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Pteridines. XXXIX. Synthesis of 2,4-Diamino-7-alkenylpteridines and Their 8-Oxides[1,2]

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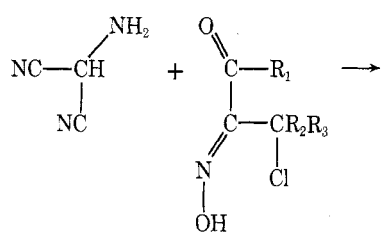
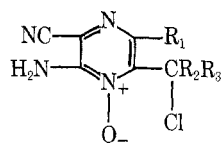
A versatile and flexible route to a variety of 2,4-diamino-7-alkenylpteridines is described. Condensation of aminomalononitrile with α-oximino-β-chloro aldehydes (prepared by the addition of nitrosyl chloride to α,β-unsaturated aldehydes) gives 2-amino-3-cyano-6-(1-chloroalkyl)pyrazine 1-oxides (**1–4**). The 6-chloromethyl compound (**1**) was converted to the stable phosphorane **10** which was condensed with aldehydes to give a series of 2-amino-3-cyano-6-alkenylpyrazine 1-oxides (**16**) which were cyclized with guanidine to 2,4-diamino-7-alkenylpteridine 8-oxides (**17**). Deoxygenation of **1** with phosphorus trichloride in THF gave 2-amino-3-cyano-6-chloromethylpyrazine (**5**), which was carried through an analogous sequence of steps to give a series of 2,4-diamino-7-alkenylpteridines (**15**). These pteridines are potential intermediates for the synthesis of derivatives carrying multifunctional substituents at position 7 which would be isomeric with the naturally occurring 6-substituted cofactors biopterin and neopterin.

We have recently described a new and general approach to the unequivocal synthesis of pteridines bearing olefinic substituents at position 6, suitable for eventual elaboration into the family of 6-substituted pterins represented by biopterin, neopterin, and related compounds.[3] The key steps in this synthetic sequence involved the initial condensation of aminomalononitrile with β-chloropyruvaldoxime to give 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide and the subsequent elaboration of the olefinic side chains via the Wittig synthesis. Final cyclization with guanidine gave the desired 6-substituted pteridines, which were readily hydrolyzed with dilute acid or base to pterins. The present paper describes the unequivocal synthesis of a series of isomeric 2,4-diaminopteridines substituted at position 7 with olefinic groups suitable for final elaboration into structural analogues of the naturally occurring 6-substituted pterins.

Application of the same oxime cyclization principle to the preparation of pyrazine intermediates suitable for cyclization to 7-substituted pteridines would require that aminomalononitrile tosylate be condensed with an α-oximino-β-chloro aldehyde. Fortunately, such intermediates are readily accessible by addition of nitrosyl chloride to α,β-unsaturated aldehydes.[4] Thus, reaction of aminomalononitrile with α-oximino-β-chloropropionaldehyde (from the addition of nitrosyl chloride to acrolein) gave 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide (**1**). This condensation is apparently completely general; condensation of aminomalononitrile with the α-oximinocarbonyl compounds derived by addition of nitrosyl chloride to crotonaldehyde, 2-pentenal, and 2-cyclohexenone gave the corresponding pyrazine 1-oxides **2**, **3**, and **4**. All of the subsequent reactions described in this paper were carried out with the parent chloromethylpyrazine **1**, but we would anticipate that these various derivatization reactions would be equally effective with other 6-(α-chloroalkyl)pyrazines such as **2**, **3**, and **4**.

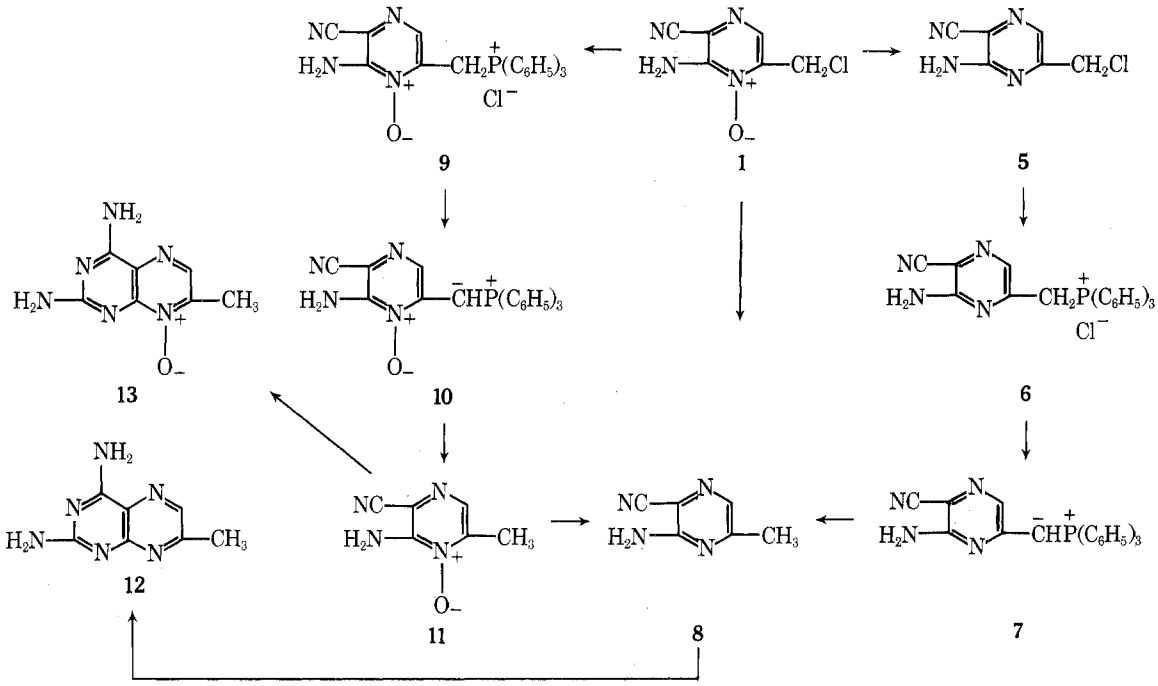




1, $R_1 = R_2 = R_3 = H$
2, $R_1 = R_2 = H$; $R_3 = CH_3$
3, $R_1 = R_2 = H$; $R_3 = C_3H_7$
4, $R_1, R_2 = -CH_2CH_2CH_2-$; $R_3 = H$

We first examined the deoxygenation of **1** to 2-amino-3-cyano-6-chloromethylpyrazine (**5**). Although many methods are available for reductive deoxygenation of aromatic *N*-oxides,[5] the conversion of **1** to **5** is at least potentially complicated by the presence of three reactive substituents, of which two (the cyano and chloromethyl groups) would be expected to be extremely susceptible to reduction. The best conditions appeared to involve heating **1** with phosphorus trichloride in tetrahydrofuran as solvent. Use of the more customary solvents for such deoxygenation reactions

Scheme I



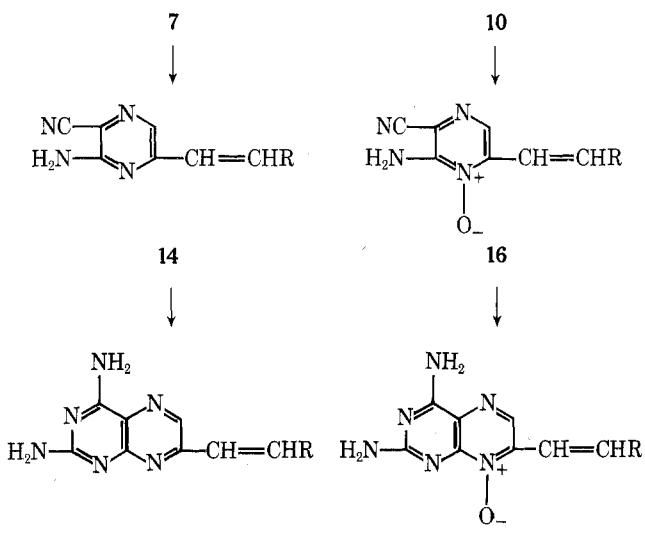
(chloroform, dioxane) led to slow reactions which were accompanied by the formation of numerous unidentified byproducts. The optimum reaction conditions (see Experimental Section) were determined by TLC monitoring of the reaction mixture; refluxing was discontinued at the moment of complete disappearance of starting material.

Treatment of **5** with triphenylphosphine in dimethylformamide resulted in smooth conversion to the corresponding triphenylphosphonium salt **6**, which was converted to the stable methylenetriphenylphosphorane (Wittig reagent) **7** by treatment with aqueous sodium bicarbonate. The structure of this phosphorane was confirmed by hydrolysis in boiling 30% aqueous ethanol to 2-amino-3-cyano-6-methylpyrazine (**8**), identical with the compound prepared by sodium hydrosulfite reduction of the initial 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide (**1**).

Treatment of **1** with triphenylphosphine in dimethylformamide solution analogously led to the triphenylphosphonium salt **9**, which was likewise converted with aqueous sodium bicarbonate into the methylenetriphenylphosphorane (Wittig reagent) **10**. The structure of this latter compound was confirmed by hydrolysis in 30% aqueous ethanol to 2-amino-3-cyano-6-methylpyrazine 1-oxide (**11**), which could be readily deoxygenated with sodium hydrosulfite to **8**, identical with the compound prepared by reduction of **1**, or by hydrolysis of **7**, as described above. Finally, cyclization of **8** and **11** with guanidine in methanol solution in the presence of sodium methoxide resulted in the formation of 2,4-diamino-7-methylpteridine (**12**) and its corresponding *N*-oxide (**13**). Compound **12** was identical with a sample of 2,4-diamino-7-methylpteridine prepared by the method of Seeger.[6] The above reactions are schematically summarized in Scheme I.

The phosphoranes **7** and **10** were converted to olefins by reaction with aldehydes in refluxing tetrahydrofuran (see Scheme II). Long reaction periods (1–5 days) were required, as expected for highly stabilized Wittig reagents. The phosphorane **10** was less reactive than its deoxygenated counterpart **7**. For example, condensation of **7** with benzaldehyde was complete in 1 day, but 5 days were required for the comparable condensation with **10**. In no instance was anil formation observed between the aldehyde

Scheme II

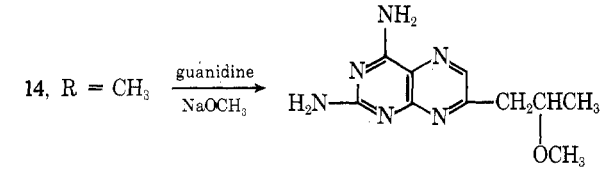


R = CH_3, CH_2OH, COOH, C_6H_5, 3,4-diClC_6H_3, 3,4-$(OCH_2O)C_6H_3$, 2-thienyl, 3-pyridyl

and the 2-amino group of either **7** or **10**. This side reaction, which might have been expected to complicate the above Wittig syntheses, is undoubtedly inhibited by the very weak basicity of the pyrazine amino groups in **7** and **10**. With the single exception of the product arising from the condensation of **10** with glyoxylic acid (**16**, R = COOH), all of the olefins prepared from **7** and **10** (i.e., **14** and **16**) had the trans configuration, as judged by careful analysis of the NMR spectra of the crude (as well as recrystallized) reaction products. Infrared spectral data also confirmed the trans configuration for these olefins. The condensation of **10** with glyoxylic acid proceeded exceptionally rapidly in boiling tetrahydrofuran (20 min) and gave a 50:50 mixture of the cis and trans isomers of **16**, R = COOH. No attempt was made to devise reaction conditions which would provide exclusively trans product. It should be noted that the formation of trans olefins in the above Wittig syntheses

significantly simplifies the subsequent projected utilization of these olefinic intermediates for the preparation of pteridines isomeric with biopterin, neopterin, etc., all of which possess the erythro configuration of the 6-substituted polyhydroxypropyl side chains.

The olefinic pyrazine precursors 14 and 16 were converted to 2,4-diaminopteridines and the corresponding 8-oxides (15 and 17, respectively) by condensation with guanidine in the presence of sodium methoxide. This procedure for the conversion of *o*-aminonitriles to fused 2,4-diaminopyrimidines has been thoroughly documented and needs no further discussion here.[7] In all of the pteridines prepared in this fashion (see Experimental Section), the trans configuration of the olefinic side chain was retained, as judged by NMR. The only abnormal reaction course observed was in the cyclization of 14 (R = CH_3), which resulted in the formation of 2,4-diamino-7-(2-methoxypropyl)pteridine (18) by Michael addition of methanol to the C=C bond. At-



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tempted condensation of the corresponding *N*-oxide (16, R = CH_3) with guanidine under the same reaction conditions failed to give the desired product (17, R = CH_3); the complex mixture of compounds resulting from this condensation is still under investigation. It should be noted that similar complications do not arise in the guanidine cyclization of the isomeric 2-amino-3-cyano-5-(1-propenyl)pyrazine and its corresponding *N*-oxide.[3]

It is apparent that the condensation of aminomalononitrile with α-oximino-β-chloropropionaldehyde to give 1, followed by the series of simple conversions discussed above leading ultimately to the pteridines 15 and 17, constitutes a versatile synthetic route to precursors of the 7-substituted isomers of the biopterin and neopterin series of pteridine natural products. These extensions of the present work will be discussed in future papers in this series.

Experimental Section

2-Amino-3-cyano-6-chloromethylpyrazine 1-Oxide (1). A mixture of 20.2 g (0.08 mol) of aminomalononitrile tosylate and 9.7 g (0.08 mol) of α-oximino-β-chloropropionaldehyde[4] in 250 ml of 2-propanol was stirred overnight at room temperature. The precipitate which had formed was collected by filtration, suspended in 100 ml of methanol, and filtered again to give 6.0 g (41%) of 1, mp 245 °C dec. The analytical sample, mp 250 °C dec, was obtained as pale yellow flakes by recrystallization from methanol.

Anal. Calcd for $C_6H_5ClN_4O$: C, 39.01; H, 2.71; N, 30.38; Cl, 19.25. Found: C, 39.20; H, 2.75; N, 30.64; Cl, 19.55.

2-Amino-3-cyano-6-(1-chloroethyl)pyrazine 1-Oxide (2). A mixture of 7.6 g (0.03 mol) of aminomalononitrile tosylate and 4.1 g (0.03 mol) of α-oximino-β-chlorobutyraldehyde[4] in 100 ml of 2-propanol was treated as described above to give 2.2 g (37%) of 2, mp 222 °C dec. The analytical sample was obtained as pale yellow needles, but without change in the melting point, by recrystallization from methanol.

Anal. Calcd for $C_7H_7N_4OCl$: C, 42.33; H, 3.55; N, 28.21; Cl, 17.85. Found: C, 42.36; H, 3.37; N, 28.50; Cl, 17.79.

2-Amino-3-cyano-6-(1-chlorobutyl)pyrazine 1-Oxide (3). In the same manner as described above, condensation of 13.1 g (0.052 mol) of aminomalononitrile tosylate and 8.5 g (0.052 mol) of α-oximino-β-chlorocapraldehyde[4] in 100 ml of 2-propanol gave 0.7 g (6%) of 3, mp 155–157 °C dec. The analytical sample was prepared by vacuum sublimation at 100 °C (0.1 mm).

Anal. Calcd for $C_9H_{11}N_4OCl$: C, 47.68; H, 4.86; N, 24.72; Cl, 15.67. Found: C, 47.96; H, 4.91; N, 25.00; Cl, 15.46.

2-Amino-3-cyano-8-chloro-5,6,7,8-tetrahydroquinoxaline 1-Oxide (4). Nitrosyl chloride was passed into a stirred solution of 6.45 g (0.067 mol) of 2-cyclohexenone in 45 ml of diethyl ether, held at approximately −40 °C, until 4.4 g (0.067 mol) had been absorbed. Stirring was continued for a further 2 h while the reaction mixture was allowed to warm to room temperature. The white solid which had separated was collected by filtration and washed with methanol followed by diethyl ether to give 5.3 g (72%) of the dimer of 2-nitroso-3-chlorocyclohexanone, mp 93–94 °C dec. Since microanalysis of the crude dimer indicated that it was pure (Anal. Calcd for $C_6H_8NO_2Cl$: C, 44.51; H, 4.95; N, 8.67; Cl, 21.98. Found: C, 44.94; H, 4.95; N, 8.77; Cl, 22.20), and attempted recrystallization resulted in decomposition, it was used directly in the next step. Conversion to the monomer was effected by suspension of 1.61 g of the above dimer in 20 ml of Me_2SO and heating at 50 °C for 10 min. The resulting solution was poured into 50 ml of ice water, the monomeric 2-oximino-3-chlorocyclohexanone was extracted with ether and dried over anhydrous $MgSO_4$, and the ether was evaporated. Addition of 0.76 g (3 mmol) of aminomalononitrile tosylate to the resulting 0.76 g (3 mmol) of crude 2-oximino-3-chlorocyclohexanone in 3 ml of 2-propanol and stirring overnight at room temperature gave a solid which was collected by filtration and recrystallized from methanol to give 0.23 g (13%) of 4, mp 186–187 °C dec.

Anal. Calcd for $C_9H_9N_4OCl$: C, 48.11; H, 4.04; N, 24.94; Cl, 15.78. Found: C, 48.38; H, 4.25; N, 25.46; Cl, 15.42.

2-Amino-3-cyano-6-methylpyrazine (8). To a solution of 1.85 g (0.01 mol) of 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide in 50 ml of boiling water was added, in small portions and with stirring, 6.0 g (0.03 mol) of sodium hydrosulfite. The reaction mixture was boiled for an additional 5 min and then cooled to give 0.87 g (65%) of pure 8, mp 212–213 °C dec, as light tan needles.

Anal. Calcd for $C_6H_6N_4$: C, 53.72; H, 4.51; N, 41.77. Found: C, 53.90; H, 4.64; N, 41.74.

2-Amino-3-cyano-6-chloromethylpyrazine (5). A mixture of 9.3 g of 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide, 30 ml of phosphorus trichloride, and 500 ml of THF was heated under reflux for 1 h. A homogeneous solution resulted after the first 15 min of heating. The resulting dark brown solution was poured over ice, neutralized with sodium bicarbonate, and extracted with three 200-ml portions of ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$ and evaporated to dryness, and the resulting dark brown solid (6.9 g, 82%) dissolved in 100 ml of methanol, decolorized with Norit, concentrated, and cooled. Filtration then gave 4.8 g (56%) of 5 as a light brown powder, mp 174 °C dec. The analytical sample was prepared in the form of a pale yellow, microcrystalline solid by sublimation at 100 °C (0.1 mm).

Anal. Calcd for $C_6H_5N_4Cl$: C, 42.73; H, 2.97; N, 33.22; Cl, 21.07. Found: C, 42.69; H, 3.19; N, 32.94; Cl, 21.38.

(1-Oxy-2-amino-3-cyano-6-pyrazinyl)methyltriphenylphosphonium Chloride (9). A solution of 5.54 g (0.03 mol) of 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide, 8.8 g (0.03 mol) of triphenylphosphine, and 60 ml of DMF was stirred at 80–90 °C for 40 min. The reaction mixture was then cooled, 600 ml of diethyl ether added, and the resulting precipitate collected by filtration and washed with ether–methanol (1:1) to give 12.3 g (92%) of 9 as pale yellow flakes, mp 239–240 °C dec.

Anal. Calcd for $C_{24}H_{20}N_4OClP$: Cl, 7.95. Found: Cl, 7.84.

(2-Amino-3-cyano-6-pyrazinyl)methyltriphenylphosphonium Chloride (6). In the same manner as described above, 2-amino-3-cyano-6-chloromethylpyrazine (1.0 g, 6 mmol) was converted to 6 by stirring with 1.57 g (6 mmol) of triphenylphosphine in 12 ml of DMF, yield 2.16 g (85%) of 6, mp 271 °C dec (from methanol–ether).

Anal. Calcd for $C_{24}H_{20}N_4ClP$: Cl, 8.25. Found: Cl, 8.38.

(1-Oxy-2-amino-3-cyano-6-pyrazinyl)methylenetriphenylphosphorane (10). To a solution of 5.0 g (11.3 mmol) of (1-oxy-2-amino-3-cyano-6-pyrazinyl)methyltriphenylphosphonium chloride in 150 ml of water was added 1.26 g (15.0 mmol) of sodium bicarbonate, and the resulting slurry was stirred at room temperature for 1 h. The precipitated deep yellow solid was collected by filtration and washed with water to give 4.3 g (98%) of 10, mp 240–241 °C dec, which was used directly for subsequent Wittig condensations with aldehydes. The analytical sample was prepared in the form of deep yellow platelets, mp 243–244 °C dec, by recrystallization from ethanol.

Anal. Calcd for $C_{24}H_{19}N_4OP$: C, 70.20; H, 4.64; N, 13.66. Found: C, 69.99; H, 4.84; N, 13.58.

(2-Amino-3-cyano-6-pyrazinyl)methylenetriphenylphosphorane (7). In the same manner as described above, treatment of 1.0 g (2.3 mmol) of (2-amino-3-cyano-6-pyrazinyl)methyltriphenylphosphonium chloride with 0.3 g (3.5 mmol) of sodium bi-

carbonate gave 0.85 g (93%) of **7**, mp 243–244 °C dec. Recrystallization from DMF–methanol gave deep yellow prisms, mp 249–250 °C dec.

Anal. Calcd for $C_{24}H_{19}N_4P$: C, 73.10; H, 4.82; N, 14.21. Found: C, 72.86; H, 5.02; N, 14.10.

Hydrolysis of 7 to 2-Amino-3-cyano-6-methylpyrazine (8). A solution of 0.1 g of the phosphorane **7** in 10 ml of 30% aqueous ethanol was heated under reflux for 5 h. The resulting solution was concentrated to a small volume by evaporation under reduced pressure, and the precipitated solid was collected by filtration, triturated with benzene, and then recrystallized from methanol to give 0.03 g (88%) of 2-amino-3-cyano-6-methylpyrazine, mp 212–213 °C dec. The product was identical with an authentic sample of **8** prepared as described above by reduction of 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide with sodium hydrosulfite.

Hydrolysis of 10 to 2-Amino-3-cyano-6-methylpyrazine 1-Oxide (11). A solution of 2.0 g of the phosphorane **10** in 150 ml of 30% aqueous ethanol was heated under reflux for 2.5 h and concentrated under reduced pressure and the resulting precipitate was collected by filtration, dried, and triturated for 30 min in 50 ml of benzene. Filtration then gave 0.69 g (95%) of **11** as light brown needles, mp 244–245 °C dec. The analytical sample was prepared in the form of pale yellow needles, mp 246–247 °C dec, by sublimation at 180 °C (0.1 mm).

Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.77; H, 4.13; N, 37.43.

Reduction of 11 to 2-Amino-3-cyano-6-methylpyrazine (8). To a solution of 50 mg (0.33 mmol) of 2-amino-3-cyano-6-methylpyrazine 1-oxide in 1.5 ml of boiling water was added slowly and with stirring 104 mg (0.6 mmol) of sodium hydrosulfite. The resulting reaction mixture was boiled for an additional 10 min and cooled, and the fine crystalline precipitate was collected by filtration and recrystallized from methanol, yield 20 mg (45%), mp 212–213 °C dec. The product was identical in all respects with an authentic sample of **8** prepared as described above by hydrolysis of the phosphorane **7**, or by reduction of **1**.

2-Amino-3-cyano-6-styrylpyrazine 1-Oxide (16, R = C_6H_5). A solution of 2.0 g (4.9 mmol) of **10** and 2.0 g (18.8 mmol) of benzaldehyde in 100 ml of dry THF was heated under reflux for 5 days and evaporated to dryness under reduced pressure, and the residual solid was triturated with benzene for 30 min. Filtration then gave 1.0 g (86%) of **16**, R = C_6H_5, as fine yellow needles, mp 270–271 °C dec. The analytical sample, mp 280–281 °C dec, was prepared by sublimation at 180 °C (0.1 mm).

Anal. Calcd for $C_{13}H_{10}N_4O$: C, 65.53; H, 4.23; N, 23.52. Found: C, 65.49; H, 4.41; N, 23.39.

2-Amino-3-cyano-6-styrylpyrazine (14, R = C_6H_5). A solution of 2.0 g (5.1 mmol) of **7** and 2.0 g (18.8 mmol) of benzaldehyde in 100 ml of dry THF was heated under reflux overnight and then evaporated to dryness under reduced pressure. The residue was triturated for 30 min in 50 ml of benzene and then filtered to give 0.95 g (84%) of a bright yellow solid, mp 218–219 °C. The analytical sample, mp 222–223 °C, was prepared by sublimation at 180 °C (0.1 mm).

Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 70.01; H, 4.53; N, 25.25.

2-Amino-3-cyano-6-(1-propenyl)pyrazine 1-Oxide (16, R = CH_3). A solution of 2.05 g (5 mmol) of the phosphorane **10** and 2.2 g (50 mmol) of acetaldehyde in 50 ml of dry THF was stirred at 60 °C in a pressure bottle for 3 days and then evaporated to dryness under reduced pressure. The residue was triturated with 50 ml of benzene at room temperature for 30 min and then filtered to give 0.70 g (80%) of yellow crystals of **16**, R = CH_3, mp 185–186 °C dec. The analytical sample, mp 187–188 °C dec, was prepared by sublimation at 120 °C (0.1 mm).

Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.56; H, 4.74; N, 32.09.

2-Amino-3-cyano-6-(1-propenyl)pyrazine (14, R = CH_3). A solution of 3.0 g of the phosphorane **7** and 2.4 g of acetaldehyde in 60 ml of dry DMF was stirred at room temperature for 24 h in a pressure bottle and then poured into ice water. The precipitate which formed was collected by filtration, dried, and triturated with benzene for 30 min. Filtration then gave 0.85 g (75%) of **14**, R = CH_3, as a light brown powder, mp 184–185 °C. The analytical sample was obtained as a pale yellow powder, mp 189–190 °C, by sublimation at 120 °C (0.1 mm).

Anal. Calcd for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.85; H, 5.16; N, 34.83.

2-Amino-3-cyano-6-(3-hydroxy-1-propenyl)pyrazine 1-Oxide (16, R = CH_2OH). A solution of 1.95 g (4.7 mmol) of the phosphorane **10** and 1.5 g (25 mmol) of glycolaldehyde in 50 ml of dry THF was heated under reflux for 18 h and then evaporated to dryness. The residue was washed thoroughly with water, dried, and then triturated for 30 min at room temperature with 50 ml of benzene. Filtration gave 0.73 g (80%) of **16**, R = CH_2OH, as a yellow, microcrystalline solid, mp 114–115 °C dec. The product was obtained in the form of light yellow needles, mp 117 °C dec, by recrystallization from methanol.

Anal. Calcd for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.16. Found: C, 50.18; H, 4.43; N, 29.32.

2-Amino-3-cyano-6-[2-(2-thienyl)vinyl]pyrazine 1-Oxide (16, R = 2-Thienyl). A solution of 2.05 g (5 mmol) of the phosphorane **10** and 2.2 g (20 mmol) of thiophene-2-carboxaldehyde in 50 ml of THF was heated under reflux for 2 days and then evaporated to dryness under reduced pressure. The residue was triturated for 1 h at room temperature with 50 ml of benzene and then filtered to give 1.1 g (89%) of **16**, R = 2-thienyl, as a light brown solid, mp 229–230 °C dec. Recrystallization from THF gave light tan crystals, mp 232–233 °C dec.

Anal. Calcd for $C_{11}H_8N_4OS$: C, 54.10; H, 3.28; N, 22.95; S, 13.11. Found: C, 53.93; H, 3.46; N, 22.66; S, 12.89.

2-Amino-3-cyano-6-(2-carboxyvinyl)pyrazine 1-Oxide (16, R = COOH). A solution of 2.05 g (5 mmol) of the phosphorane **10** and 1.1 g (15 mmol) of glyoxylic acid in 50 ml of dry THF was heated under reflux for 20 min and then evaporated to dryness. The residue was treated as described above to give 0.99 g (96%) of a bright yellow solid, mp >234 °C dec, which appeared to be a mixture of approximately 50% trans and 50% cis isomers.

Anal. Calcd for $C_8H_6N_4O_3$: C, 46.60; H, 2.93; N, 27.18. Found: C, 46.34; H, 3.18; N, 27.28.

2-Amino-3-cyano-6-[2-(3-pyridyl)vinyl]pyrazine 1-Oxide (16, R = 3-Pyridyl). In the same manner as described above, a solution of 2.05 g of the phosphorane **10** and 1.61 g of nicotinaldehyde was condensed in THF to give 1.04 g (87%) of **16**, R = 3-pyridyl, as fine yellow crystals, mp 258 °C dec. The product could be recrystallized from tetrahydrofuran–benzene without change in the melting point.

Anal. Calcd for $C_{12}H_9N_5O$: C, 60.24; H, 3.79; N, 29.28. Found: C, 59.97; H, 4.02; N, 29.12.

2-Amino-3-cyano-6-(3,4-dichlorostyryl)pyrazine (14, R = 3,4-$Cl_2C_6H_3$). A solution of 10.0 g of the phosphorane **7** and 8.8 g of 3,4-dichlorobenzaldehyde in 300 ml of THF was stirred at room temperature for 24 h and then worked up as described above, yield, 5.9 g (80%), mp 249–250 °C.

Anal. Calcd for $C_{13}H_8N_4Cl_2$: C, 53.64; H, 2.75; N, 19.24; Cl, 24.39. Found: C, 53.73; H, 3.03; N, 19.14; Cl, 24.06.

2-Amino-3-cyano-6-(3,4-methylenedioxystyryl)pyrazine [14, R = 3,4-$(OCH_2O)C_6H_3$]. Condensation of 10.0 g of the phosphorane **7** with 11.4 g of piperonal, under the conditions described above, gave 5.82 g (86%) of **14**, R = 3,4-$(OCH_2O)C_6H_3$, as a bright yellow powder, mp 273–274 °C. The analytical sample was obtained by recrystallization from DMF without change in the melting point.

Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.09; H, 4.01; N, 21.00.

2,4-Diamino-7-methylpteridine 8-Oxide (13). Guanidine hydrochloride (0.48 g, 5 mmol) was added to a solution of 0.665 g (12.3 mmol) of sodium methoxide in 30 ml of absolute methanol, and the precipitated sodium chloride was removed by filtration. To the filtrate was added 0.50 g (3.34 mmol) of 2-amino-3-cyano-6-methylpyrazine 1-oxide and the reaction mixture was heated under reflux for 18 h. It was then cooled to room temperature, and the precipitated solid was collected by filtration, washed with methanol, and recrystallized from DMF to give 0.53 g (83%) of a bright yellow solid, mp 295–296 °C dec.

Anal. Calcd for $C_7H_8N_6O$: C, 43.75; H, 4.20; N, 43.73. Found: C, 43.84; H, 4.20; N, 43.47.

The following pteridines were prepared in the same manner from guanidine and the appropriate 2-amino-3-cyano-6-substituted pyrazine (or its 1-oxide).

2,4-Diamino-7-methylpteridine (12): 81% yield, mp (from DMF) 347 °C dec. This compound was identical in all respects (ir, uv, NMR, and TLC) with an authentic sample of 2,4-diamino-7-methylpteridine prepared by the method of Seeger.[6]

Anal. Calcd for $C_7H_8N_6$: C, 47.42; H, 4.58; N, 47.71. Found: C, 47.75; H, 4.75; N, 47.69.

2,4-Diamino-7-styrylpteridine 8-Oxide (17, R = C_6H_5): 88% yield, mp (from DMF) 273–274 °C dec.

Anal. Calcd for $C_{14}H_{12}N_6O$: C, 59.99; H, 4.32; N, 29.99. Found: C, 59.76; H, 4.29; N, 29.80.

2,4-Diamino-7-styrylpteridine (15, R = C_6H_5): 89% yield, mp (from DMF) 303 °C dec.

Anal. Calcd for $C_{14}H_{12}N_6$: C, 63.62; H, 4.58; N, 31.80. Found: C, 63.43; H, 4.77; N, 31.86.

2,4-Diamino-7-(2-methoxypropyl)pteridine (18): 60% yield, mp (from methanol) 223–224 °C dec.

Anal. Calcd for $C_{10}H_{14}N_6O$: C, 51.27; H, 6.02; N, 35.88. Found: C, 51.26; H, 6.05; N, 35.73.

2,4-Diamino-7-(3,4-dichlorostyryl)pteridine (15, R = 3,4-$Cl_2C_6H_3$): 79.5% yield, mp (from trituration with hot DMF) 338–339 °C dec.

Anal. Calcd for $C_{14}H_{10}N_6Cl_2$: C, 50.45; H, 3.00; N, 25.22; Cl, 21.32. Found: C, 50.36; H, 3.25; N, 25.24; Cl, 21.47.

2,4-Diamino-7-(3,4-methylenedioxystyryl)pteridine [15, R = 3,4-$(OCH_2O)C_6H_3$]: 91% yield, mp (from trituration with hot methanol) 334–335 °C dec.

Anal. Calcd for $C_{15}H_{12}N_6O_2$: C, 58.44; H, 3.92, N, 27.26. Found: C, 58.47; H, 3.94; N, 27.51.

Registry No.—**1**, 58091-59-1; **2**, 58091-60-4; **3**, 58091-61-5; **4**, 58091-62-6; **5**, 58091-63-7; **6**, 58091-64-8; **7**, 58091-65-9; **8**, 58091-66-0; **9**, 58091-67-1; **10**, 58091-68-2; **11**, 58091-69-3; **12**, 4215-07-0; **13**, 58091-70-6; **14** (R = Me), 58091-71-7; **14** (R = Ph), 58091-72-8; **14** (R = 3,4-diClC_6H_3), 58091-73-9; **14** [R = 3,4-$(OCH_2O)C_6H_3$], 58091-74-0; **15** (R = Ph), 58091-75-1; **15** (R = 3,4-diClC_6H_3), 58091-76-2; **15** [R = 3,4-$(OCH_2O)C_6H_3$], 58091-77-3; **16** (R = Me), 58091-78-4; **16** (R = Ph), 58091-79-5; **16** (R = CH_2OH), 58091-80-8; **16** (R = 2-thienyl), 58091-81-9; *cis*-**16** (R = CO_2H), 58091-82-0; **16** (R = CO_2H), 58091-83-1; **16** (R = 3-pyridyl), 58091-84-2; **17** (R = Ph), 58091-85-3; **18**, 58091-86-4; aminomalonitrile tosylate, 5098-14-6; α-oximino-β-chloropropionaldehyde, 4815-01-4; α-oximino-β-chlorobutyraldehyde, 4749-21-7; α-oximino-β-chlorocapraldehyde, 58091-87-5; 2-nitroso-3-chlorocyclohexanone dimer, 58091-89-7; 2-oximino-3-chlorocyclohexanone, 58091-90-0; triphenylphosphine, 603-35-0; benzaldehyde, 100-52-7; acetaldehyde, 75-07-0; glycolaldehyde, 141-46-8; thiophene-2-carboxaldehyde, 98-03-3; glyoxylic acid, 298-12-4; nicotinaldehyde, 500-22-1; 3,4-dichlorobenzaldehyde, 6287-38-3; piperonal, 120-57-0; guanidine HCl, 15827-40-4.

References and Notes

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(2) This work was supported by a grant (CA-12876) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.
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Covalent Amination. Substituent Effects on the Site of Addition of Ammonia to Quaternized Pyridines and Pyrazines

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1,3-Disubstituted pyridinium ions react completely at about −40 °C with ammonia to give covalent amination products. Addition occurs at C-6 when the C-3 group is $CONH_2$, CO_2CH_3, CF_3, or $COCH_3$. Addition at C-2 results when the 3 substituent is Cl or I, and a mixture is found for the 3-CN compound. Parent 1-methyl- and 1-benzylpyridinium ions do not yield 2 adducts unless powdered KOH is added to neutralize ammonium ion. 1-Methoxypyridinium ions at −50 °C give adducts which open to 5-amino-2(*cis*),4(*trans*)-pentadienal oxime *O*-methyl ether. 1-Methyl-3-substituted pyrazinium ions react at the 2 position when the substituent is Cl or CH_3O and at the 6 position in the $CONH_2$ case. 1-Methylpyrazinium ion first forms a 2 adduct and then a 2,3 diadduct.

Many heteroaromatic molecules are known to undergo "covalent hydration" reactions in aqueous solution.[1] In the presence of acid or base, solvent adds to an annular carbon atom to form a covalently bonded hydrate. Quaternization of an annular nitrogen atom greatly promotes such a reaction with water; the product, a "pseudobase", may be in equilibrium with its ring-opened carbonyl tautomer.[2,3] The influence of structure on the position of hydration as well as on rates and equilibria involving aromatic material, its hydroxy adduct, and ring-opened isomer has long intrigued chemists.[4] Recognition of the existence of covalent hydrates in solution has allowed otherwise puzzling chemistry to become understandable.

Covalent amination involving ammonia as solvent has been a largely overlooked counterpart to hydration. No doubt this primarily is a consequence of the greater difficulty in handling ammonia with its low boiling point, −33 °C. However, NMR now makes examination of ammonia reaction mixtures at a variety of temperatures easy, if not routine, and provides access to an area of investigation which is likely to be as rewarding as that involving aqueous solutions.

Already, recognition of the covalent amination process is providing new insight into reactions of heteroaromatic molecules in ammonia. Many simple heteroaromatic molecules such as quinoline,[5] isoquinoline,[5] the three diazines,[6] and their halogenated derivatives[7] react rapidly and completely with ammonia containing amide ion to give anionic σ complexes in which an amino group is bonded to an annular carbon atom. This discovery makes understandable the surprising rearrangement reactions involving amide ion in ammonia and the halogenated derivatives of the heteroaromatic compounds.[8–10]

We now report the results of reactions involving quaternized heteroaromatic molecules and ammonia free of amide ion. Adducts having an amino group bonded to an annular carbon atom are produced in a reaction which is the amination counterpart to pseudobase formation in aqueous solution. Two ring systems, quaternized pyridines and pyrazines, are extensively studied. The site of amination is found to depend on substituents bonded to carbon. In some cases a single adduct is observed, in others, mixtures of adducts. Even diadducts are formed. Ring-opened isomers may be observed as well. The present study supplements our preliminary communication which revealed that many kinds of heterocyclic rings containing a quaternized nitrogen atom undergo covalent amination in ammonia.[11] The accompanying article shows that sulfur and carbon nucleo-