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Studies on Pyrimidine Derivatives and Related Compounds. LXVII.[1] Reaction of Thiadiazolium Derivatives with Dialkyl Acylphosphonates

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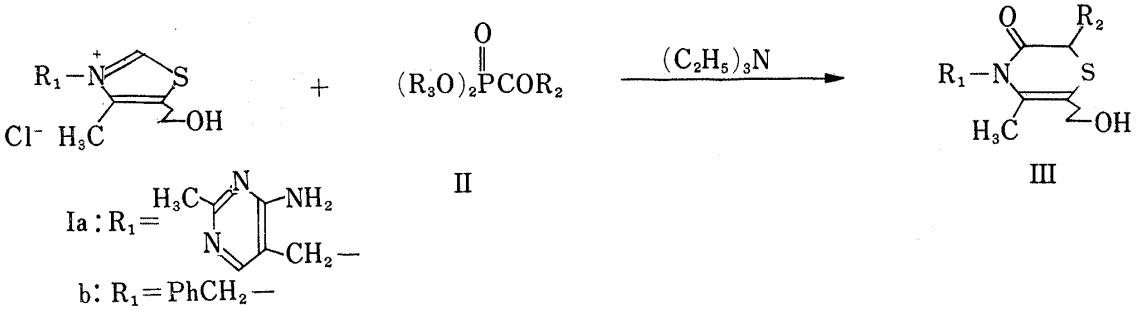
Reaction of 1,2,4-thiadiazolium salts with dialkyl acylphosphonates (II) afforded ring expanded products, 1,2,4-thiadiazine derivatives. In the reaction of 4-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-methyl-1,2,4-thiadiazolium bromide hydrobromide (VII) with dialkyl benzoylphosphonates (IIb, c), however, 10a(1-dialkylphosphoroyl)benzyl-4,5,10,10a-tetrahydro-3,8-dimethyl-1,2,4-thiadiazolo[4′,5′-1,2]pyrimido[4,5-*d*]pyrimidine (VIIIb, c) were obtained as major products and the 1,2,4-thiadiazine derivative (IX) as a minor product. Acid treatment of VIIIb, c gave XIb, c, which were intermediates of the reaction of the thiadiazolium salt (VII) with phosphonate (IIb, c), and these were converted to VIIIb, c and IX by alkaline hydrolysis.

In previous papers,[3–5] we reported that thiamine (Ia) or other thiazolium salts react with dialkyl acylphosphonates (II) to give the ring expanded products, 1,4-thiazine derivatives (III), in a good yield. The mechanism of this ring expansion reaction was clarified by the isolation of a phosphate intermediate using 5(2-benzoyloxy)ethyl-3-benzyl-4-methylthiazolium halides as model compounds.[5] Now, application of this novel reaction to other azolium salts such as 1,2,4-thiadiazolium derivatives has been examined.

Reaction of 4-benzyl-3-methyl-1,2,4-thiadiazolium bromide (IV) with diethyl acetyl (benzoyl)phosphonate (IIa, b) in the presence of triethylamine gave an oily product Va, $C_{12}H_{14}ON_2S$ in 9.7% yield (or analogous Vb, mp 100—102°, $C_{17}H_{16}ON_2S$), accompanied by a small amount of 4-benzyl-3-methyl-1,2,4-thiadiazolin-5-thione (VI), mp 92—94°, $C_{10}H_{10}N_2S_2$. The structure of Va was confirmed as 4-benzyl-5,6-dihydro-3,6-dimethyl-5-oxo-4H-1,2,4-thiadiazine on the basis of the presence of an amido carbonyl band at 1690 cm^{-1} in its infrared (IR) absorption spectrum and a $>CH-CH_3$ group in its proton magnetic resonance (PMR) spectrum.

Next, this reaction was tried with VII which contained the same pyrimidine moiety as thiamine. On carrying out this reaction at −60° using diethyl benzoylphosphonate (IIb) or dimethyl benzoylphosphonate (IIc), although VII was unstable and decomposed to the acetamidine derivative (XIIa) on recrystallization from ethanol or water, a crystalline product VIIIb, mp 139° (decomp.), $C_{20}H_{26}O_4N_5SP$ or homologous VIIIc, mp 149° (decomp.), $C_{18}H_{22}O_4N_5SP$ were obtained in about 17% yield. Under moist conditions, however, a new product IX, mp 169° (decomp.), $C_{16}H_{17}ON_5S$ was formed in addition to VIII. The analytical data of the first product VIIIb showed it to be a 1:1 adduct of the thiadiazole and the phosphonate. Ultraviolet (UV) absorption spectrum of VIIIb showed the existence of a 4-alkylamino pyrimidine moiety (λ_{max}^{EtOH} mμ (log ε): 239.5 (4.16), 281.5 (3.80)).[6] Action of ethylisocya-

1) Part LXVI: A. Takamizawa and H. Sato, *Chem. Pharm. Bull.* (Tokyo), **18**, 1201 (1970).
2) Location: *Fukushima-ku, Osaka.*
3) A. Takamizawa, Y. Hamashima, Y. Sato, H. Sato, S. Tanaka, H. Ito, and Y. Mori, *J. Org. Chem.*, **31**, 2951 (1966).
4) A. Takamizawa and Y. Sato, *Chem. Pharm. Bull.* (Tokyo), **14**, 742 (1966).
5) A. Takamizawa, Y. Hamashima, and H. Sato, *J. Org. Chem.*, **33**, 4038 (1968).
6) A. Takamizawa, K. Hirai, Y. Hamashima, Y. Matsumoto, and S. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **16**, 1764 (1968).



nate on VIIIb afforded the N-ethylcarbamate (X), mp 137°, $C_{23}H_{31}O_5N_6SP$, the UV spectrum of which showed maxima at 237.5 mμ (log ε 4.06), 277.5 (4.02). This UV spectrum pattern was similar to that of N-ethylcarbamoylthiamine free base,[7] which exhibited maxima at 240.0 mμ (log ε 3.86) and 281.5 (3.92). The IR spectrum of VIIIb in chloroform solution showed no carbonyl band, but a single NH band at 3390 cm^{-1} and strong P=O and P–O–C bands at 1260, 1030 cm^{-1} respectively. In its PMR spectrum in deuterio chloroform solution, signals for two olefinic methyls, pyrimidine-C_5-methylene protons, a pyrimidine nucleus proton, two ethoxy groups and phenyl protons were seen in addition to the most characteristic benzylic proton at τ 4.25 as a doublet (J=10.0 Hz) due to hydrogen-phosphorus coupling. On the basis of the structure of the thiazolium-thiazine intermediate, 5(2-benzoyloxy)ethyl-3-benzyl-2(1-diethylphosphoroyl)benzyl-4-methylthiazolium halides, which were isolated in the reaction of 5(2-benzoyloxy)ethyl-3-benzyl-4-methylthiazolium salts with diethyl benzoylphosphonate,[5] it was supposed that this compound might have the structure of 10a(1-diethylphosphoroyl) benzyl-4,5,10,10a-tetrahydro-3,8-dimethyl-1,2,4-thiadiazolo[4′,5′-1,2] pyrimido-[4,5-*d*]pyrimidine (VIIIb). The structure of the second product IX was assigned as 4(4-amino-2-methyl-5-pyrimidinyl)methyl-3-methyl-6-phenyl-4H-1,2,4-thiadiazin-5(6H)-one on the basis of the presence of an amido carbonyl band at 1670 cm^{-1} in its IR spectrum and a >CH–Ph group in its PMR spectrum which appeared at τ 4.88 (1H, s) and 2.65 (5H, s) in deuterated dimethyl sulfoxide.

Treatment of VIIIb, c with ethanolic hydrogen chloride[8] caused ring opening and resulted in the formation of amorphous products (XIb, c), which were converted to VIIIb, c and IX in about 2:1 ratio on alkaline hydrolysis. Therefore, these amorphous compounds (XI) might be the intermediates in the reaction in which thiadiazolium (VII) was converted into VIIIb, c and IX, however, these intermediates (XI) were very unstable and easily decomposed to an acetamidine derivative (XIIb) on standing at room temperature and during purification; so, in order to isolate this intermediate in a more stable form, the same treatment with the N-ethylcarbamoyl derivative (X) of VIIIb was tried. On concentration of the ethanolic hydrogen chloride solution of X at 20° *in vacuo*, colourless crystals (XIII), mp 187° (decomp.), $C_{23}H_{33}O_5N_6SCl_2P\cdot H_2O$ were precipitated. The PMR spectrum of this compound (XIII) in deuterated dimethylsulfoxide solution showed three N–H protons at τ 1.05, 0.43, −0.02 and a characteristic benzylic proton at τ 4.39 as a doublet (J=8.4 Hz), indicating the ring opening of the tetrahydropyrimidine of X. Alkali treatment of XIII gave XIV, mp 168—170° (decomp.), $C_{19}H_{22}O_2N_6S$, which was identified with the N-carbamoylated product of IX. This intermediate XIII, however, was also unstable and decomposed to XV on recrystallization from ethanol with heat.

From the above results, it may be concluded that the reaction of 4(4-amino-2-methyl-5-pyrimidinyl)methyl-3-methyl-1,2,4-thiadiazolium bromide (VII) with dialkyl benzoylphos-

7) A. Takamizawa, K. Hirai, S. Matsumoto, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **17**, 462 (1969).
8) The acid treatment of thiamine free base (XVII) or N-ethylcarbamoylthiamine free base (XVI) resulted in the ring opening of the tetrahydropyrimidine ring to give thiamine chloride hydrochloride or N-ethylcarbamate of thiamine (see ref. 7).

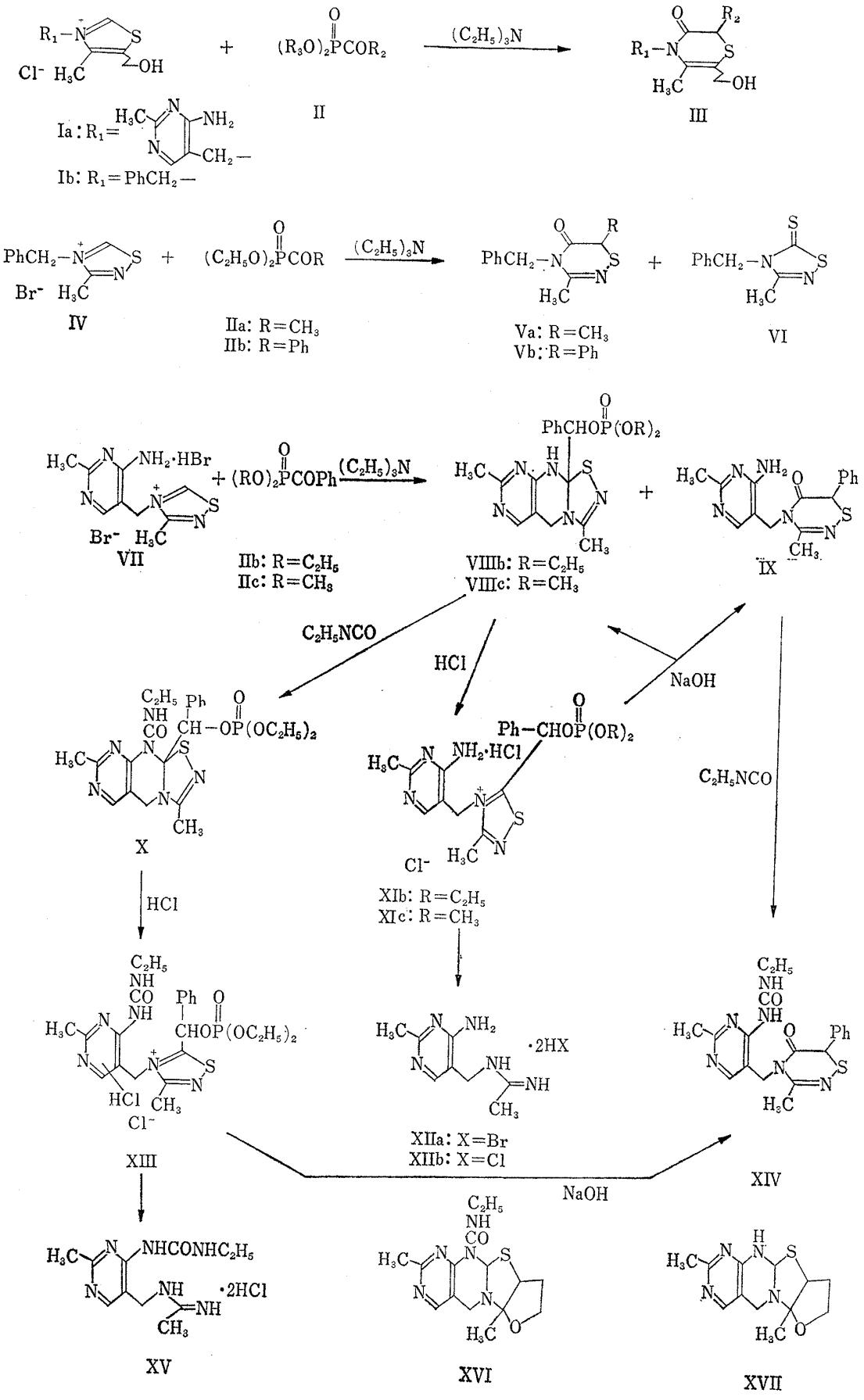


Chart 1

phonates (II) proceeded *via* the intermediate (XI) as shown in Chart 2, the structure of which is quite analogous with the thiazolium-thiazine intermediate.[5] Thus, nucleophilic attack by the pyrimidine C_4 amino group at the C_5 position of the thiadiazolium intermediate, replacing it by a powerfully electron-withdrawing nitrogen atom, resulted in the tricyclic phosphate (VIII) without ring expansion; on the other hand, the base catalized hydration-elimination reaction of intermediate (XI) under moist conditions produced the ring expanded 1,2,4-thiadiazine derivative.

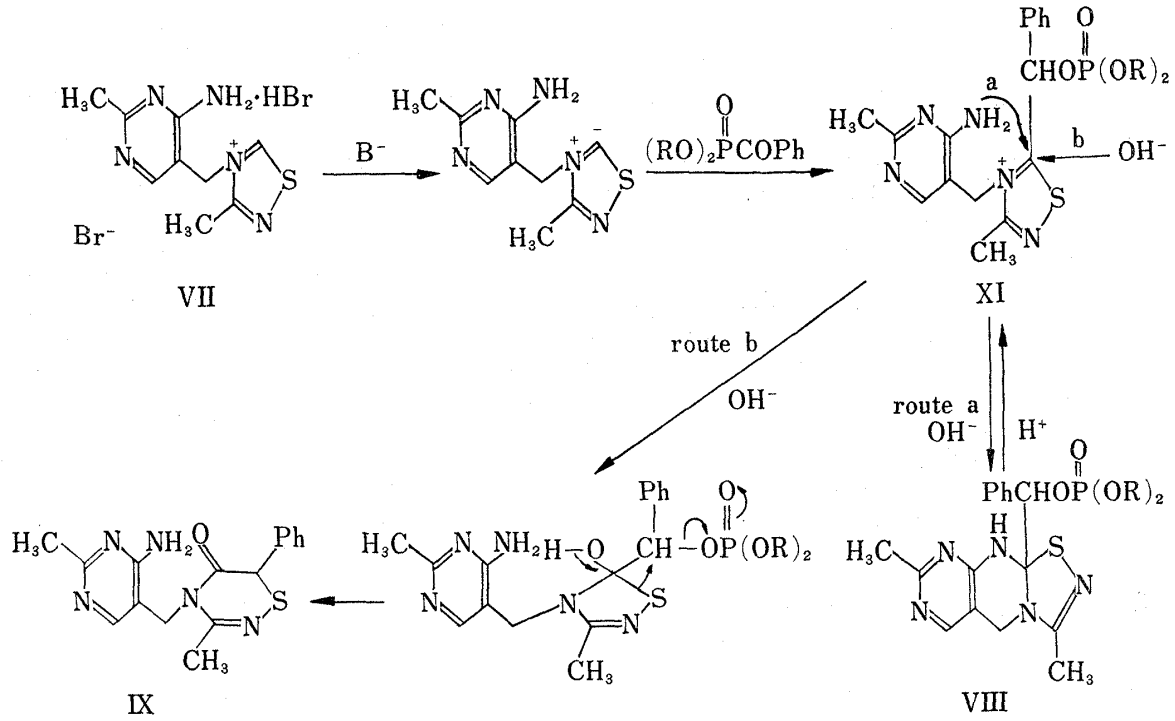


Chart 2

Experimental

All melting points are uncorrected. PMR spectra were taken with a Varian A-60 Spectrometer in $CDCl_3$ or d_6-DMSO containing TMS and in D_2O solution containing DSS as an internal standard. Signal multiplicites are represented by s (singlet), d (doublet), t (triplet), q (quartet), b (broad) and m (multiplet).

4-Benzyl-3-methyl-1,2,4-thiadiazolium Bromide (IV)——A mixture of 0.78 g of 3-methyl-1,2,4-thiadiazole[9] (bp 129—132.5°) and 1.30 g of benzyl bromide was heated at 100—120° for 2 hr under a N_2 stream. After cooling, the precipitated brown crystals were recrystallized from EtOH to give 1.23 g of IV, mp 201—203° (decomp.). *Anal.* Calcd. for $C_{10}H_{11}N_2SBr$: C, 44.28; H, 4.08; N, 10.33. Found: C, 44.51; H, 4.20; N, 10.67.

Reaction of 4-Benzyl-3-methyl-1,2,4-thiadiazolium Bromide (IV) with Diethyl Acetylphosphonate (IIa)——To a suspension of 5.42 g of 4-benzyl-3-methyl-1,2,4-thiadiazolium bromide (IV) and 4.68 g of diethyl acetylphosphonate (IIa) in 30 ml of dry DMF was added dropwise 4.1 g of triethylamine under a dry N_2 stream at 3—5° with stirring. Stirring was continued for 1 hr below 5°, then the reaction mixture was allowed to stand overnight at room temperature. Precipitated triethylamine hydrobromide was removed by filtration and the filtrate was concentrated *in vacuo* at 40° and resulting brown oil was dissolved in $CHCl_3$, washed repeatedly with 5% aqueous NaOH solution and water, dried over anhydrous Na_2SO_4. After removal of the solvent, the residue, 8.7 g was chromatographed on silica gel with $CHCl_3$–MeOH. From the first fraction 67 mg of sulfur, and from the second fraction, after recrystallization from ether, 20 mg of 4-benzyl-3-methyl-1,2,4-thiadiazolin-5-thione (VI), mp 92—94°, were obtained. UV λ_{max}^{EtOH} mμ (log ε): 309.5 (4.16). IR ν_{max}^{Nujol} cm^{-1}: 1195 (C=S). PMR ($CDCl_3$) τ: 7.65 (s, 3H, =C–CH_3), 4.58 (s, 2H, Ph–CH_2–N), 2.71 (m, 5H, C_6H_5). *Anal.* Calcd. for $C_{10}H_{10}N_2S_2$: C, 54.02; H, 4.53; N, 12.60; S, 28.84. Found: C, 53.85; H, 4.62;

9) J. Goerdeler, J. Ohm, and O. Tegtmeyer, *Chem. Ber.*, **89**, 1534 (1956).

N, 12.97; S, 28.86. The third fraction gave 450 mg of oily 4-benzyl-3,6-dimethyl-4H-1,2,4-thiadiazin-5(6*H*)-one (Va). UV λ_{max}^{EtOH} mμ (log ε): 235 (shoulder), 311.0 (3.36). IR ν_{max}^{Film} cm^{-1}: 1690 (N–C=O). PMR ($CDCl_3$) τ: 8.54 (d, J=7.0 Hz, 3H, >CH–CH_3), 7.80 (s, 3H, =C–CH_3), 6.48 (q, J=7.0 Hz, 1H, –CH–), 4.83, 5.05 (ABq, J=16.5 Hz, 2H, Ph–CH_2–N), 2.75 (m, 5H, C_6H_5). *Anal.* Calcd. for $C_{12}H_{14}ON_2S$: C, 61.51; H, 6.02; N, 11.96; S, 13.69. Found: C, 61.53; H, 6.10; N, 11.83; S, 13.79.

Reaction of 4-Benzyl-3-methyl-1,2,4-thiadiazolium Bromide (IV) with Diethyl Benzoylphosphonate (IIb)——To a suspension of 5.42 g of 4-benzyl-3-methyl-1,2,4-thiadiazolium bromide (IV) and 6.4 g of diethyl benzoylphosphonate (IIb) in 30 ml of dry DMF was added dropwise 4.1 g of triethylamine under a dry N_2 stream at 3—5° with stirring. Treatment of this reaction mixture as above gave 260 mg of sulfur, 23 mg of 4-benzyl-3-methyl-1,2,4-thiadiazolin-5-thione (VI) and 460 mg of 4-benzyl-3-methyl-6-phenyl-4*H*-1,2,4-thiadiazin-5(6*H*)-one (Vb), mp 100—102°, which was recrystallized from EtOH–ether. UV λ_{max}^{EtOH} mμ (log ε): 311.5 (3.42). IR ν_{max}^{Nujol} cm^{-1}: 1680 (N–C=O). PMR ($CDCl_3$) τ: 7.86 (s, 3H, =C–CH_3), 5.33 (s, 1H, –C–H), 4.92 (s, 2H, Ph–CH_2–N), 2.75 (m, 5H, CH_2–C_6H_5), 2.64 (s, 5H, >CH–C_6H_5). *Anal.* Calcd. for $C_{17}H_{16}ON_2S$: C, 68.89; H, 5.44; N, 9.45. Found: C, 69.13; H, 5.38; N, 9.25.

4(4-Amino-2-methyl-5-pyrimidinyl)methyl-3-methyl-1,2,4-thiadiazolium Bromide Hydrobromide (VII)——A solution of 11.32 g of 4-amino-2-methyl-5-bromomethyl pyrimidine hydrobromide and 4.0 g of 3-methyl-1,2,4-thiadiazole in 15 ml of dry DMF was heated at 65° for 20 hr under a N_2 stream. After cooling, the precipitate were collected by filtration and washed with cold DMF, to give 8.33 g of 4(4-amino-2-methyl-5-pyrimidinyl)methyl-3-methyl-1,2,4-thiadiazolium bromide hydrobromide (VII), mp 230—240° (decomp.). *Anal.* Calcd. for $C_9H_{13}N_5SBr_2$: C, 28.21; H, 3.42; N, 18.28; S, 8.37; Br, 41.72. Found: C, 28.57; H, 3.51; N, 18.02; S, 8.00; Br, 40.80. Recrystallization of VII from H_2O gave N (4-amino-2-methyl-5-pyrimidinyl)-methyl acetamidine dihydrobromide (XIIa), mp 278° (decomp.) in quantitative yield. *Anal.* Calcd. for $C_8H_{15}N_5Br_2$: C, 28.17; H, 4.43; N, 20.53. Found: C, 28.22; H, 4.58; N, 19.99.

Reaction of 4(4-Amino-2-methyl-5-pyrimidinyl)methyl-3-methyl-1,2,4-thiadiazolium Bromide Hydrobromide (VII) with Diethyl Benzoylphosphonate (IIb) under Dry Conditions——To a suspension of 1.53 g of 4(4-amino-2-methyl-5-pyrimidinyl)methyl-3-methyl-1,2,4-thiadiazolium bromide hydrobromide (VII) and 1.26 g of diethyl benzoylphosphonate (IIb) in 10 ml of dry DMF was added dropwise 1.62 g of triethylamine under a dry N_2 stream at −60° with stirring. The reaction mixture was kept at −60° for 3 days, precipitated triethylamine hydrobromide was removed by filtration and the filtrate was concentrated *in vacuo* at 40°. The residue was dissolved in $CHCl_3$, washed with water and the solvent was evaporated *in vacuo* after drying over anhydrous Na_2SO_4. The residual brown oil (2.36 g) was chromatographed on silica gel, and the fraction which eluated with 2—5% MeOH–$CHCl_3$ was recrystallized from ethylacetate to give 480 mg of VIIIb as colourless needles, mp 139° (decomp.). UV λ_{max}^{EtOH} mμ (log ε): 239.5 (4.16), 281.5 (3.80). IR ν_{max}^{Nujol} cm^{-1}: 3200 (NH), 1270 (P=O), 1030 (P–O–C). PMR ($CDCl_3$) τ: 8.94, 8.68 (2×t·d, J=7.0, 1.2 Hz, 6H, 2×CH_2–CH_3), 8.00 (s, 3H, =C–CH_3), 7.53 (s, 3H, Pm–C_2–CH_3), 6.5—5.7 (m, 4H, 2×O–CH_2–), 5.63, 5.28 (ABq, J=16.0 Hz, 2H, Pm–C_5–CH_2–), 4.25 (d, J=10.0 Hz, 1H, Ph–CH<), 2.58 (bs, 5H, C_6H_5), 2.00 (s, 1H, Pm–C_6–H). *Anal.* Calcd. for $C_{20}H_{26}O_4N_5SP$: C, 51.82; H, 5.66; N, 15.11; P, 6.68. Found: C, 51.73; H, 6.07; N, 14.71; P, 7.24.

Reaction of 4(4-Amino-2-methyl-5-pyrimidinyl)methyl-3-methyl-1,2,4-thiadiazolium Bromide Hydrobromide (VII) with Diethyl Benzoylphosphonate (IIb) under Moist Conditions——To a stirred suspension of 5.62 g of VII and 4.62 g of IIb in 30 ml of DMF containing 0.2 ml of water was added 6.1 g of triethylamine under a N_2 stream at −60° and stirring was continued for a week at −60°. After treatment as above, the residual oil (5.25 g) was extracted with ethylacetate. Evaporation of solvent gave 550 mg of colourless needles, mp 139° (decomp.) which was identified with VIIIb obtained above by IR comparison. The insoluble part (4.5 g) was chromatographed on basic alumina and the fraction which eluated with benzene–ethylacetate (50:50) was crystallized. Recrystallization from MeOH gave 323 mg of IX, mp 168—170° (decomp.). UV λ_{max}^{EtOH} mμ (log ε): 232.5 (4.14), 277.0 (3.73), 312.0 (3.43). IR ν_{max}^{Nujol} cm^{-1}: 3400, 3130 (NH_2), 1670 (N–CO), 1592 (Ph). PMR (d_6-DMSO) τ: 7.82 (s, 3H, =C–CH_3), 7.70 (s, 3H, Pm–C_2–CH_3), 5.15 (bs, 2H, Pm–C_5–CH_2), 4.88 (s, 1H, >C–H), 3.23 (m, 2H, NH_2), 2.65 (s, 5H, –C_6H_5), 2.48 (s, 1H, Pm–C_6–H). *Anal.* Calcd. for $C_{16}H_{17}ON_5S$: C, 58.69; H, 5.24; N, 21.39; S, 9.80. Found: C, 58.26; H, 5.26; N, 21.58; S, 9.65. Further eluation with benzene-ethylacetate (20:80) and ethylacetate gave 420 mg of VIIIb.

Reaction of 4(4-Amino-2-methyl-5-pyrimidinyl)methyl-3-methyl-1,2,4-thiadiazolium Bromide Hydrobromide (VII) with Dimethyl Benzoylphosphonate (IIc)——To a suspension of 5.6 g of VII and 4.6 g of IIc in 30 ml of dry DMF was added 6.1 g of triethylamine under a dry N_2 stream at −60° with stirring, and the mixture was maintained at −60° for 3 days. After treatment as mentioned above, extraction from the residue with ethylacetate gave 710 mg of VIIIc as colourless needles, mp 149° (decomp.). UV λ_{max}^{EtOH} mμ (log ε): 240.0 (4.12), 277.5 (3.87). IR ν_{max}^{Nujol} cm^{-1}: 3200 (NH), 1270 (P=O), 1045 (P–O–C). PMR ($CDCl_3$) τ: 7.97 (s, 3H, =C–CH_3), 7.52 (s, 3H, Pm–C_2–CH_3), 6.50, 6.22 (2×d, J=11.0 Hz, 6H, 2×–OCH_3), 5.57, 5.31 (ABq, J=17.5 Hz, 2H, Pm–C_5–CH_2), 4.22 (d, J=9.5 Hz, 1H, Ph–CH–), 2.55 (m, 5H, C_6H_5), 2.00 (s, 1H, Pm–C_6–H). *Anal.* Calcd. for $C_{18}H_{22}O_4N_5SP$: C, 49.65; H, 5.09; N, 16.08; P, 7.11. Found: C, 49.22; H, 5.67; N, 13.51; P, 6.43.

Acid Treatment of VIIIb (or VIIIc)——To a stirred solution of 120 mg of VIIIb (or VIIIc) in 5 ml of EtOH was added 0.18 ml of 10% HCl–EtOH under icecooling. After cooling and stirring for 1 hr, the solution was evaporated *in vacuo* at 20° and the resulting oil was dissolved in MeOH and precipitated with ethylacetate to give 110 mg of amorphous XIb (or XIc). Crystallization from EtOH or water resulted in N (4-amino-2-methyl-5-pyrimidinyl)methylacetamidine dihydrochloride (XIIb), mp 290° (decomp.). *Anal.* Calcd. for $C_8H_{15}N_5Cl_2$: C, 38.10; H, 6.00; N, 27.78; Cl, 28.12. Found: C, 38.03; H, 5.92; N, 27.73; Cl, 27.53. It was identified with the ion exchanged product from AgCl treatment of XIIa by IR comparison.

Base Treatment of Amorphous XIb (or XIc)——To a suspension of 40 mg of amorphous XIb (or XIc) in 5 ml of EtOH was added 0.108 ml of 5% NaOH under icecooling with stirring. After continued stirring for 1 hr, the reaction mixture was evaporated *in vacuo* at 20° and the residue was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to leave 30 mg of yellow oil. The TLC separation on alumina plates gave 8 mg of VIIIb (or VIIIc) and 4 mg of IX which were identified in IR comparison with the compounds obtained above.

Carbamoylation of VIIIb——To a solution of 435 mg of VIIIb in 3 ml of dry DMF was added 500 mg of ethylisocyanate and the mixture was stirred for 3 days at 20°. The reaction mixture was poured in 25 ml of ethylacetate and the solution was washed with water. Removal of the solvent *in vacuo* after drying over anhydrous Na_2SO_4 left crystals, which were recrystallized from ethylacetate to give 390 mg of X, mp 137°. UV λ_{max}^{EtOH} mμ (log ε): 237.5 (4.06), 277.5 (4.02). IR ν_{max}^{Nujol} cm^{-1}: 3220 (NH), 1680 (CO), 1265 (P=O), 970 (P–O–C). PMR ($CDCl_3$) τ: 9.3—8.5 (m, 9H, 3×CH_3), 8.26 (s, 3H, =C–CH_3), 7.37 (s, 3H, Pm–C_2–CH_3), 6.9—5.9 (m, 6H, 3×CH_2), 5.50, 4.85 (ABq, J=15.0 Hz, 2H, Pm–C_5–CH_2), 3.94 (d, J=10.0 Hz, 1H, Ph–CH<), 2.8—2.2 (m, 5H, C_6H_5), 1.79 (s, 1H, Pm–C_6–H), −0.69 (m, 1H, NH). *Anal.* Calcd. for $C_{23}H_{31}O_5N_6SP$: C, 51.67; H, 5.85; N, 15.72; S, 6.00; P, 5.80. Found: C, 51.95; H, 6.25; N, 15.61; S, 6.52; P, 5.38.

Acid Treatment of X——To a stirred solution of 120 mg of X in 5 ml of EtOH was added 0.18 ml of 10% HCl–EtOH under icecooling. After continued stirring and cooling for 1 hr, removal of EtOH *in vacuo* left crystals, which were washed with cold EtOH to give 78 mg of XIII, mp 187° (decomp.). UV λ_{max}^{EtOH} mμ (log ε): 224.5 (4.38), 272.5 (4.10). IR ν_{max}^{Nujol} cm^{-1}: 3260 (NH), 1750 (C=O), 1270 (P=O), 1030 (P–O–C). PMR (d_6-DMSO) τ: 9.1—8.6 (m, 9H, 3×CH_3), 7.77, 7.32 (2×s, 6H, 2×=C–CH_3), 7.15—6.45 (m, 2H, NH–CH_2–), 6.45—5.62 (m, 4H, 2×OCH_2–), 5.47 (bs, 2H, Pm–C_5–CH_2), 4.39 (d, J=8.4 Hz, 1H, Ph–CH<), 2.58 (s, 5H, C_6H_5), 1.42 (s, 1H, Pm–C_6–H), 1.05, 0.43, −0.02 (3×m, 3H, 3×NH). *Anal.* Calcd. for $C_{23}H_{33}N_6O_5SCl_2P\cdot H_2O$: C, 44.16; H, 5.64; N, 13.44; Cl, 11.34; P, 4.95. Found: C, 44.50; H, 5.83; N, 13.60; Cl, 11.79; P, 4.31. Recrystallization of XIII from EtOH resulted in XV, mp 213—215°. UV λ_{max}^{EtOH} mμ (log ε): 236.5 (4.13), 269 (3.89). IR ν_{max}^{Nujol} cm^{-1}: 3330 (NH), 1712 (C=O). PMR (D_2O) τ: 8.76 (t, J=7.5 Hz, 3H, –CH_3), 7.62, 7.17 (2×s, 6H, 2×=C–CH_3), 6.60 (q, J=7.5 Hz, 2H, –CH_2–), 5.35 (s, 2H, Pm–C_5–CH_2), 1.52 (s, 1H, Pm–C_6–H). *Anal.* Calcd. for $C_{11}H_{20}ON_6Cl_2$: C, 40.87; H, 6.24; N, 26.00. Found: C, 40.53; H, 6.50; N, 25.75.

Base Treatment of XIII——To a suspension of 40 mg of XIII in 5 ml of EtOH was added 0.108 ml of 5% NaOH under icecooling with stirring, and stirring was continued for 2 hr. After $CHCl_3$ extraction as mentioned above, the residue, 28 mg, was separated on silica gel TLC plates to give 10 mg of XIV, mp 168—170° (decomp.), which was recrystallized from acetone. UV λ_{max}^{EtOH} mμ (log ε): 236.0 (4.25), 271.0 (3.96), 313 (3.46). IR ν_{max}^{Nujol} cm^{-1}: 3230 (NH), 1684 (C=O). PMR (d_6-DMSO) τ: 8.85 (t, J=7.0 Hz, 3H, –CH_2–CH_3), 7.82 (s, 3H, =C–CH_3), 7.50 (s, 3H, Pm–C_2–CH_3), 6.73 (2H, m, –CH_2–), 4.95 (bs, 2H, Pm–C_5–CH_2), 4.88 (s, 1H, >C–H), 2.66 (s, 5H, –C_6H_5), 2.14 (s, 1H, Pm–C_6–H), 1.12, 0.92 (2×m, 2H, 2×NH). *Anal.* Calcd. for $C_{19}H_{22}O_2N_6S$: C, 57.26; H, 5.57; N, 21.09; S, 8.05. Found: C, 57.16; H, 5.80; N, 20.74; S, 8.23.

Carbamoylation of IX——To a solution of 67 mg of IX in 2 ml of dry DMF was added 0.5 ml of ethylisocyanate and the mixture was stirred for 3 days at room temperature, then heated at 80° for 3 hr. After evaporation of the solvent *in vacuo*, the residue was dissolved in $CHCl_3$ and washed with water. The $CHCl_3$ layer was dried over anhydrous Na_2SO_4, and the solvent removed to give 33 mg of colourless needles, mp 168—170° (decomp.), which were recrystallized from ethylacetate. The IR spectrum of this product was identical with that of XIV obtained above.

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