4 can be considered as reactive difunctional (two atoms of Cl) monomers useful in polycondensation processes leading to the linear-chain polymers (for example by reaction with diphenols). The parent tetrachloro compounds 1 and 2 can in turn be expected to yield cyclolinear polymers by direct reaction with aromatic, *p*-diols in a manner similar to the case reported by Kajiwara.[6]

Experimental Section

General Methods. All substitution experiments were carried out in an atmosphere of dry argon in a standard glass apparatus. Moisture was excluded by calcium chloride drying tubes.

Melting points were measured on a Boetius microscope hot stage and are uncorrected.

The IR spectra were performed as Nujol or halocarbon mulls on a UR-120 Carl Zeiss Jena spectrophotometer. The ^1H NMR spectra were recorded on a Varian XL-100 spectrometer using Me_4Si as an internal standard. The proton-noise-decoupled ^{31}P NMR spectra were obtained on a JEOL FX-60 spectrometer at 24.3 MHz by using 85% H_3PO_4 as an external standard. The mass spectra were recorded on a LKB 9000 mass spectrometer at a 70-eV electron energy and at an ion source temperature of 290 °C. TLC experiments were carried out on Merck Precoated silica gel 60 plates (solvent system 1:1 benzene–hexane). Visualization was performed by pyridine–*m*-toluidine (1:1) reagent for all chlorine-containing cyclophosphazenes (**1–4**)[13] and by Millon's reagent[14] for all aryloxy-substituted cyclophosphazenes (**1–6**).

Materials. 3,3,5,5-Tetrachloro-1,1-(1,1′-dioxy-2,2′-binaphthyl)cyclotriphosphazene (1) and 3,3,5,5-tetrachloro-1,1-(2,2′-dioxy-1,1′-binaphthyl)cyclotriphosphazene (2) were obtained and purified according to the method described previously:[7] mp 310 °C (**1**), 283 °C (**2**). **Sodium phenolate (7)** was prepared by the reaction of sodium and phenol carried out in tetrahydrofuran solvent. Phenol was freshly distilled before use; mp 41 °C. Tetrahydrofuran was distilled from potassium hydroxide pellets and then dried over calcium hydride. Argon was passed through concentrated sulfuric acid and then through 4-Å molecular sieves.

Synthesis. 3,5-Diphenoxy-3,5-dichloro-1,1-(1,1′-dioxy-2,2′-binaphthyl)cyclotriphosphazene (3) and 3,5-Diphenoxy-3,5-dichloro-1,1-(2,2′-dioxy-1,1′-binaphthyl)cyclotriphosphazene (4). Under an argon atmosphere a solution of 0.02 M C_6H_5ONa in tetrahydrofuran (50 mL) was added dropwise over a 1-h period to a stirred solution of 0.01 mol (5.61 g) of **1** or **2** in 100 mL of THF at 30–40 °C. The substitution was found to proceed almost quantitatively on addition of phenolate as no traces of base were indicated in the reaction mixture immediately after the addition was completed. To ensure completion, we refluxed the mixture for 2–3 h. The sodium chloride formed in the reaction was removed by centrifugation and determined by titration with 0.01 N $AgNO_3$. The cold solution was poured into excess H_2O to yield a white solid, which was isolated by filtration, washed on the filter with water, dried in air, and finally dried under vacuum (yield of the crude product 6.32 g from **1** or 6.48 g from **2**). The product was purified by column chromatography on silica with hexane–benzene (2:1). When the eluted fractions were allowed to stand overnight, compound **3** or **4** crystallized directly in the form of white crystals: mp 202 °C (**3**), 213 °C (**4**); yield 5.60 g (82.8%) of **3**, 5.42 g (80.3%) of **4**; IR (Nujol mull) 3070 (CH_{Ar}), 1590, 1485 (Ar skeleton) 1265, 1255, 1185, 1160, and 1085 (POC_{Ar} and P=N) cm^{-1} (**3**); 3070, 1620, 1590, 1500, 1270, 1250, 1210 (**4**); UV (cyclohexane) λ_{max} 215 nm (ϵ 5.2×10^4), 259 (1.18×10^5), 272 (3.6×10^4) (**3**); 216 (1.4×10^5), 262 (1.0×10^4), 305 (1.8×10^4) (**4**); ^1H NMR ($CDCl_3$) δ 7.0–7.9 (m, 20 H), 8.0–8.1 (m, 2 H) ppm (**3**); 6.9–7.4 (m, 17 H), 7.6–8.0 (m, 5 H) ppm (**4**); ^{31}P NMR, Table I; mass spectrum, *m/e* (relative intensity) 679 [17.1, $(M + 4)^+$], 677 [75.1, $(M + 2)^+$, 675 [100, M^+], (**3**); 679 [15.2, $(M + 4)^+$], 677 [69.5, $(M + 2)^+$], 675 [100, M^+] (**4**). Anal. Calcd for $C_{32}H_{22}O_4Cl_2N_3P_3$: C, 56.70; H, 3.26; Cl, 10.50; N, 6.21; P, 13.75. Found (for **3**): C, 56.54; H, 3.76; Cl, 10.3; N, 6.14; P, 13.40. Found (for **4**): C, 56.32; H, 3.78; Cl, 10.45; N, 6.17; P, 13.54.

3,3,5,5-Tetraphenoxy-1,1-(1,1′-dioxy-2,2′-binaphthyl)-cyclotriphosphazene (5) and 3,3,5,5-Tetraphenoxy-1,1-(2,2′-dioxy-1,1′-binaphthyl)cyclotriphosphazene (6). Under an argon atmosphere a solution of 0.042 mol of sodium phenolate in 50 mL of tetrahydrofuran was added dropwise with stirring to a boiling solution of 5.59 g (0.01 mol) of **1** and **2** in 100 mL of THF. When the addition was completed, the mixture was refluxed for 4–5 h until TLC showed complete reaction of the chlorine atoms in **1** or **2**. This could be deduced from the absence of any colored spots after the developed TLC plates were sprayed with pyridine–*m*-toluidine (1:1) detecting reagent.[14] After the precipitate was centrifuged free of sodium chloride, the slightly alkaline filtrate was poured into an excess of cold 5% aqueous HCl to yield a gray solid which was isolated and purified by recrystallization from benzene-heptane (1:2). The white crystals formed by crystallization were heated under vacuum at 100 °C to remove retained solvent: yield 7.05 g (89.1%) of **5** (mp 185 °C) or 6.78 g (85.7%) of **6** (mp 158 °C); IR (Nujol mull) 3075 (CH_{Ar}), 1590, 1485 (Ar skeleton), 1265, 1185, 1160 (PCC_{Ar} and P=N) cm^{-1} (**5**); 3070, 1590, 1485, 1260, 1230, 1200, 1180, 1160 cm^{-1} (**6**); UV (cyclohexane) λ_{max} 215 (ϵ 5.0×10^4), 259 (1.14×10^5), 272 (3.8×10^4) (**5**); 216 (1.43×10^5), 263 (1.1×10^4), 305 (1.5×10^4) (**6**); ^1H NMR δ 7.05–7.30 (m, 8 H), 7.35–7.70 (m, 4 H), 7.75–7.90 (m, 20 H) (**5**); 6.62–7.42 (m, 28 H), 7.65–7.85 (m, 4 H) (**6**); ^{31}P NMR, Table I; mass spectrum, *m/e* (relative intensity) 791 [100, M^+], 698 [57.2, $(M - OC_6H_5)^+$] (for **5**); 791 [67.0, M^+], [100, 698 $(M - OC_6H_5)^+$] (for **6**). Anal. Calcd for $C_{44}H_{32}O_6N_3P_3$: C, 66.68; H, 4.03; N, 5.32; P, 11.75. Found (for **5**): C, 66.90; H, 4.31; N, 5.54; P. 11.61. Found (for **6**): C, 66.15; H, 4.27; N, 5.52; P, 11.82.

Acknowledgment. The author thanks Professor Z. J. Jedliński for many helpful suggestions, Mrs. W. Kania for measuring the UV spectra, and Mr. R. Szylwański for technical assistance in carrying out the experiments.

Registry No. 1, 72881-41-5; 2, 72866-26-3; 3, 76529-28-7; 4, 76529-29-8; 5, 76529-30-1; 6, 76529-31-2; 7, 139-02-6.

Reaction of Methyl Iodide with Gramine and with Nitro-Substituted Gramines

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Gramine methiodides are important intermediates in the synthesis of tryptamines, tryptophans, indoleacetic acids, and other indole derivatives having a two-carbon side chain at the 3-position.[1,2] Preparation of gramine methiodide (**2a**) by alkylation of gramine (**1a**) with methyl iodide is complicated by formation of bis[(indol-3-yl)methyl]dimethylammonium iodide (**3a**),[3,4] as shown in Scheme I. The same problem exists when other alkylating agents are used.[3,5] Schöpf and Thesing[3] and Geissman and Armen,[4] who first elucidated this reaction sequence, suggested several ways to suppress the formation of **3a**.

We have found that controlling the product ratio in this set of reactions is more difficult than previously recognized. Although Geissman and Armen generated gramine methiodide (**2a**) in neat methyl iodide,[4] others[6] have interpreted their results to mean that a large excess of methyl iodide in ethanol is sufficient. We find, however, that the product

(1) Sundberg, R. J. "The Chemistry of Indoles"; Academic Press: New York, 1970; pp 94–98.
(2) Remers, W. A. In "Indoles. Part One"; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; pp 200–203.
(3) Schöpf, C.; Thesing, J. *Angew. Chem.* **1951**, *63*, 377–378.
(4) Geissman, T. A.; Armen, A. *J. Am. Chem. Soc.* **1952**, *74*, 3916–3919.
(5) Hester, J. B., Jr. *J. Org. Chem.* **1964**, *29*, 1158–1160.
(6) Brown, R. K.; Garrison, R. A. *J. Am. Chem. Soc.* **1955**, *77*, 3839–3842.

Scheme I

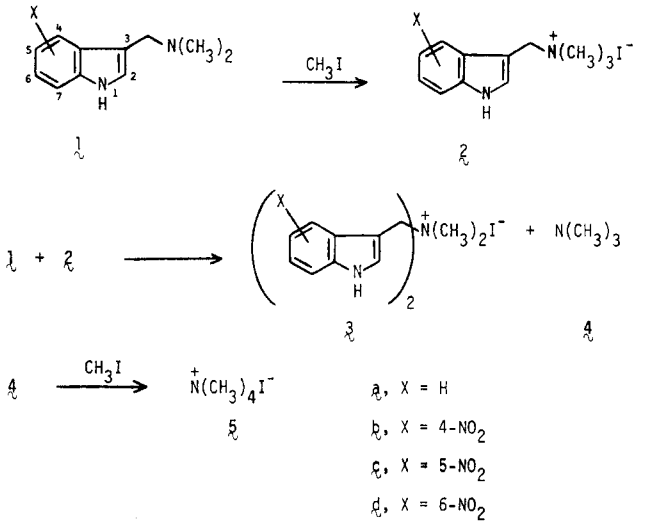


Table I. Ratio of Monoindolyl to Bisindolyl Products Obtained from Reaction of Methyl Iodide with Gramine and 4-, 5-, or 6-Nitrogramine

starting material	in abs EtOH	in neat CH_3I
1a	2/1	5/1
b	3/1	1/5
c	1/1	2/1
d	2/1	4/1

ratios obtained in neat methyl iodide differ markedly from those found in a 15-fold excess of methyl iodide in ethanol. Moreover, we find that the ratio of monoindolyl product to bisindolyl product is sensitive to the presence and location of substituents on the benzene ring. Finally, contrary to previous reports[3,6] of the instability of these methiodides, we find that, once purified, gramine methiodide (**2a**) and bis[(indol-3-yl)methyl]dimethylammonium iodide (**3a**) are stable at room temperature for up to 2 years and that the corresponding nitro derivatives (**2b–d** and **3b–d**) are stable in deuterated dimethyl sulfoxide for at least 1 month.

The product mixtures obtained by reaction of unsubstituted gramine (**1a**) and of 4-, 5-, and 6-nitrogramines (**1b–d**) in neat methyl iodide and in a 15-fold excess of methyl iodide in absolute ethanol were examined by ^1H NMR. Integration of the methylene peaks in the spectra for the product mixtures from gramine (**1a**), 5-nitrogramine (**1c**), and 6-nitrogramine (**1d**) and integration of the methyl peaks in the 220-MHz spectra for the product mixtures from 4-nitrogramine (**1b**) allowed the ratio of monoindolyl to bisindolyl product in each product mixture to be determined (see Table I) Peak assignments required preparation of pure gramine methiodide (**2a**), bis[(indol-3-yl)methyl]dimethylammonium iodide (**3a**), tetramethylammonium iodide (**5**), 4-nitrogramine methiodide (**2b**), and bis[(4-nitroindol-3-yl)methyl]dimethylammonium iodide (**3b**). As seen in Table II, ^1H NMR spectra of gramine methiodide (**2a**), **3a**, and **5** allowed assignment of the methylene and methyl peaks in the spectra of the crude product mixtures obtained from gramine (**1a**). The spectra for pure **2a**, **3a**, and **5** also provided standards against which the product mixtures for the nitro-substituted gramines **1b–d** could be compared. These spectra indicate that, like gramine (**1a**) itself, 5- and 6-nitrogramine (**1c** and **1d**) yield higher ratios of monoindolyl to bisindolyl product when the reaction is run in methyl iodide than when ethanol is used as solvent.

Table II. ^1H NMR Chemical Shifts[a] of Methyl and Methylene Protons in Unsubstituted and Nitro-Substituted Gramine Methiodides (Monoindolyl Products) and the Corresponding Bis(indolylmeth-3-yl)dimethylammonium Iodides (Bisindolyl Products)

	assignment				
compd	CH_2 of bis compd	CH_2 of mono compd	5 CH_3	CH_3 of mono compd	CH_3 of bis compd
2a[c]		4.69		3.07	
3a[c]	4.82				2.90
5[c]			3.13		
2b[c]		4.87		2.91	
3b[c]	4.87				2.60
1a[d]	4.83	4.70	3.15[b]	3.07	2.93
b[d]	4.88	4.88	3.15[b]	2.92	2.60
c[d]	4.95	4.84	3.17[b]	3.12	2.95
d[d]	4.94	4.80	3.16[b]	3.13	2.94

[a] In $(CD_3)_2SO$ in parts per million relative to Me_4Si. [b] Peak height increased on addition of **5**. [c] Pure compound. [d] Mixture of products from this compound.

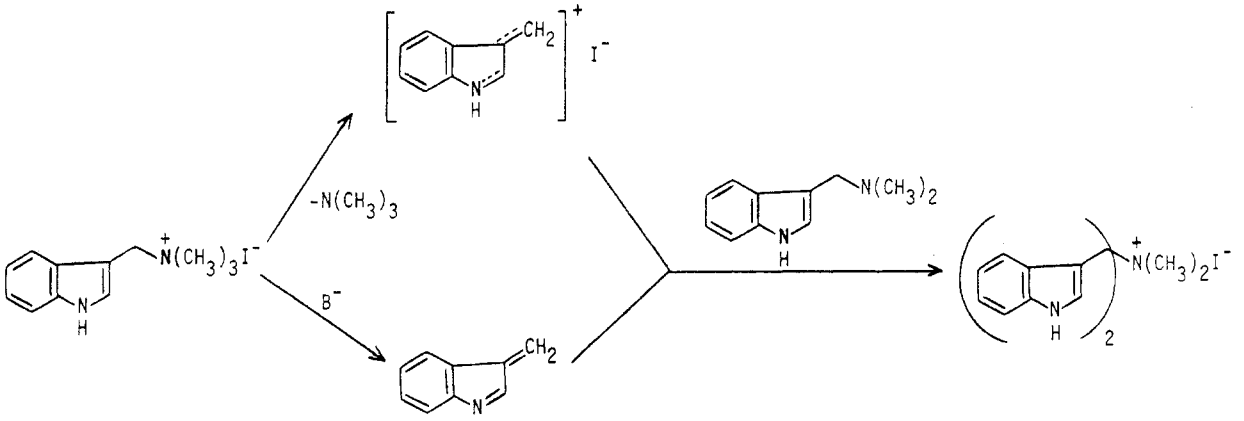
The anomalous appearance of the spectra for the product mixtures of 4-nitrogramine (**1b**; see Table II) is comprehensible only when it is realized that (1) the chemical shifts for the methylene protons in the 4-nitro-substituted monoindolyl and bisindolyl products are coincidentally identical, (2) the 4-nitro group shifts the methyl protons upfield in both the monoindolyl and bisindolyl products, and (3) in contrast to the behavior of the other three gramines, 4-nitrogramine affords more bisindolyl product in neat methyl iodide than it does in ethanolic solution. This explanation for the ^1H NMR spectra of the product mixtures for 4-nitrogramine was confirmed by obtaining pure samples of the monoindolyl (**2b**) and the bisindolyl (**3b**) compounds.

Examination of CPK molecular models of the nitro-substituted products provides useful insights into the anomalous chemical shifts observed for 4-nitrogramine methiodide (**2b**) and bis[(4-nitroindol-3-yl)methyl]dimethylammonium iodide (**3b**). Steric interference between the 4-nitro substituent and the 3-alkyl side chain forces the nitro group out of coplanarity with the benzene ring. In this orientation, the anisotropic nitro group[7] shields protons in the side chain, causing an upfield shift of the methyl hydrogens in **2b** and **3b** compared with the methyl hydrogens in the 5- and 6-nitro isomers **2c,d** and **3c,d**. The closeness of the nitro function to the methylene protons in the 4-nitro isomers **2b** and **3b** explains why the monoindolyl and bisindolyl methylene protons in these compounds exhibit the same chemical shift.

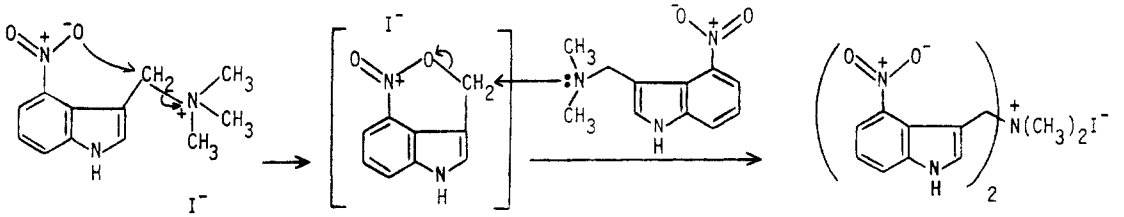
The proximity of the nitro group to the methylene carbon in 4-nitrogramine methiodide (**2b**) may also explain its propensity to form bis[(4-nitroindol-3-yl)methyl]dimethylammonium (**3b**) in neat methyl iodide. Two elimination–addition mechanisms thought to generate the bisindolyl product in the case of gramine methiodide (**2a**) and various methyl-substituted derivatives[2] are shown in Scheme II. The reduction of steric strain and the restoration of π overlap by the nitro-group with the benzene ring as **2b** reaches the transition states leading to either intermediate could explain the greater tendency of 4-nitrogramine methiodide (**2b**) to undergo elimination relative to 5- and 6-nitrogramine methiodide (**2c** and **2d**). If the elimination–addition occurs stepwise, via a carbo-

(7) Jackman, L. M.; Sternhall, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969; p 94.

Scheme II



Scheme III



nium ion, the partial positive charge on the side chain might also be stabilized by the partial negative charge on the oxygens of the neighboring 4-nitro group in a geometry not possible for the 5- and 6-nitro isomers. Alternatively, 4-nitrogramine methiodide (**2b**) could form the bisindolyl product (**3b**) via the intermediate shown in Scheme III. Although steric hindrance might discourage an ordinary S_N2 mechanism, such an internal nucleophilic displacement is more likely.[8,9] All three mechanisms (internally stabilized elimination–addition, either stepwise or base-catalyzed concerted, or intramolecular displacement) would be expected to be less significant in a hydroxylic, charge-stabilizing solvent like ethanol than in methyl iodide and would be compatible, therefore, with the more conventional behavior of 4-nitrogramine (**1b**) with excess methyl iodide in ethanol.

Experimental Section

Melting points were determined on a Büchi melting point apparatus and are corrected. ^{1}H NMR spectra were recorded on Varian EM-390 and HR-220 spectrometers using tetramethylsilane as an internal standard. Low-resolution, field-desorption mass spectra were obtained on a Varian-MAT 731 spectrometer equipped with a Varian-MAT combination electron impact–field desorption ion source. Microanalyses were performed by Mr. Josef Nemeth and his staff at the University of Illinois. Gramine (**1a**) was purchased from Aldrich and methyl iodide from Eastman. The syntheses of 4-, 5-, and 6-nitrogramines (**1b–d**) are described elsewhere.[5,6,10,11]

Gramine Methiodide (2a), Bis[(indol-3-yl)methyl]dimethylammonium Iodide (3a), and Tetramethylammonium Iodide (5). Gradual addition of gramine (**1a**) to stirred methyl iodide gave, after isolation and recrystallization as described by Geissman and Armen,[4] the following compounds. Gramine methiodide (**2a**): white crystals; mp 167.5–170.5 °C (lit.[4,12] mp 168–169 °C); ^{1}H NMR ($(CD_3)_2SO$) δ 3.07 (s, 9, $^+N(CH_3)_3$), 3.29 (s, H_2O, exchanges with D_2O), 4.69 (s, 2, CH_2), 7.0–8.0 (m, 5, aromatic H), 11.47 (br s, 1, NH, exchanges with D_2O). Bis(indol-3-ylmethyl)dimethylammonium iodide (**3a**): white crystals; mp 170.5 °C (lit.[4] mp 171–171.5 °C); ^{1}H NMR ($(CD_3)_2SO$) δ 2.90 (s, 6, $^+N(CH_3)_2$), 3.32 (s, H_2O, exchanges with D_2O), 4.82 (s, 4, CH_2), 7.0–8.0 (m, 10, aromatic H), 11.56 (br s, 2, NH, exchanges with D_2O). Tetramethylammonium iodide (**5**): white crystals; mp >320 °C (lit.[4,13] mp >300 °C, >355 °C); ^{1}H NMR ($(CD_3)_2SO$) δ 3.13 (s, $^+N(CH_3)_4$); ^{1}H NMR (D_2O) δ 3.20 (s, $^+N(CH_3)_4$), both in agreement with a published spectrum[14] of this compound in D_2O.

4-Nitrogramine Methiodide. In a 20-mL, round-bottomed flask was dissolved 0.100 g of 4-nitrogramine (**1b**) in 10 mL of absolute ethanol. To this was added 0.75 mL of methyl iodide. The flask was stoppered, and the reaction mixture was stirred for 4 h at room temperature. Solvent and excess methyl iodide were removed by rotary evaporation at room temperature under reduced pressure. The yellow residue was dissolved in methanol and filtered to remove tetramethylammonium iodide, and the filtrate was evaporated to dryness as before. The residue was triturated with 20 mL of water and filtered, and the aqueous filtrate was evaporated to dryness. This residue was dissolved in acetone, filtered, and evaporated to dryness again. The resulting yellow solid weighed 0.023 g (14%): mp 182–183 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 2.91 (s, 9, $^+N(CH_3)_3$), 3.28 (s, H_2O, exchanges with D_2O), 4.87 (s, 2, CH_2), 7.40 (pseudo t, i.e., overlapping dd, 1, $J_{6,5} = J_{6,7} = 7.8$ Hz, 6-H), 7.99, 8.04, and 8.13 (dd, dd, and s, 3, $J_{7,6} = 7.8$ Hz, $J_{7,5} = 1.2$ Hz, $J_{5,6} = 7.8$ Hz, $J_{5,7} = 1.2$ Hz, 7-H, 5-H, and 2-H), 12.60 (br s, 1, NH, exchanges with D_2O); field-desorption mass spectrum (10 mA), m/e 234 ($M^+ - I$).

Anal. Calcd for $C_{12}H_{16}N_3O_2I$: C, 39.91; H, 4.47; N, 11.63; I, 35.13. Found: C, 39.78; H, 4.37; N, 11.69; I, 35.08.

Bis[(4-nitroindol-3-yl)methyl]dimethylammonium Iodide. To 0.100 g of 4-nitrogramine (**1b**) in a 10-mL, round-bottomed flask was added 5 mL of methyl iodide. The flask was stoppered, and the suspension was stirred for 1 h at room temperature, giving a yellow precipitate. The reaction mixture was evaporated to dryness at room temperature under reduced pressure, and the residue was dissolved in methanol and filtered. After the filtrate was evaporated to dryness as before, the residue was triturated with 50 mL water and the insoluble material collected by filtration.

(8) Ball, S. S.; Andrews, L. J.; Keefer, R. M. *J. Org. Chem.* **1979**, *44*, 525–530.
(9) Schneller, S. W.; Luo, J.-K. *J. Org. Chem.* **1980**, *45*, 4045–4048.
(10) Cavallini, G.; Ravenna, V. *Farmaco, Ed. Sci.* **1958**, *13*, 105–112; *Chem. Abstr.* **1958**, *52*, 20126.
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(12) Torralba, A. F.; Myers, T. C. *J. Org. Chem.* **1957**, *22*, 972–975.
(13) Ostwald, W.; Roederer, H. *Kolloid-Z.* **1938**, *82*, 174–194.
(14) "Sadtler Standard Spectra: Nuclear Magnetic Resonance Spectra"; Sadtler Research Laboratories: Philadelphia, 1969; spectrum no. 6822.

The air-dried yellow solid weighed 0.073 g (44%): mp 195 °C; ^{1}H NMR 2.60 (s, 6, $^+$N(CH$_3$)$_2$), 3.32 (s, H$_2$O, exchanges with D$_2$O), 4.87 (s, 4, 2 (CH$_2$)), 7.39 (pseudo t, i.e., overlapping dd, 2, $J_{6,5}$ = $J_{6,7}$ = 8.4 Hz), 7.98 (2 d, coincident, 4, $J_{5,6}$ = 8.4 Hz, $J_{7,6}$ = 8.4 Hz, 5-H, 7-H), 8.20 (s, 2, 2-H), 12.56 (br s, 2, NH, exchanges with D$_2$O); field-desorption mass spectrum (15 mA), m/e 394 (M$^+$ − I).

Anal. Calcd for $C_{20}H_{20}IN_5O_4$: C, 46.08; H, 3.87. Found: C, 46.04; H, 3.72.

Product Mixtures. Each reaction was repeated several times. Increasing the scale of the reaction 200-fold or increasing or decreasing the amount of methyl iodide used or the time of reaction by 50% had no effect on the observed product mixture. For large-scale versions of these reactions, solid starting material was added slowly in portions to neat methyl iodide or to a solution of methyl iodide in absolute ethanol.

(A) Reaction in Neat Methyl Iodide. To 0.015 g of gramine (**1a**) or 4-, 5-, or 6-nitrogramine (**1b–d**) in a 5-mL vial was added 0.5 mL of methyl iodide. The vial was capped, and the suspension was stirred at room temperature for 2 h, by which time a colorless oil, in the case of gramine (**1a**), or a yellow precipitate, in the case of the nitrogramines (**1b–d**), had formed. The reaction mixture was evaporated to dryness at room temperature under reduced pressure, and a ^{1}H NMR spectrum of the residue was obtained in (CD$_3$)$_2$SO.

(B) Reaction in a Large Excess of Methyl Iodide in Absolute Ethanol. In a 5-mL vial, 0.015 g of gramine (**1a**) or 4-, 5-, or 6-nitrogramine (**1b-d**) was dissolved in 1.25-mL of absolute ethanol. To this was added 0.075 mL of methyl iodide. The vial was capped, and the solution was stirred at room temperature for 4 h, by which time a precipitate had formed. The reaction mixture was evaporated to dryness at room temperature under reduced pressure, and a ^{1}H NMR spectrum of the residue was obtained in (CD$_3$)$_2$SO.

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Registry No. **1a**, 87-52-5; **1b**, 7150-46-1; **1c**, 3414-64-0; **1d**, 6954-87-6; **2a**, 5457-31-8; **2b**, 23099-33-4; **2c**, 76599-76-3; **2d**, 22979-90-4; **3a**, 76599-77-4; **3b**, 76599-78-5; **3c**, 76599-79-6; **3d**, 76599-80-9; **5**, 75-58-1; CH$_3$I, 74-88-4.

Phosphoric Amides. 3.[1] Acidic Cleavage of the Phosphorus–Nitrogen Bond in Acyclic and Cyclic Phosphoramidates

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The acidic hydrolysis of carboxylic amides proceeds according to the A$_O$T2 mechanism, involving the rate-determining formation of the oxonium-type intermediate from the O-protonated form of substrate conjugate acid.[2] On the other hand, the generally accepted mechanism for the acid-catalyzed solvolysis of phosphoramidates involves the protonation at the nitrogen atom followed by the bimolecular, direct displacement at phosphorus (A-S$_N$2-P mechanism).[3] Such a mechanism accounts well for the facile cleavage of the P–N bond under acidic conditions,[3] as well as for the predominant inversion of configuration observed in solvolysis of chiral phosphoramidates.[4] However, some examples of the solvolysis resulting in a considerable retention of configuration have been reported. Chiral *O,S*-dialkyl phosphoroamidothioates solvolyze in alcohols at high acid concentrations with up to 86% of retention,[5] and a low stereospecificity was observed for the BF$_3$-catalysed solvolysis of cyclic and optically active phosphoramidates.[6] Although it has been demonstrated that the first case involves, in fact, the double inversion process,[7] in the second case the formation of a pentacoordinated intermediate followed by pseudorotation has been postulated.[4] Such a mechanism requires the addition of a nucleophile to the O-protonated substrate to form the trigonal-bipyrimidal intermediate with the nitrogen substituent initially in the equatorial position. The internal proton (or Lewis acid) transfer from oxygen to nitrogen would be followed by pseudorotation and amine departure, resulting in the retention of configuration at phosphorus.

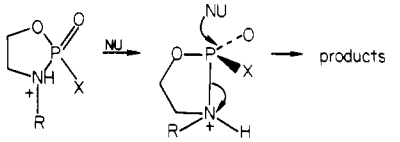
We tested the possibility of the solvolysis pathway following the O-protonated, pentacoordinated, intermediate mechanism by a kinetic approach. Although the oxygen-protonated form (A) of the substrate's conjugate acid is certainly a thermodynamically favored one,[8] the A-S$_N$2-P mechanism requires that the N-protonated tautomeric structure (B) represents the reactive form, attacked by a nucleophile in a rate-determining step (Scheme I). If the P–N bond is cleaved in a rate-determining step,

Scheme I

$$\underset{\text{A}}{X_2P^+(OH)NR_2} \overset{H^+}{\rightleftharpoons} X_2P(O)NR_2 \overset{H^+}{\rightleftharpoons} \underset{\text{B}}{X_2P(O)NHR_2^+} \xrightarrow{NU} TS$$

or if the P^V intermediate is formed from the N-protonated substrate, the application of Westheimer's theory on the nucleophilic displacement in cyclic phosphoryl systems[9] leads to the conclusion that the P–N bond cleavage in B should be subject to steric acceleration in compounds with the nitrogen and phosphorus atoms incorporated into a five-membered ring (Scheme II). Strongly electronegative ammonium nitrogen should preferentially occupy the apical position, suitable for the P–N cleavage step.[10] On the other hand, if the rate-determining step involves the nucleophilc attack at the O-protonated substrate, cyclic

Scheme II



TS or tbp intermediate

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