the C-4 proton would be coupled ($J \simeq 4$ cps) to the C-2 and C-3 protons;[4] this is not observed in the spectrum. Second, the same proton of structure XIII should appear at lower field ($\delta \simeq 3$ ppm) which is not observed. Tables I and II present in a condensed form all of the nmr data for compounds VI and XI.

Experimental Section

3-Methylfuran (I) was prepared as described elsewhere[9] and was distilled before use, bp 56° (622 mm).[10]

Bromolactonic Acid VI.—A mixture of 18.1 g (0.22 mole) of 3-methylfuran (I) and 19.7 g (0.10 mole) of maleic anhydride dissolved in 100 ml of water was stirred vigorously at room temperature for 72 hr. The layers were separated and the water layer was treated with bromine until the dark color persisted. The mixture was filtered and the white solid was washed with cold water to yield 14.0 g of bromolactonic acid VI (25% over-all from maleic anhydride). Recrystallization from water gave white creamish plates, mp 212–215°.

Anal.[11] Calcd for $C_9H_9BrO_5$: C, 39.01; H, 3.27. Found: C, 38.98; H, 3.18.

Bromolactone Methyl Ester VII.—A suspension of 3.0 g (0.0108 mole) of bromolactonic acid VI in 100 ml of ether was esterified with an excess of distilled diazomethane in ether. The solid remaining in suspension was filtered off, washed with ether, and dried to yield 2.8 g (89%) of bromolactone methyl ester VII, mp 162–163°.

***exo-cis*-3,6-Endoxo-5-methyl-Δ^4-tetrahydrophthalic anhydride** was prepared according to the procedure of Rinkes[5] with slight modifications. To a warm solution of 7.3 g (0.074 mole) of maleic anhydride in 9 ml of dry benzene was added 6.15 g (0.075 mole) of compound I. The reaction mixture was refrigerated for 30 min. The solvent was then removed at room temperature. The crude solid was washed with ether and dried to yield 13.0 g (98%) of the anhydride of compound IV, mp 77–79°,[12] which showed no traces of the *endo* adduct. This compound was used without any further purification.

Bromolactonic Acid XI.—To a solution of 5.0 g (0.028 mole) of the anhydride of compound IV in 60 ml of 1 *N* sodium hydroxide solution was slowly added an excess of bromine. After addition was complete, a white solid formed and the reaction mixture was acidified to assure complete precipitation. Recrystallization from water gave 4.5 g (58%) of bromolactonic acid XI, mp 232–245° dec.

Anal. Calcd for $C_9H_9BrO_5$: C, 39.01; H, 3.27. Found: C, 38.68; H, 3.12.

Nmr spectra were measured at approximately 30° with a Varian A-60 nmr spectrometer. TMS was used as an external standard. The spectra for all substances were measured in K_2CO_3–D_2O solutions except for compound VII which was measured in $CDCl_3$.

(9) D. M. Burnes, "Organic Syntheses", Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 628.

(10) All boiling and melting points are uncorrected.

(11) The microanalyses were performed by Franz Pascher, Mikroanalytisches Laboratorium, Bonn, Germany.

(12) Rinkes[5] reports mp 82° after two recrystallizations from ether.

Potential Folic Acid Antagonists. II. Deaza Analogs of Methotrexate. II.[1] 2,4-Diamino-6-methyl-3-deazapteridine

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Received January 17, 1966

The preparation of 2,4-diamino-6-methyl-3-deazapteridine (6,8-diamino-2-methylpyrido[2,3-*b*]pyrazine, XVI) was accomplished by a 10-step synthesis from diethyl 4-chloro-3-nitro-2,6-pyridinedicarbamate (Ia). A key step in the sequence was the preparation of ethyl 6-chloro-4-[(diphenylmethyl)amino]-5-nitro-2-pyridinecarbamate (VIII). Unsuccessful routes to XVI are also discussed.

Our interest in the structural requirements for binding to and, therefore, inhibiting the enzymes involved in folic acid metabolism led us to attempt the synthesis of deaza analogs of aminopterin and methotrexate.[2] The synthesis of such diaminodeaza compounds are, however, fraught with more difficulties than are the syntheses of the parent pteridines, since four rather than two isomers can be formed in the reactions usually employed in the synthesis of folic acid and pteridine analogs.[3] Because of this additional complication, we chose, and have described in a previous publication,[2] an unambiguous method for the synthesis of 2,4-diamino-6-methyl-1-deazapteridine (5,7-diamino-3-methylpyrido[3,4-*b*]-pyrazine), a possible intermediate in the synthesis of 1-deazaaminopterin or 1-deazamethotrexate. Briefly, this method involved the reaction of aminoacetone semicarbazone with diethyl 4-chloro-3-nitro-2,6-pyridinedicarbamate (Ia)[2] followed by hydrolysis of the semicarbazone and then reduction of the nitro group. The intermediate aminoketopyridine thus formed cyclized spontaneously to the dihydro 1-deazapteridine which was oxidized to the desired ring system. A suitable modification of this reaction sequence has now been used for the preparation of the isomeric 2,4-diamino-6-methyl-3-deazapteridine (6,8-diamino-2-methylpyrido[2,3-*b*]pyrazine, XVI).

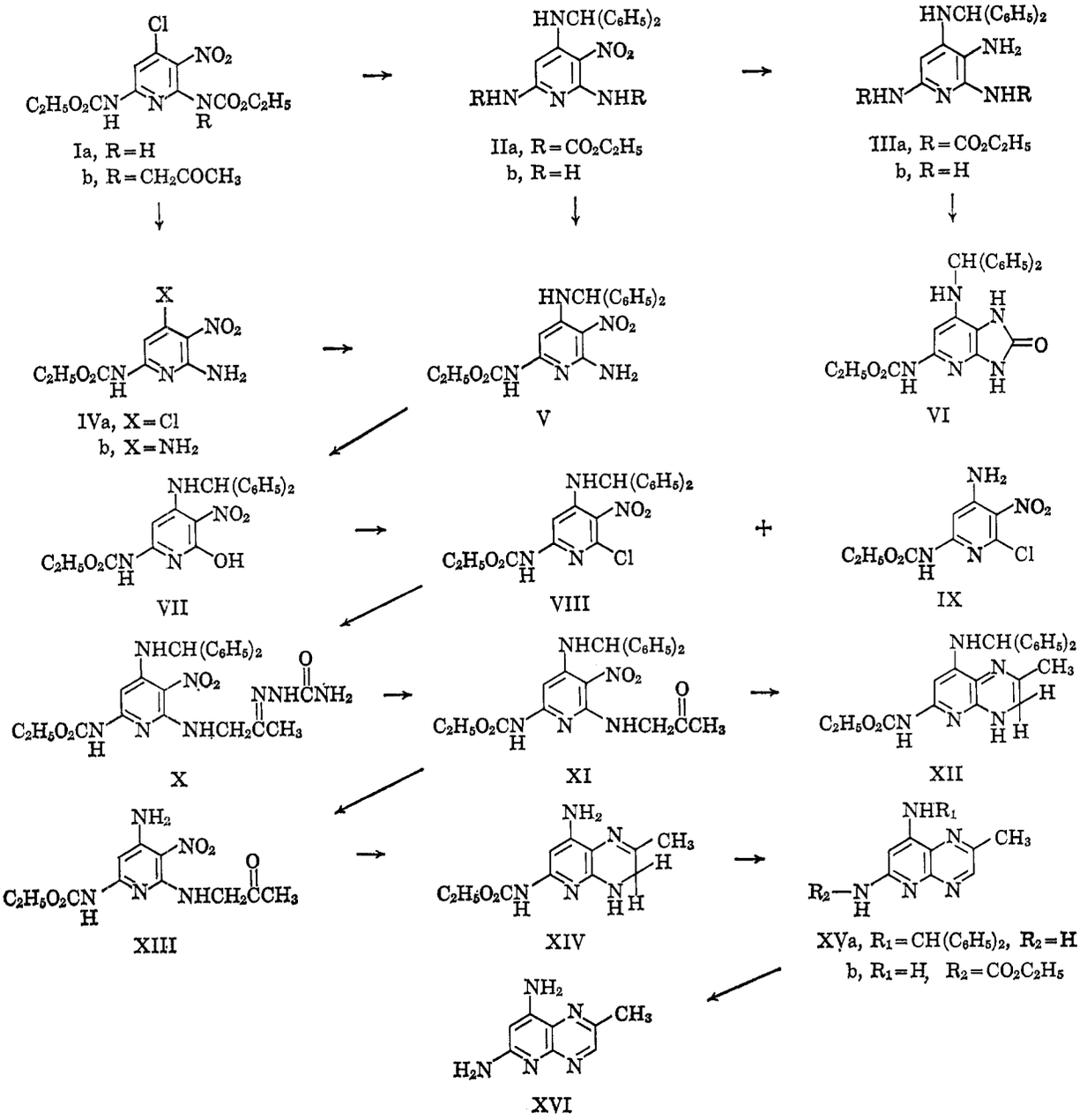
Several early attempts to synthesize the desired 3-deazapteridine ring system were based on building the pyrazine ring from the vicinal nitrogen atoms in compound Ia (Scheme I). The alkylation of Ia with chloroacetone to give Ib was considered as a starting point for the synthesis of the 3-deazapteridine XVI. Our inability to isolate Ib, however, precluded this approach. Another scheme involved the preparation of the 2,3-diaminopyridine IIIb and condensation of the latter with pyruvaldehyde to give XVa. Reaction of Ia with aminodiphenylmethane in methanol containing sodium acetate gave diethyl 4-[(diphenylmethyl)amino]-3-nitro-2,6-pyridinedicarbamate (IIa), the urethan groups of which were hydrolyzed with methanolic ammonia at 139° to give 2,6-diamino-4-[(diphenylmethyl)amino]-3-nitropyridine (IIb). Reduction of the nitro group of IIb to give IIIb was attempted with Raney nickel; however, hydrogen uptake was incomplete and a complex mixture of products was

(1) This work was supported by funds from the C. F. Kettering Foundation and from the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH-43-64-51.

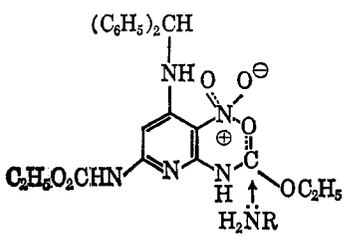
(2) For part I of this series, see J. A. Montgomery and N. Wood, *J. Org. Chem.*, **29**, 734 (1964).

(3) Many of these reactions are described by E. L. R. Stokstad, *Vitamins* (N. Y.), **3**, 91 (1954).

SCHEME I



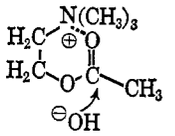
obtained. A third route, the condensation of ethyl 6-amino-4-[(diphenylmethyl)amino]-5-nitro-2-pyridinecarbamate (V) (see below) with pyruvaldehyde, was eliminated from consideration by the unsuccessful reaction of V with benzaldehyde under forcing conditions. The preparation of XVI from V, however, was effected by a more indirect route involving ethyl 6-chloro-4-[(diphenylmethyl)amino]-5-nitro-2-pyridinecarbamate (VIII). Two paths were used for conversion of Ia to the aminopyridine V. The first route involved the conversion of IIa to V by a transamidation reaction with cyclopentylamine in refluxing methanol.



Preferential reaction of this urethan group can be attributed to electron withdrawal by the adjacent nitro group. In addition "electrostatic bonding" between the nitro and carbonyl groups may aid this aminolysis.[4]

The alternate synthesis of V, which afforded a higher over-all yield and less difficulties in purification, involved the hydrolysis of Ia in refluxing triethylamine containing 1 equiv of water and reaction of the resulting ethyl 6-amino-4-chloro-5-nitro-2-pyridinecarbamate (IVa) with aminodiphenylmethane in methanol con-

(4) An analogy can be drawn to the increased rate of hydrolysis in base of acetylcholine bromide as compared to ethyl acetate due to "electrostatic bonding."



See W. Davis and W. Ross, *J. Chem. Soc.*, 3056 (1950); J. Butterworth, D. Eley, and G. Stone, *Biochem. J.*, **53**, 30 (1953).

taining triethylamine. The cleavage of the same urethan group of Ia was also effected with methanolic ammonia, but in this reaction ammonia also replaced the chloro group to give ethyl 4,6-diamino-5-nitro-2-pyridinecarbamate (IVb). The latter was also prepared from IVa and methanolic ammonia.

An attempt to transform the aminopyridine V directly to the chloropyridine VIII with sodium nitrite in concentrated hydrochloric acid[5] was unsuccessful. Diazotization of the primary amine of V with isoamyl nitrite in glacial acetic acid gave ethyl 4-[(diphenylmethyl)amino]-6-hydroxy-5-nitro-2-pyridinecarbamate (VII), which was chlorodehydroxylated with phosphorus oxychloride to give VIII. Repetition of the chlorodehydroxylation on a larger scale resulted in the isolation of ethyl 4-amino-6-chloro-5-nitro-2-pyridinecarbamate (IX) in addition to the benzhydryl compound VIII. Cleavage of the benzhydryl group can be attributed to hydrogen chloride generated in the chlorination reaction. Aminoacetone[6] was converted to its semicarbazone[7] which reacted readily with VIII in ethanol at room temperature to give ethyl 6-acetonylamino-4-[(diphenylmethyl)amino]-5-nitro-2-pyridinecarbamate semicarbazone (X). The semicarbazone X was hydrolyzed in warm 1 *N* hydrochloric acid to the parent ketone (XI) in near quantitative yield.

Catalytic reduction of the nitro group of XI was expected to give ethyl 3,4-dihydro-8-[(diphenylmethyl)amino]-2-methylpyrido[2,3-*b*]pyrazine-6-carbamate (XII) by spontaneous cyclization of the intermediate ethyl 6-acetonylamino-5-amino-4-[(diphenylmethyl)amino]-2-pyridinecarbamate. This assumption was based on an earlier experiment in which IIa was reduced with Raney nickel to diethyl 3-amino-4-[(diphenylmethyl)amino]-2,6-pyridinedicarbamate (IIIa) and cyclized in refluxing propanol to ethyl 7-[(diphenylmethyl)amino]imidazo[4,5-*b*]pyridin-2(3H)-one-5-carbamate (VI). The synthesis of XII was successful; however, the slow hydrogenation of XI in the presence of Raney nickel and difficulties encountered in isolating the low yield of XII made the development of a more effective procedure desirable. The use of palladium on charcoal as catalyst in the reduction of XI resulted in overhydrogenation and formation of a mixture of products. In an effort to obtain a more easily reducible compound, the benzhydryl group of XI was removed with hydrogen bromide in acetic acid giving ethyl 6-acetonylamino-4-amino-5-nitro-2-pyridinecarbamate (XIII) as the hydrobromide. Overhydrogenation again occurred when XIII or its hydrobromide was hydrogenated with palladium on charcoal. Catalytic hydrogenation of XIII with Raney nickel, however, proceeded smoothly and was followed by spontaneous cyclization of the intermediate ethyl 6-acetonylamino-4,5-diamino-2-pyridinecarbamate to give a 51% yield of ethyl 8-amino-3,4-dihydro-2-methylpyrido[2,3-*b*]pyrazine-6-carbamate (XIV). Oxidation of the dihydro compound (XIV) with potassium permanganate in acetone gave ethyl 8-amino-2-methylpyrido[2,3-*b*]pyrazine-6-carbamate (XVb). 6,8-Diamino-2-methylpyrido[2,3-*b*]pyrazine (XVI) was prepared by treatment of XVb with potassium hydroxide in refluxing ethanol, and was isolated as the hydrochloride by acidification of the reaction mixture with hydrochloric acid.

Work is in progress on the synthesis of 3-deazaaminopterin and 3-deazamethotrexate *via* XVI or by suitable modification of the reaction sequence from VIII or IX developed by these experiments.

(5) A. Chichibabin and M. Rjasanzew, *J. Russ. Phys. Chem. Soc.*, **47**, 1571 (1915).
(6) A. Albert and S. Matsuura, *J. Chem. Soc.*, 5131 (1961).
(7) W. R. Boon and T. Leigh, *ibid.*, 1497 (1951).

Experimental Section

Melting points were determined on a Kofler Heizbank and are corrected. The ultraviolet absorption spectra were determined in aqueous solution with a Cary Model 14 spectrophotometer (sh designates shoulder), whereas the infrared absorption spectra were determined in pressed potassium bromide disks with Perkin-Elmer Models 221-G and 521 spectrophotometers.

Diethyl 4-[(Diphenylmethyl)amino]-3-nitro-2,6-pyridinedicarbamate (IIa).—A solution of Ia (89.8 g, 0.270 mole), aminodiphenylmethane (51.0 g, 0.278 mole), and sodium acetate (22.2 g, 0.270 mole) in ethanol (925 ml) was refluxed for 5.5 hr. The hot solution was diluted with ethanol (2.6 l.), heated to the boiling point, and filtered. Refrigeration of the filtrate formed a yellow crystalline product which was collected by filtration, washed with cold ethanol, and dried at 78° *in vacuo* over phosphorus pentoxide: yield, 92.3 g (71%); mp 108–109°, solidifies and remelts at 174°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1 (cloudy), 224 (25.4), 256 (26.3), 360 (13.2), pH 7 (cloudy), 233 (28.0), 258 (25.4), 364 (16.8), pH 13 (unstable), 240, 371; σ, in cm^{-1}, 3340, 3240 (NH), 3090, 3060, 3030, 2980, 2930, 2910 (CH), 1760, 1740 (C=O), 1610, 1570, 1490 (C=C, C=N), 1540, 1330 (NO_2), 1190 (C—O—C), 740, 695 (monosubstituted phenyl).

Anal. Calcd for $C_{24}H_{25}N_5O_6$: C, 60.12; H, 5.26; N, 14.61. Found: C, 59.95; H, 5.25; N, 14.55.

2,6-Diamino-4-[(diphenylmethyl)amino]-3-nitropyridine (IIb).—A solution of IIa (500 mg, 1.04 mmoles) and liquid ammonia (15 ml) in methanol (35 ml) was heated in a stainless steel bomb at 139° for 23 hr. The solution was evaporated to dryness and the residue was crystallized from boiling ethanol (25 ml) to give 227 mg (65%) of brown-green crystals: mp 256°. The product was recrystallized for analysis from ethanol (Norit) to give yellow crystals: mp 260°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1, 225 (35.7), 275 (8.11), 345 (11.3), pH 7 and 13, insoluble; σ, in cm^{-1}, 3480, 3460, 3235, 3180 (NH), 1655 (NH); 1595, 1580, 1495 (C=C, C=N), 1555, 1310 (NO_2), 740, 700 (monosubstituted phenyl).

Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.89. Found: C, 64.68; H, 5.36; N, 20.82.

Diethyl 3-Amino-4-[(diphenylmethyl)amino]-2,6-pyridinedicarbamate (IIIa).—A solution of IIa (1.00 g, 2.09 mmoles) in ethanol (100 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 5% palladium on charcoal (1 g). After 37 min the solution had absorbed the theoretical amount of hydrogen. The solution was filtered and evaporated to dryness at room temperature *in vacuo*. The residue was rapidly dissolved in hot ethanol (10 ml) and refrigerated to prevent deazapurine formation. The gray crystalline product which formed was collected by filtration and dried *in vacuo* over phosphorus pentoxide: yield, 631 mg (67%); mp >260°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1, 242 (38.4), 271 (14.7), 300 (9.74), pH 7, 235 (34.9), 258 (sh) (12.8), 293 (7.25), pH 13, 235 (31.3), 258 (sh) (14.7), 295 (8.4); σ, in cm^{-1}, 3435, 3400, 3370, 3260 (NH), 3090, 3060, 3030, 2980, 2830, 2810 (CH), 1710 (C=O), 1615 (NH), 1585, 1540, 1515 (C=C, C=N), 1220 (C—O—C), 740, 700 (monosubstituted phenyl).

Anal. Calcd for $C_{24}H_{27}N_5O_4$: C, 64.12; H, 6.06; N, 15.58. Found: C, 63.94; H, 5.98; N, 15.23.

Ethyl 6-Amino-4-chloro-5-nitro-2-pyridinecarbamate (IVa).—A solution of Ia (1.00 g, 3.01 mmoles) in triethylamine (10 ml) and water (54.0 mg, 3.01 mmoles) was refluxed for 4 hr. The solution was evaporated to dryness *in vacuo*, and the residue recrystallized from 50% aqueous ethanol to give yellow needles, which were dried at 78° *in vacuo* over phosphorus pentoxide: yield, 535 mg (68%); mp 166°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1, 231 (11.6), 264 (9.40), 295 (sh) (4.36), 391 (8.18), pH 7, 231 (10.6), 265 (9.76), 295 (sh) (4.36), 395 (8.04), pH 13, 283 (5.45), 326 (4.83), 400 (15.4); σ, in cm^{-1}, 3480, 3380, 3350, 3130 (NH), 3050, 2960 (CH), 1760, 1750 (C=O), 1610 (NH), 1590, 1560, 1485 (C=C, C=N), 1540, 1320 (NO_2), 1210 (C—O—C).

Anal. Calcd for $C_8H_9ClN_4O_4$: C, 36.86; H, 3.48; N, 21.50. Found: C, 37.03; H, 3.49; N, 21.53.

Ethyl 4,6-Diamino-5-nitro-2-pyridinecarbamate (IVb).—A solution of IVa (1.00 g, 3.84 mmoles) in about 30% (v/v) methanolic ammonia (50 ml) in a Parr bomb was heated at 40° for 20 hr. The resulting mixture was evaporated to dryness, and the residue was recrystallized from 2:1 water–ethanol and then water to give the product: yield, 550 mg (59%); mp 187°.

Anal. Calcd for $C_8H_{11}N_5O_4$: C, 36.86; H, 3.48; Cl, 13.60; N, 21.50. Found: C, 36.90; H, 3.78; Cl, 13.80; N, 21.70.

Under these conditions I also gave this product.

Ethyl 6-Amino-4-[(diphenylmethyl)amino]-5-nitro-2-pyridinecarbamate (V). A. A solution of IVa (1.00 g, 3.84 mmoles), aminodiphenylmethane (1.00 g, 5.46 mmoles), and triethylamine (0.780 g, 7.68 mmoles) in methanol (15 ml) was contained in a flask equipped with condenser and drying tube and heated in an oil bath at 73° for 63 hr. The yellow crystalline precipitate of V that deposited from the reaction mixture at room temperature was collected by filtration, washed with methanol (1 ml), and dried *in vacuo* over phosphorus pentoxide at 100°: yield, 1.35 g (86%); mp 195°. The analytical sample was obtained by recrystallization from ethanol: mp 197°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1, 216 (39.4), 243 (33.6), 269 (sh) (10.26), 346 (16.7), pH 7 (unstable), 222, 265 (sh), 363, pH 13 (unstable), 267, 363, σ, in cm^{-1}, 3480, 3425, 3360, 3310, 3275, 3150 (NH), 3050, 3020, 2970, 2930 (CH), 1740, 1710 (C=O), 1590 (NH), 1590, 1570, 1490 (C=C, C=N), 1550 (sh), 1300 (NO_2), 1200 (C—O—C), 740, 700 (monosubstituted phenyl).

Anal. Calcd for $C_{21}H_{21}N_5O_4$: C, 61.90; H, 5.20; N, 17.19. Found: C, 62.08; H, 5.07; N, 17.34.

B. Treatment of IIa (1.00 g, 2.09 mmoles) with a solution of cyclopentylamine (195 mg, 2.30 mmoles) in methanol (100 ml) at reflux temperature for 6 hr also gave V in 66% yield, mp 197°, after evaporation of the reaction mixture to dryness and two recrystallizations from ethanol.

Ethyl 7-[(Diphenylmethyl)amino]imidazo[4,5-*b*]pyridin-2(3H)-one-5-carbamate (VI).—A solution of IIIa (200 mg, 0.445 mmole) in 1-propanol (5 ml) was heated at reflux temperature for 2.5 hr. Refrigeration of the resulting solution formed 140 mg (78%) of white crystalline product: mp >280°, after drying *in vacuo* over phosphorus pentoxide; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1, 246 (39.2), 277 (17.9), 305 (19.5), pH 7 (unstable), 240, 261, 290, pH 13, 237 (33.2), 298 (17.6); σ, in cm^{-1}, 3400, 3310, 3170, 3070, 3030, 2980, 2930 (CH, NH), 1740 (sh), 1690 (C=O), 1630, 1540, 1495 (C=C, C=N), 1200 (C—O—C), 740, 700 (monosubstituted phenyl).

Anal. Calcd for $C_{22}H_{21}N_5O_3$: C, 65.49; H, 5.25; N, 17.36. Found: C, 65.41; H, 5.23; N, 17.40.

Ethyl 4-[(Diphenylmethyl)amino]-6-hydroxy-5-nitro-2-pyridinecarbamate (VII).—A solution of isoamylnitrite (33.2 g, 0.284 mole) in glacial acetic acid (500 ml) was added to a solution of V (77.1 g, 0.189 mole) in glacial acetic acid (2.5 l.), which had been cooled to just above the freezing temperature. The solution was refrigerated overnight, heated slowly to 100° over a period of 1 hr, and maintained at this temperature for 1 hr. The resulting solution was evaporated to dryness *in vacuo*, and the residue was dried for 1 hr at 60° *in vacuo* over phosphorus pentoxide. Crystallization of the crude product (79 g) from ethanol gave pure VII as yellow needles, which were dried *in vacuo* over phosphorus pentoxide: yield, 48.0 g (62%); mp *ca.* 261° dec; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1, 236 (sh) (28.6), 266 (sh) (7.05), 353 (17.5), pH 7, 236 (sh) (27.0), 266 (sh) (7.05), 353 (17.1), pH 13, 255 (12.1), 281 (6.61), 361 (13.9); σ, in cm^{-1}, 3260, 3110, 3030, 2990, 2930 (NH, CH), 1780 (sh), 1740, 1730 (sh) (C=O), 1650 (NH), 1630, 1570, 1480 (C=C, C=N), 1550 (NO_2), 1210 (C—O—C), 740, 700 (monosubstituted phenyl).

Anal. Calcd for $C_{21}H_{20}N_4O_5$: C, 61.76; H, 4.94; N, 13.72. Found: C, 61.88; H, 4.94; N, 13.79.

Ethyl 6-Chloro-4-[(diphenylmethyl)amino]-5-nitro-2-pyridinecarbamate (VIII).—A suspension of VII (1.40 g, 3.43 mmoles) in phosphorus oxychloride (28 ml) was stirred at room temperature for 1 hr. The clear solution was heated at 80° for 30 min and evaporated at room temperature under high vacuum to a thick syrup. The syrup was stirred with ice (25 g) until a crystalline solid formed. The yellow solid was collected by filtration washed with water (10 ml) and dried *in vacuo* over phosphorus pentoxide. Refrigeration of a solution of the solid in ethanol (40 ml) afforded the title compound as yellow crystals: yield, 460 mg; mp 153–154°. Addition of water to the mother liquors and refrigeration of the mixture gave an additional 254 mg of product, mp 154°. The total yield was 714 mg (49%); λ_{max}, in mμ ($\epsilon \times 10^{-3}$) (unstable at all pH values), pH 1, 234, 263, 330, pH 7, 228, 258, 321, 371, pH 13, 223, 252, 330, 371; σ, in cm^{-1}, 3350 (NH), 3070, 3030, 2980, 2930 (CH), 1750 (C=O), 1610, 1520, 1490 (sh) (C=C, C=N), 1550, 1300 (NO_2), 1200 (C—O—C), 740, 700 (monosubstituted phenyl).

Anal. Calcd for $C_{21}H_{19}ClN_4O_4$: C, 59.09; H, 4.49; N, 13.13. Found: C, 59.30; H, 4.53; N, 13.30.

In an 81.4-g run VIII was obtained in only 33% yield. Fractional recrystallization of the evaporated mother liquors from ethanol gave an 18% yield of a by-product identified as **ethyl 4-amino-6-chloro-5-nitro-2-pyridinecarbamate (IX)**: mp 284–286°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1 and 7, 222 (28.1), 244 (sh) (15.1), 308 (5.83), pH 13, 223 (20.3), 237 (sh) (18.5), 273 (8.18), 370 (8.89); σ, in cm^{-1}, 3480, 3340, 3210 (NH), 3090, 2990, 2930 (CH), 1710 (C=O), 1630 (NH), 1651, 1510 (C=C, C=N), 1535, 1310 (NO_2), 1210 (C—O—C).

Anal. Calcd for $C_8H_9ClN_4O_4$: C, 36.86; H, 3.48; N, 21.50. Found: C, 37.22; H, 3.67; N, 21.35.

Ethyl 6-Acetonylamino-4-[(diphenylmethyl)amino]-5-nitro-2-pyridinecarbamate Semicarbazone (X).—Solid aminoacetone semicarbazone hydrochloride (9.00 g, 53.9 mmoles) was added to a cold solution of sodium ethoxide prepared from sodium metal (1.24 g, 53.9 g-atoms) and anhydrous ethanol (250 ml). The resulting suspension was stirred at room temperature for 1.75 hr and added to a suspension of VIII (10.0 g, 23.4 mmoles) in ethanol (750 ml). After stirring the mixture for 43 hr, the yellow crystalline precipitate was collected by filtration, washed with water, and dried *in vacuo* over phosphorus pentoxide: yield, 8.50 g; mp 190°, solidifies and remelts at 234°. An additional 1.00 g of product was obtained from the mother liquors by stirring for 48 hr; total yield, 9.50 g (78%). The analytical sample was obtained by recrystallization of a portion of the product from ethanol: mp 233–234°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1, 222 (23.4), 244 (19.0), 356 (10.5), pH 7, 224 (28.6), 262 (sh) (11.6), 290 (sh) (6.32), 362 (9.12), pH 13, 225 (28.1), 262 (sh) (11.6), 364 (9.91); σ, in cm^{-1}, 3470, 3440, 3310 (NH), 3030, 2980, 2925, 2850 (CH), 1745, 1700 (C=O), 1600, 1570, 1490 (C=C, C=N), 1530, 1310 (sh) (NO_2), 1200 (C—O—C), 740, 700 (monosubstituted phenyl).

Anal. Calcd for $C_{25}H_{23}N_8O_5$: C, 57.68; H, 5.43; N, 21.53. Found: C, 57.90; H, 5.57; N, 21.67.

Ethyl 6-Acetonylamino-4-[(diphenylmethyl)amino]-5-nitro-2-pyridinecarbamate (XI).—A suspension of finely ground X (8.00 g, 15.4 mmoles) in ethanol (25 ml) and 1 *N* hydrochloric acid (271 ml) was stirred at 50° for 4 hr and refrigerated for 16 hr. The solid was collected by filtration, washed with water (100 ml), and dried *in vacuo* over phosphorus pentoxide; yield, 7.00 g (98%): mp 225–226° dec; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1 (unstable), 222, 245 (sh), 359, pH 7 (unstable), 228, 262, 363, pH 13 (unstable), 224, 260, 362; σ, in cm^{-1}, 3350, 3300 (sh) (NH), 3030, 2920, 2850 (CH), 1740, 1730 (C=O), 1590, 1570, 1480 (C=C, C=N), 1530 (NO_2), 1200 (C—O—C), 735, 690 (monosubstituted phenyl).

Anal. Calcd for $C_{24}H_{25}N_5O_5$: C, 62.19; H, 5.44; N, 15.11. Found: C, 61.87; H, 5.40; N, 15.40.

Ethyl 3,4-Dihydro-8-[(diphenylmethyl)amino]-2-methylpyrido[2,3-*b*]pyrazine-6-carbamate (XII).—A suspension of XI (216 mg, 0.466 mmole) in ethanol (25 ml) was stirred with Raney nickel (580 mg weighed wet with ethanol) in the presence of hydrogen at atmospheric pressure and room temperature for 8 days. The reaction mixture was heated to reflux temperature momentarily three times during the hydrogenation. The reduction mixture was diluted with ethanol (25 ml), heated to boiling, and filtered through Celite under nitrogen. Refrigeration of the filtrate formed a yellow precipitate which was collected by filtration, recrystallized from ethanol, and dried *in vacuo* over phosphorus pentoxide: yield, 74.0 mg (38%); mp 197°. Thin layer chromatography indicated the presence of slight impurities in the product: λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1, 239 (25.1), 269 (21.4), 325 (11.8), pH 7 (unstable), 226, 271, 282 (sh), 343 (13.1), pH 13 (unstable), 226, 271, 282 (sh), 340; σ, in cm^{-1}, 3390, 3280 (NH), 3060, 3025, 2975, 2930, 2900 (CH), 1730 (sh), 1705 (C=O), 1610, 1585, 1545, 1505, 1490 (C=C, C=N), 1200 (C—O—C), 730, 695 (monosubstituted phenyl).

Anal. Calcd for $C_{24}H_{25}N_5O_2$: C, 69.38; H, 6.07; N, 16.86. Found: C, 69.09; H, 5.73; N, 16.90.

Ethyl 6-Acetonylamino-4-amino-5-nitro-2-pyridinecarbamate (XIII) Hydrobromide.—Ethyl 6-acetonylamino-4-[(diphenylmethyl)amino]-5-nitro-2-pyridinecarbamate (XI, 3.00 g, 6.48 mmoles) was dissolved in a solution of phenol (600 mg) in 10%

hydrogen bromide in acetic acid (90 ml). After standing overnight at room temperature, the solution was refrigerated. The crystalline precipitate that deposited was collected by filtration under nitrogen and dried *in vacuo* over phosphorus pentoxide: yield, 2.28 g (93%); mp *ca.* 228° with predarkening and softening; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1, 221 (24.8), 238 (26.2), 268 (sh) (8.91), 340 (12.0), pH 7 (unstable), 215, 237, 256, 280, 344, pH 13, 215 (20.7), 258 (sh) (8.91), 298 (sh) (6.36), 348 (12.4); σ, in cm^{-1}, 3405, 3240, 3150, 3010, 2950, 2915 (NH, CH), 1750, 1720 (C=O), 1660, 1640 (NH), 1610, 1510, 1480 (C=C, C=N), 1555, 1320 (NO_2), 1220 (C—O—C).

Anal. Calcd for $C_{11}H_{15}N_5O_5 \cdot HBr$: C, 34.93; H, 4.27; Br, 21.13; N, 18.52. Found: C, 35.03; H, 4.49; Br, 21.1; N, 18.33.

Ethyl 8-Amino-3,4-dihydro-2-methylpyrido[2,3-*b*]pyrazine-6-carbamate (XIV).—Aqueous 1 *N* sodium hydroxide (9.17 ml, 9.17 mmoles) was added dropwise under nitrogen to a stirred suspension of XIII hydrobromide (3.81 g, 10.1 mmoles) in ethanol (180 ml) and N,N-dimethylformamide (90 ml). The resulting solution was hydrogenated at room temperature and atmospheric pressure in the presence of Raney nickel (1.0 g, weighed wet with ethanol). After 16 hr the solution had absorbed 103% of the theoretical amount of hydrogen. The solution was filtered through Celite under nitrogen, evaporated to dryness *in vacuo* at 60°, and the residual oil was triturated with water (10 ml). The resultant yellow solid was collected by filtration, dissolved in hot methanol (30 ml), and treated with charcoal. The yellow crystals that deposited were collected by filtration, washed with methanol, and dried *in vacuo* over phosphorus pentoxide: yield, 1.17 g (51%); mp >260°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1, 232 (27.0), 318 (12.0), pH 7, 223 (29.2), 256 (sh) (15.3), 327 (7.91), pH 13, 223 (29.2), 256 (sh) (15.6), 327 (7.79); σ, in cm^{-1}, 3480, 3360, 3230 (NH), 2980, 2930, 2900, 2780 (CH), 1720 (C=O), 1620 (NH), 1620, 1590, 1540, 1520 (C=C, C=N), 1210 (C—O—C).

Anal. Calcd for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.10. Found: C, 53.01; H, 5.99; N, 27.74.

Ethyl 8-Amino-2-methylpyrido[2,3-*b*]pyrazine-6-carbamate (XVb).—Ethyl 8-amino-3,4-dihydro-2-methylpyrido[2,3-*b*]pyrazine-6-carbamate (XIV, 1.09 g, 4.37 mmoles) was dissolved in warm acetone (250 ml), and the solution was allowed to cool to room temperature. A 0.27% solution of potassium permanganate in acetone was added slowly with stirring over a period of 1 hr until the color of permanganate persisted (*ca.* 2.08 mmoles was consumed). The manganese dioxide was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The ultraviolet absorption spectrum and thin layer chromatogram of the yellow residue (0.910 g, 84%) were identical with those of an analytical sample obtained by recrystallization from ethanol: mp >260°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1, 228 (30.9), 250 (sh) (12.7), 323 (18.0), pH 7, 225 (30.0), 263 (23.7), 331 (10.3), pH 13, 226 (26.2), 263 (22.6), 334 (9.64); σ, in cm^{-1}, 3480, 3430, 3290, 3180, 3110, 2980, 2920 (NH, CH), 1730 (C=O), 1620 (sh) (NH), 1610, 1575, 1540, 1520, 1500 (C=C, C=N), 1200 (C—O—C).

Anal. Calcd for $C_{11}H_{13}N_5O_2$: C, 53.43; H, 5.30; N, 28.33. Found: C, 53.26; H, 5.39; N, 28.24.

6,8-Diamino-2-methylpyrido[2,3-*b*]pyrazine (XVI) Hyrochloride.—A suspension of XVb (700 mg, 2.83 mmoles) in a solution of potassium hydroxide (4.00 g, 71.3 mmoles) in ethanol (60 ml) was stirred at reflux under nitrogen for 7 hr. The resulting solution was cooled to room temperature, made slightly acidic with 6 *N* hydrochloric acid, and evaporated to dryness *in vacuo* at 40°. The residue was extracted with boiling ethanol (70 ml); the extract was evaporated to dryness *in vacuo*. The residue was recrystallized from hot 0.2 *N* hydrochloric acid (6 ml) with charcoal treatment to give the product as tan needles in two crops, which were dried at 78° *in vacuo* over phosphorus pentoxide: yield, 492 mg (82%); mp >260°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1, 221 (36.9), 334 (15.9), pH 7, 220 (33.7), 255 (9.32), 341 (12.1), pH 13, 220 (25.6), 259 (15.9), 354 (9.56); σ, in cm^{-1}, 3500, 3420, 3380, 3310, 3170 (NH), 1650 (NH), 1630 (sh), 1600 (sh), 1545, 1490 (C=C, C=N).

Anal. Calcd for $C_8H_9N_5 \cdot HCl$: C, 45.39; H, 4.76; N, 33.09. Found: C, 45.55; H, 5.02; N, 33.10.[8]

Acknowledgment.—The authors are indebted to Dr. W. J. Barrett and the members of the Analytical Chemistry Section of Southern Research Institute who performed the spectral and microanalytical determinations reported, and to Mr. W. E. Fitzgibbon and the Organic Preparations Section of Southern Research Institute who carried out the large-scale synthesis of some of the compounds.

(8) The Kjeldahl procedure was used for the nitrogen analysis due to low values obtained by the Dumas method.

Organic Sulfur Compounds. XV. Cationic Addition of O,O′-Diethylthiophosphoric Acid to Olefins

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Received December 15, 1965

O,O′-Diethylthiophosphoric acid (phosphorothioic acid O,O′-diethyl ester) was added to isobutylene, isoprene, styrene, indene, cyclopentene, and norbornene by a cationic mechanism. The predominant formation of O,O′-diethyl-S-alkylthiophosphates was observed. In accordance with the Markovnikov rule, S-*t*-butyl-, S-α-phenylethyl-, S-1-indanyl-, and S-cyclopentylthiophosphates were formed with high selectivities. From isoprene the S-(3-methyl-2-butenyl)- and S-2-(2-methyl-3-butenyl)thiophosphates were obtained in a 4:1 ratio. With norbornene O- and S-alkylation was observed in an exceptionally high ratio of 2:3. It was shown that addition occurs only to strained cyclic olefins or to olefins which form on protonation relatively stable carbonium ions.

During the course of our investigation of the free-radical addition of O,O′-dialkylthiophosphoric acid (phosphorothioic acid O,O′-dialkyl esters) to unsaturates, we became concerned with the possibility of concurrent cationic additions in such systems. The cationic addition of O,O′-dialkyldithiophosphoric acids to olefins is a well-studied reaction, and the relevant literature indicates that it is rather generally applicable, *i.e.*, independent from the structure of the olefin.[1] Similar additions of O,O′-dialkylthiophosphoric acids, however, appear to be hardly investigated. Only a few ionic additions to nonhydrocarbon unsaturates, such as alkyl propiolates[2] and phenyl vinyl ethers or phenyl vinyl sulfides[3] have been described in the patent literature. While these additions were investigated as synthetic methods to obtain thiophosphate (phosphorothioate) esters of potential interest as insecticides,[4,5] no study of the scope or mechanism of such additions was made.

(1) W. E. Bacon and W. M. LeSuer, *J. Am. Chem. Soc.*, **76**, 670 (1954).

(2) L. A. Miller and G. H. Birum, U. S. Patent 3,059,014 (1962).

(3) G. Schrader, German Patent 1,070,171 (1959).

(4) G. Schrader, "Die Entwicklung neuer insektizider Phosphorsäure-Ester," Verlag Chemie, Weinheim, 1963.

(5) K. Sasse, "Methoden der Organischen Chemie," Houben–Weyl, Vol. XII/2, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1964, pp 652–681.