19b**) was carried out as described in the literature.[14]

Acknowledgment. We are indebted to Drs. C. A. Landheer for carrying out mass spectroscopy, to Mr. H. Jongejan for microanalyses, and to Mr. A. van Veldhuizen for measuring ^1H and ^{13}C NMR spectra in liquid ammonia.

Appendix

The kinetic isotope effect and the percentage of telesubstitution in the amination of halogeno naphthyridines were calculated in the following way. If an unlabeled compound H reacts in a first-order reaction the concentration of H, [H], is described by

$$\ln ([H]/[H_0]) = (k_H + k)t$$

where $[H_0]$ = the concentration of H at $t = 0$, k_H = the reaction constant of the $S_N(AE)^{tele}$ reaction of the *un*deuterated compound, and k = the reaction constant of the $S_N(AE)^{ipso}$ reaction; k is assumed to be equal for the deuterated and the undeuterated compound. For a deuterated compound D we find

$$\ln ([D]/[D_0]) = (k_D + k)t$$

where $[D_0]$ = the concentration of D at $t = 0$ and k_D = the reaction constant of the $S_N(AE)^{tele}$ reaction of the deuteated compound. Combination of the equations gives

$$\frac{[k_H]}{[k_D]} = \frac{\ln [H] - \ln [H_0]}{\ln [D] - \ln [D_0]}\left(1 + \frac{k}{k_D}\right) - \frac{k}{k_D}$$

where k_H/k_D is the kinetic isotope effect of the $S_N(AE)^{tele}$ reaction. The calculation of k/k_D, which is the ratio of the reaction constants of the $S_N(AE)^{ipso}$ reaction and the $S_N(AE)^{tele}$ reaction of the deuterated compound, is shown by the example below, where d_0 = undeuterated, d_1 = mon-

11a	→	15a
18.6% d_0		73.9% d_0
66.1% d_1		22.4% d_1
15.3% d_2		3.6% d_2

odeuterated, and d_2 = dideuterated. If d_2 starting material reacts in an $S_N(AE)^{tele}$ reaction, d_1 product is formed, whereas in an $S_N(AE)^{ipso}$ reaction of d_2 starting material, d_2 product is formed (Scheme III). So if 15.3% of d_2 starting material yields 3.6% of d_2 product, 15.3 − 3.6 = 11.7% of d_1 product is formed. This means that 11.7%

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of the d_1 product is formed in an $S_N(AE)^{tele}$ reaction of the d_2 starting material, and the rest (22.4 – 11.7 = 10.7%) is formed in an $S_N(AE)^{ipso}$ reaction of d_1 starting material. So from 66.1% of d_1 product, 10.7% undergoes an $S_N(AE)^{ipso}$ reaction, and the rest (66.1 – 10.7 = 55.4%) undergoes an $S_N(AE)^{tele}$ reaction, or in other words k/k_D = 10.7/55.4 = 0.18. From k_H/k_D and k/k_D, k_H/k can be calculated. k_H/k is the ratio of the reaction rate of the $S_N(AE)^{tele}$ reaction in the undeuterated compound and the rate of the $S_N(AE)^{ipso}$ reaction.

Registry No. 6, 81044-13-5; **6** picrate, 81044-14-6; **7a**, 80935-78-0; **7b**, 81044-15-7; **8a**, 81044-16-8; **8b**, 81044-17-9; **11a**, 81044-18-0; **11b**, 81044-19-1; **11c**, 81063-98-1; **11d**, 81044-20-4; **15a**, 80935-81-5; **15b**, 81044-21-5; **15c**, 81044-22-6; **19a**, 51532-07-1; **19b**, 81044-23-7; **20a**, 81044-24-8; 2,6-naphthyridin-1(2*H*)-one, 80935-77-9; 2,6-dideuterio-1,5-naphthyridine *N*-oxide, 81044-25-9.

Synthesis of Novel Phosphorus Heterocycles: 1,3-Dihydro-2,1-Benzoxaphosphole 1-Oxides[1,2]

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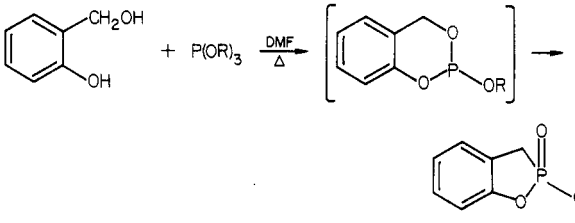
A class of novel phosphorus heterocycles, 1,3-dihydro-2,1-benzoxaphosphole 1-oxides, has been prepared by two different routes. One general approach involves the cyclization of ortho-substituted phenylphosphinic acid derivatives under either thermal or solvolytic conditions. The other route involves a novel metal–halogen exchange on the corresponding ortho-substituted aryl bromide with subsequent intramolecular transposition of the phosphorus moiety. The mechanisms for these various transformations are discussed in some detail.

Previous work in our laboratory has centered around the syntheses of phosphorus heterocycles I–III (Chart I).[3,4] Therefore, the synthesis of the oxygen analogue (IV) of heterocycle III was desired to complete this series of phosporus heterocycles. Westheimer and others have previously reported the synthesis of the monocyclic phosphorus ester V.[5]

The thrust of this paper is to describe our synthetic approaches to the 1,3-dihydro-2,1-benzoxaphosphole 1-oxide ring system IV. The spectral characteristics of this heterocycle, as well as its hydrolysis in weak base, are also discussed.

Results and Discussion

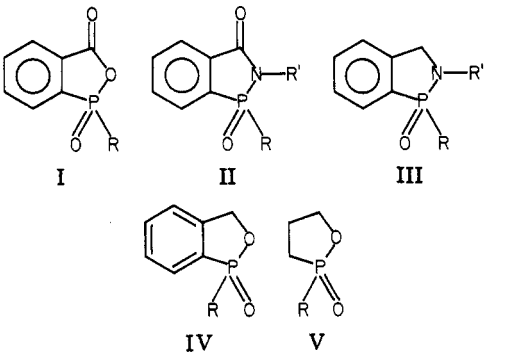
Phosphorus heterocycles IV are named 1,3-dihydro-2,1-benzoxaphosphole 1-oxides. They have not been reported but are isomeric to the so-called "phosphaindan",[6] obtained from the reaction of *o*-hydroxybenzyl alcohol with trialkyl phosphite as outlined in eq 1.



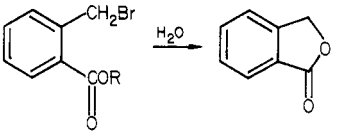
(1)

A similar synthetic approach to the 1,3-dihydro-2,1-benzoxaphosphole 1-oxide ring system was not possible, since the phosphorus moiety in IV is bonded directly to the aromatic ring. However, two general approaches for the synthesis of IV were considered. One route paralleled

Chart I



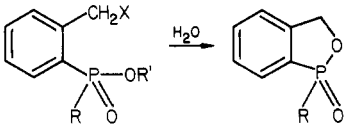
the reported synthesis of phthalide.[7] In particular, it is known that the solvolysis of *o*-carboxybenzyl bromide or its alkyl ester yielded phthalide[7] as shown in eq 2. By



(2)

R = H, alkyl

analogy, solvolysis of the corresponding phosphinate or phosphonate might provide the desired 1,3-dihydro-2,1-benzoxaphosphole 1-oxide as depicted in eq 3.



(3)

IV

Toward this end, either diethyl *o*-tolylphosphonate[8] (**1a**) or ethyl *o*-tolylmethylphosphinate[4] (**1b**) was brominated

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