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Studies on Pyrimidine Derivatives and Related Compounds. LXVI.[1] Reactions of Dialkyl Acylphosphonates with 1,3,4-Thiadiazolium Derivatives

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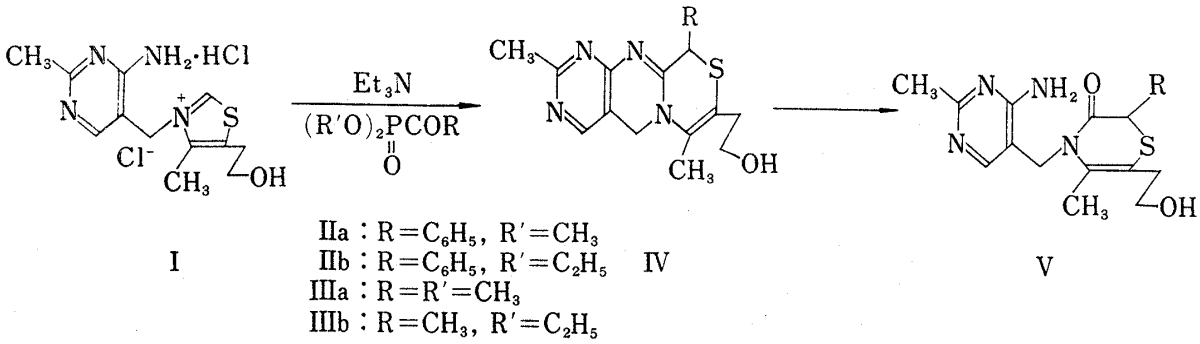
The novel reaction of 1,3,4-thiadiazolium halides (VIIa—c, VIId—e·HBr) with dialkyl acylphosphonates (IIa—b or IIIa—b) in the presence of triethylamine to give 1,3,4-thiadiazine derivatives (VIIIa—e, XIa—d) accompanied by ring expansion was described. In the reaction of VIId—e·HBr with IIa—b or IIIa—b, 10a-(1-dialkylphosphoroyl)benzyl(or ethyl)-10,10a-dihydro-5H-pyrimido[4,5-*d*]-1,3,4-thiadiazolo[3,2-*a*]-pyrimidines (Xa—e) were isolated as the intermediates. Neutral hydrolysis of Xa—e gave XIa—d, while alkaline hydrolysis of Xa—e gave tricyclic compounds (XIIa—d). Brief reaction mechanisms are discussed.

In previous papers,[3] we reported that the reactions of thiamine (B_1-HCl, I) with dialkyl acylphospyonates (IIa—b, IIIa—b) in the presence of triethylamine afforded 1-alkyl-3-(2-hydroxyethyl)-4,9-dimethyl-1,6-dihydropyrimido[4′,5′:4,5]pyrimido[2,1-*c*]-1,4-thiazines (IV) which underwent facile hydrolysis to 2-alkyl-4-(4-amino-2-methyl-5-pyrimidinyl)methyl-2,3-dihydro-6-(2-hydroxyethyl)-5-methyl-3-oxo-4H-1,4-thiazines (V) (Chart 1).



I

IIa : R=C_6H_5, R′=CH_3
IIb : R=C_6H_5, R′=C_2H_5
IIIa : R=R′=CH_3
IIIb : R=CH_3, R′=C_2H_5

IV

V

Chart 1

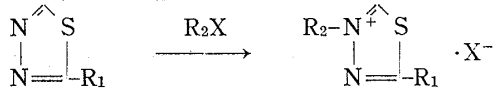
The reaction was applied to simple compounds such as 3,4-dimethylthiazolium or 3-methylbenzothiazolium salts to establish a new method for the synthesis of 1,4-thiazine derivatives from thiazolium salts.[4] The mechanism of this novel reaction was clarified using 5-(2-benzoyloxy) ethyl-3-benzyl-4-methylthiazolium halides as model compounds.[5] In order to extend the scope of the reaction, application was directed toward some 1,3,4-thiadiazolium salts (VIIIa—c and VIId—e·HBr), and the present paper concerns these results.

1) Part LXV: A. Takamizawa, K. Hirai, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **17**, 2299 (1969).
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); A. Takamizawa, Y. Hamashima, Y. Sato, and H. Sato, *Chem. Pharm. Bull.* (Tokyo), **15**, 1178 (1967); A. Takamizawa, Y. Sato, and H. Sato, *ibid.*, **15**, 1183 (1967).
4) A. Takamizawa and H. Sato, Abstracts of the Papers of the 24th Annual Meeting of the Pharmaceutical Society of Japan, 1967, p. 397.
5) A. Takamizawa, Y. Hamashima, and H. Sato, *J. Org. Chem.*, **33**, 4038 (1968).

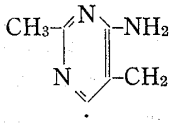
Since Olofson, *et al.*[6] had shown that the base catalyzed deprotonation of C_2-H of 3-ethyl-1,3,4-thiadiazolium chloride proceeds 3×10^3 times faster than that of 3-ethylthiazolium iodide, it seemed reasonable to expect that 1,3,4-thiadiazolium salts might serve also as very reactive materials towards dialkyl acylphosphonates.

2-Phenyl-1,3,4-thiadiazole (VIa)[7a] and 1,3,4-thiadiazole (VIb)[7b] were prepared according to the literature, and on quarternization by the appropriate alkyl halides, the corresponding 1,3,4-thiadiazolium salts (VIIa—e) were obtained (Table I).

TABLE I.



VIa: $R_1=C_6H_5$, VIb: $R_1=H$ VIIa-e

	R_1	R_2	X	mp (decomp.) (°C)	Yield (%)	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S
VIIa	C_6H_5	CH_3	I	198—199	85.2	35.55	2.96	9.22	10.55	35.85	3.05	8.68	10.66
VIIb	C_6H_5	$C_6H_5CH_2$	Br	193—195	84.6	54.08	3.94	8.41	9.61	54.07	4.66	7.90	9.13
VIIc	H	$C_6H_5CH_2$	Cl	195—197	83.5	50.82	4.27	13.17	15.07	50.84	4.24	13.27	15.23
VIId·HBr[a]	H		Br	210—215	69.5	25.41	3.20	18.52	8.48	25.57	3.46	18.35	8.61
VIIe·HBr[b]	C_6H_5	HBr	Br	210—213	77.4	34.94	3.98	14.55	6.67	34.96	4.16	14.46	6.82

a) semihydrate *b*) dihydrate

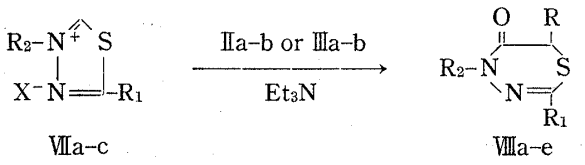
4-Methyl-2-phenyl-1,3,4-thiadiazolium iodide (VIIa) thus obtained was treated with diethyl benzoylphosphonate (IIb) in N,N-dimethyl formamide (DMF) in the presence of triethylamine to give a colorless crystalline product (VIIIa), mp 137—138°, the elementary analysis of which was in agreement with the composition $C_{16}H_{14}ON_2S$. The product VIIIa showed a strong C=O band at 1665 cm^{-1} in the infrared (IR) spectrum, and its nuclear magnetic resonance (NMR) spcetrum[8] showed signals at τ: 6.38 (N-Me,s), 5.25 (1H,s), 2.70 (s) and 2.08—2.77 (each 5H, m); it is particularly notable that the protons on the newly introduced phenyl ring were observed as a sharp singlet.

These data indicate that the structure of VIIIa should be assigned as 5,6-dihydro-4-methyl-5-oxo-2,6-diphenyl-4H-1,3,4-thiadiazine (Table II). The product VIIIb obtained from VIIa and diethyl acetylphosphonate (IIIb) showed the analogous elementary composition, ultraviolet (UV), IR and NMR spectra were comparable to those of VIIIa as shown in experimental section, and in particular the NMR spectrum of VIIIb exhibited a doublet at τ: 8.52 (3H) and a quartet at τ: 5.97 (1H) attributable to a $CH_3\cdot CH<$ system, therefore the structure of VIIIb was also confirmed as the analogue of VIIIa.

Reactions of VIIb—c with IIa—b or IIIa—b afforded analoguously 1,3,4-thiadiazine derivatives VIIIc—e, respectively (Table II).

6) R.A. Olofson and J.M. Landesberg, *J. Am. Chem. Soc.*, **88**, 4263 (1966).
7) *a*) M. Ohta, R. Hagiwara, and Y. Mizushima, *Yakugaku Zasshi*, **73**, 701 (1953); *b*) B. Föhlisch, R. Braun, and K.W. Schultze, *Angew. Chem.*, **79**, 318 (1967).
8) NMR spectra were taken with a Varian A-60 spectrometer in $CDCl_3$ solution containing TMS as an internal standard. Chemical shifts (τ), couplong constants (J, cps). Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), b (broad) and m (multiplet).

TABLE II.



VIIa-c VIIIa-e

	R_1	R_2	R	mp (°C) [bp °C/mmHg]	Yield (%)	IR λ_{max}^{Nujol} (CO) cm^{-1}	NMR chemical shift[a] C_6–C_6H_5	C_6–CH_3	C_2–H
VIIIa	C_6H_5	CH_3	C_6H_5	137—138	63.2	1665	2.70(s)	—	5.25(s)
VIIIb	C_6H_5	CH_3	CH_3	oil		1667[b]	—	8.52(d)	5.97[a](q)
VIIIc	C_6H_5	$C_6H_5CH_2$	C_6H_5	115—120	62.5	1654	2.17—2.83(s)	—	5.26(s)
VIIId	H	$C_6H_5CH_2$	C_6H_5	[140—150/0.15]		1656[b]	2.75(s)or 2.78(s)	—	5.35(d)
VIIIe	C_6H_5	$C_6H_5CH_2$	CH_3	oil		1666[b]	—	8.52(d)	6.44(q)

a) footnote 8 *b*) film

When the reaction of 3-(4-amino-2-methyl-5-pyrimidinyl)methyl-1,3,4-thiadiazolium bromide hydrobromide (VIId·HBr) with dimethyl benzoylphosphonate (IIa) was carried out carefully at −50— −60°, a colorless crystalline, 1:1 adduct Xa of VIId and IIa was obtained (mp 145—147°). The elementary analysis of Xa was in agreement with the composition $C_{17}H_{20}O_4N_5SP$, and its UV spectrum (λ_{max}^{EtOH} mμ (log ε): 240 (4.09), 279 (3.89)) indicated the dihydrothiochrome like structure. The IR spectrum (nujol mull) of Xa showed no absorption due to C=O group,while it showed an NH band at 3215 cm^{-1}, P=O bands at 1284, 1267 cm^{-1} and P–O–C bands at 1084, 1047, 1008, 989 cm^{-1}. The NMR spectrum of Xa showed signals due to the phenyl protons as a singlet at 2.55 τ and a benzylic proton as a doublet at 4.15 τ with splitting by the vicinal phosphorous (J_{PH}=9.0). From these spectral data, the structure of Xa could be assigned as 10a-(1-dimethylphosphorolyl)benzyl-10,10a-dihydro-8-methyl-5H-pyrimido[4,5-*d*]-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (Chatr 2). The reaction of VIId·HBr with IIb afforded an analogous adduct Xe which gave the expected N-methylcarbamate on methylcarbamoylation with methyl isocyanate. On heating in aq. EtOH, the adduct Xa was readily converted into XIa, mp 147—149°, elementary analysis of which ($C_{15}H_{15}ON_5S$) indicated elimination of the phosphorous moiety. The compound XIa exhibited UV absorption maxima at 228 mμ (log ε =4.14) and 277 mμ (log ε =3.83) corresponding to the monocyclic aminopyrimidine chromophore, and IR absorptions (nujol mull) due to C=O and NH_2 at 1688 cm^{-1} and 1653 cm^{-1} respectively. The NMR spectrum of XIa showed a singlet at 2.72 τ (phenyl) and a doublet at 5.30 τ due to the C_6–H splitting by the long-range coupling with the C_2–H which was observed as a doublet at 2.36 τ ($J_{2,6}$=2.0). Therefore, the structure of XIa was assigned as 4-(4-amino-2-methyl-5-pyrimidinyl) methyl-5,6-dihydro-5-oxo-6-phenyl-4H-1,3,4-thiadiazine. The compound XIa was also obtained by the reaction of VIId·HBr with IIa or IIb at room temperature in the presence of pyridine as weak base catalyst.

On the other hand, by the careful treatment with aq. alkali such as $NaHCO_3$, Na_2CO_3 or NaOH, Xa was converted into XIIa, obtained as pale yellow crystals of mp 129—132°. The elementary analysis of XIIa was in agreement with the composition $C_{15}H_{13}N_5S$ and it showed no IR absorption due to C=O, and the UV absorptions of XIIa were observed at 235 $m\mu^{sh}$ (log ε=3.68) and 372 mμ (log ε=3.81). The NMR spectrum of XIIa showed a singlet at 2.60 τ due to a phenyl group and the signal due to a benzylic proton (C_6–H) was observed as a doublet at 5.02 τ coupling with C_2–H which appeared at 2.28 τ as a doublet ($J_{2,6}$=2.5).

Thus the structure of XIIa was assigned as 4,10-dihydro-7-methyl-4-phenylpyrimido[4′,5′:4,5]pyrimido[1,2-*d*]-1,3,4-thiadiazine. The compound XIIa was found to be rather unstable, and in heating or by treating with alkali, sulfur was readily eliminated to give

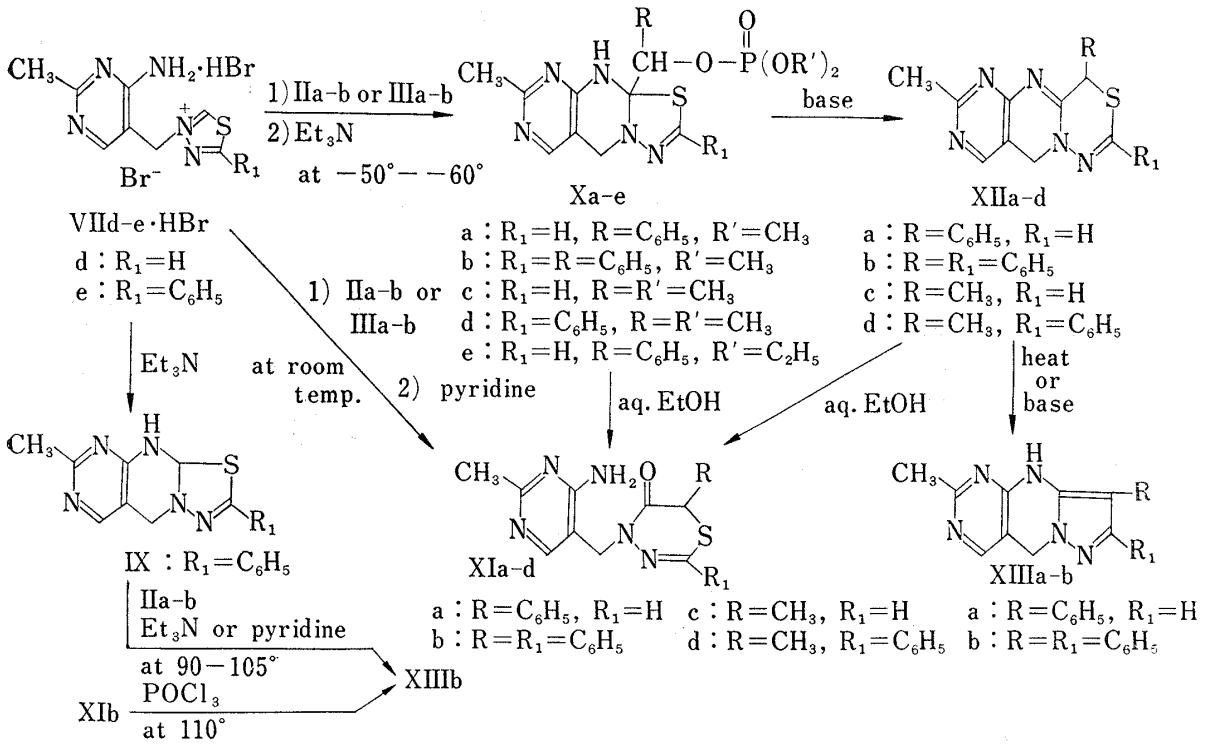


Chart 2

XIIIa accompanied by hydrolysis to give XIa in a trace quantity. XIIIa thus obtained was assigned as 5,10-dihydro-2-methyl-9-phenyl-pyrazolo[1,5-*a*]pyrimido[4,5-*d*]pyrimidine on the basis of elementary analysis, IR, UV and NMR spectral data (see Experimental), and the structure was confirmed by identification with an authentic sample synthesized by the independent pathway shown in the Chart 3.

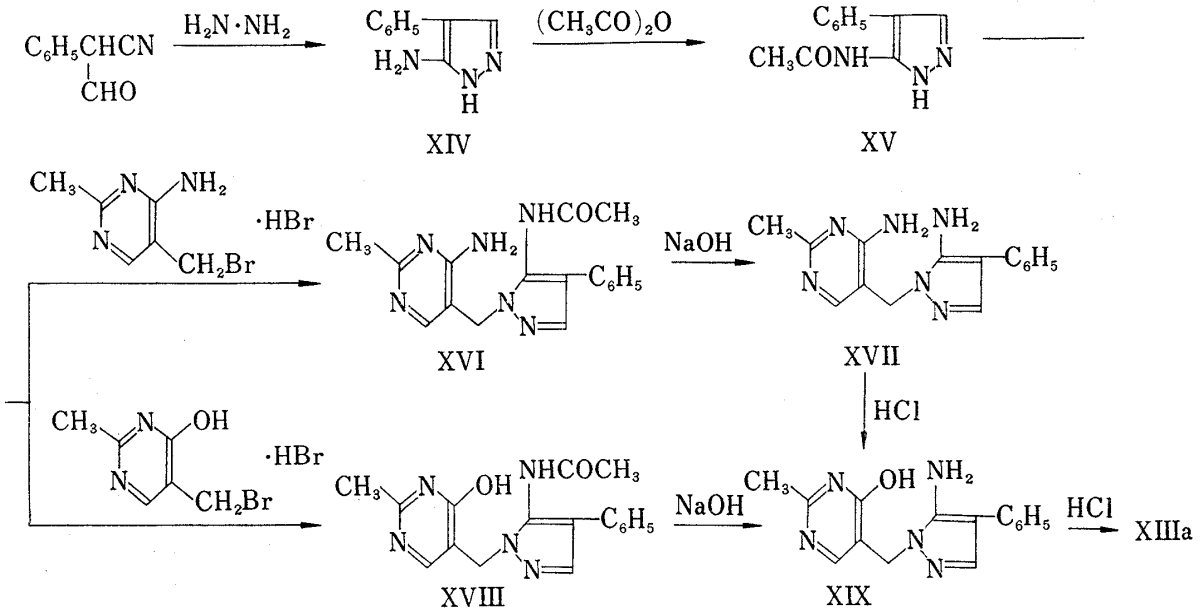


Chart 3

It is of interest to note that the alkylation of XV by 4-amino (or hydroxy)-2-methyl-5-pyrimidinylmethyl bromide hydrobromide occurred at position 1, and so XV should be assigned as 5-acetamido-4-phenylpyrazole from the result of this reaction pathway, although in a previous paper[9] it had been assigned as 3-acetamido-4-phenylpyrazole.

XIIIb was also obtained by the reactions of IIa—b with 10,10a-dihydro-8-methyl-2-phenyl-5H-pyrimido[4,5-*d*]-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (IX) which was obtainable from VIIe·HBr by treatment with triethylamine, or from XIb by heating in $POCl_3$. Reactions of VIId—e·HBr with IIa—b or IIIa—b also proceeded analogously to give Xb—d, XIb—d and XIIb—d. Attempts for the desulfurization of XIIc—d by alkali treatment failed, resulting in the normal hydrolysis to XIc—d (Chart 2).

The mechanism of the present reactions of the simple 1,3,4-thiadiazolium salts VIIa—c with dialkyl acylphosphonates, producing VIIIa—e, may be explained analogously to the previously reported mechanism[5] established for the reactions of the thiazolium salts with IIa—b or IIIa—b as shown in the Chart 4.

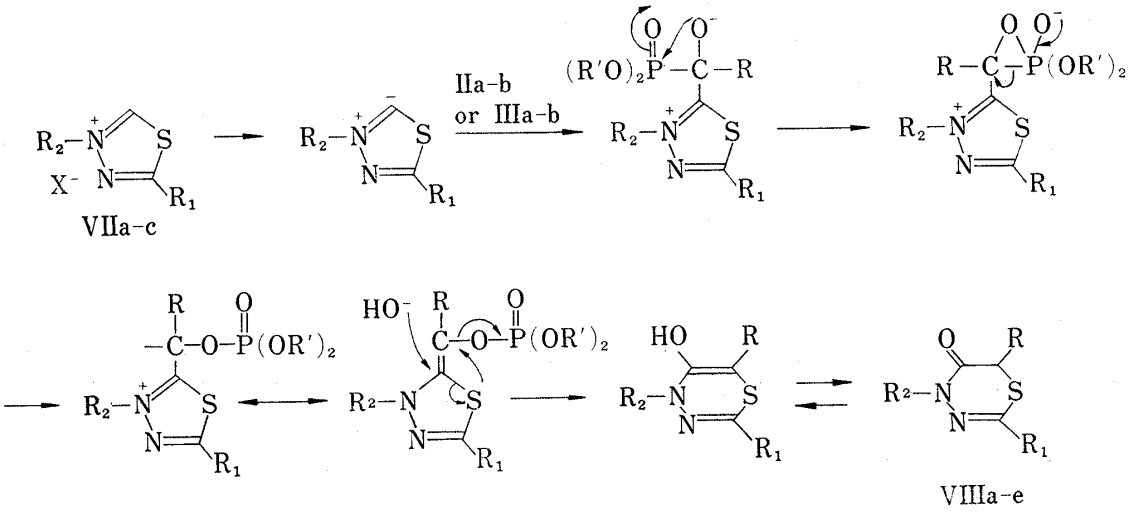


Chart 4

On the other hand, the reactions of VIId—e·HBr with IIa—b or IIIa—b when catalyzed by pyridine, which is weaker base than 4-aminopyrimidine,[10] may result the disalt XX, as the first intermediate, which would undergo ring expansion to XIa—d *via* XXI or XXII on treatment with aq. $NaHCO_3$.

In fact, when pyridine was used as a catalyst the desulfurized product XIIIa—b was not formed, therefore an alternative route involving XIIa—d as the precursor for the formation of XIa—d will be excluded (Chart 5); whereas with triethylamine catalysis the stable intermediates Xa—e were isolated.

Treatment of Xa—e with base immediately afforded XIIa—d which shows a strong UV absorption maximum at 370 mμ.

The behaviour of compounds XIIa—d toward base depended on the substituent at C_6 in the thiadiazine ring. Thus XIIa—b, which have a phenyl group at C_6, underwent ring contraction to XIIIa—b on treatment with base, accompanied by loss of the UV maximum at 370 mμ; while with aq. EtOH they were hydrolysed to XIa—b. With XIIc—d, which have a methyl group at C_6, hydrolysis to XIc—d, and not ring contraction, occurred even under basic conditions.

9) E. Anderson, J. Casey, Jr., L. Green, J. Lafferty, and H. Reiff, *J. Med. Chem.*, **7**, 259 (1964).
10) A. Takamizawa, Y. Sato, S. Nakajima, and T. Ishiba, *Shionogi Kenkyusho Nempo*, **12**, 48 (1962).

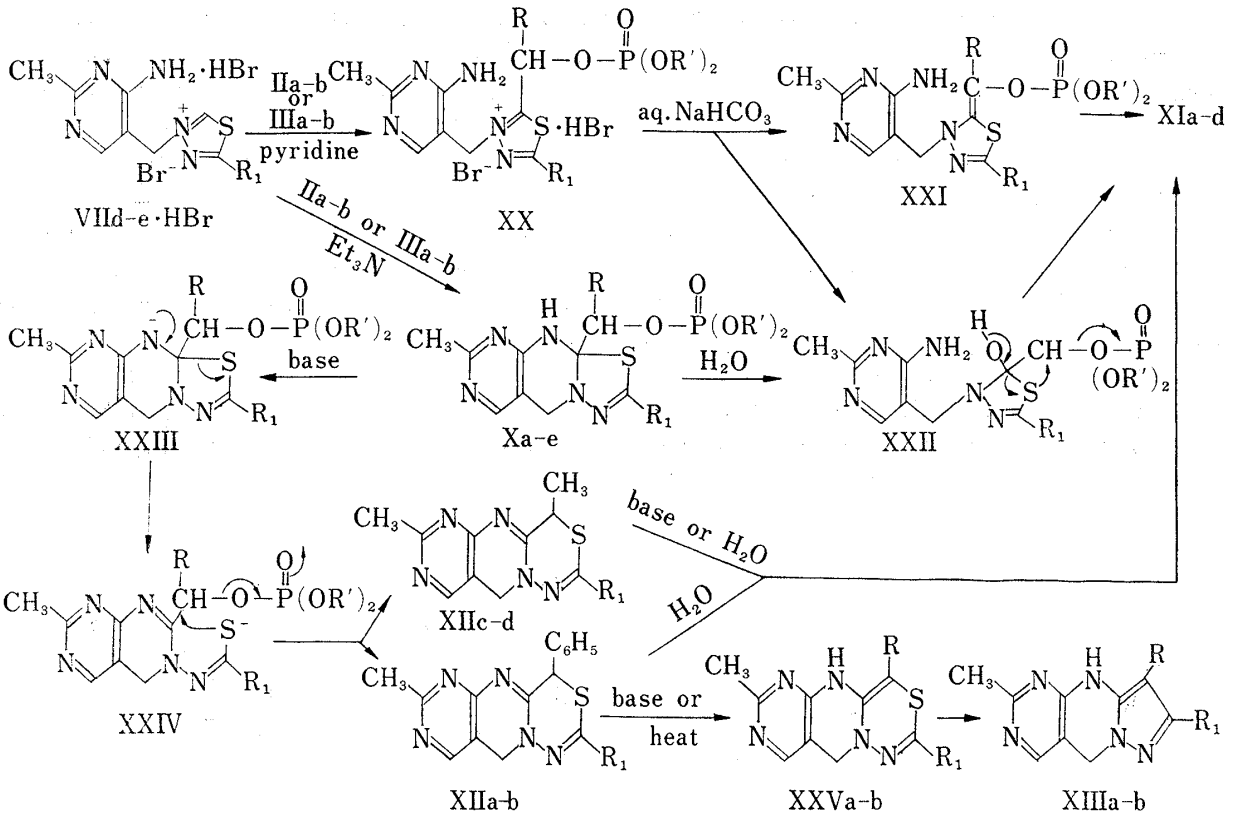


Chart 5

At the present state, these substituent effect can not be explained resonably and no precise evidence for the mechanism of this ring contraction is available, although ESR measurements on the reaction mixture may show that the reaction proceeds as a radical process. Further studies on the reaction of dialkyl acylphosphonates with some other thiadiazolium derivatives are now in progress and will be described in the near future.

Experimental[11]

4-Methyl-2-phenyl-1,3,4-thiadiazolium Iodide (VIIa)——To a solution of 3.0 g of VIa in 10 ml of MeOH, was added 10.0 g of methyl iodide, the mixture was then heated for 18 hr at 100°. The excess methyl iodide and MeOH were removed *in vacuo* and the residual crystals were washed with acetone to give 4.8 g of pale yellow crystals, mp 180—185° (decomp.). Recrystallization from MeOH gave VIIa as colorless crystals, mp 198—199° (decomp.). Analyses for this and other 1,3,4-thiadiazolium halides are given in Table I.

4-Benzyl-2-phenyl-1,3,4-thiadiazolium Bromide (VIIb)——A mixture of 10.0 g of VIa and 16.0 g of benzyl bromide was heated for 7 hr at 115°. After cooling, the reaction mixture was treated with acetone to give 17.4 g of colorless crystals. Recrystallization from EtOH gave VIIb as colorless prisms, mp 193—195° (decomp.).

3-Benzyl-1,3,4-thiadiazolium Chloride (VIIc)——To a solution of 4.1 g of VIb in MeOH was added 6.7 g of benzyl chloride, the mixture was then heated for 17.5 hr at 105°. MeOH was removed *in vacuo* and the residual crystals were washed with acetone to give 8.45 g of colorless crystals. Recrystallization from EtOH gave VIIc as colorless plates, mp 195—197° (decomp.).

3-(4-Amino-2-methyl-5-pyrimidinyl)methyl-1,3,4-thiadiazolium Bromide Hydrobromide (VIId·HBr)——To a solution of 55.2 g of 2-methyl-4-amino-5-bromomethylpyrimidine hydrobromide in 70 ml of DMF was added 20.0 g of VIb and the mixture was heated for 20 hr at 70°. After cooling, the deposited crystals were collected and washed with ether to give 50 g of pale yellow crystals. Recrystallization from aq. EtOH gave VIId·HBr semihydrate as colorless plates, mp 210—215° (decomp.).

4-(4-Amino-2-methyl-5-pyrimidinyl)methyl-2-phenyl-1,3,4-thiadiazolium Bromide Hydrobromide (VIIe·HBr)——To a solution of 40 g of 4-amino-5-bromomethyl-2-methylpyrimidine hydrobromide in 80 ml of

11) All melting points are uncorrected.

DMF was added 29.4 g of VIa and the mixture was heated for 20 hr at 65°. After cooling, the deposited crystals were collected and washed with acetone to give 48.9 g of colorless crystals. Recrystallization from aq. EtOH gave VIIe·HBr·dihydrate as colorless needles, mp 210—213° (decomp.).

5,6-Dihydro-5-oxo-4,6-disubstituted(or 2,4,6-trisubstituted) 4H-1,3,4-thiadiazines (VIIIa—e)——General Procedure: To a solution of 15.1 mmole of VIIa—c and 15.3 mmole of IIa—b or IIIa—b in 15 ml of DMF, 30.7 mmole of Et_3N (dried over Na wire) was added dropwise at 1—5° during 0.5 hr and stirred for 2 hr at 2°. After the reaction mixture had been allowed to stand overnight at room temperature, DMF was removed *in vacuo* at 45° and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 10% NaOH and H_2O successively, dried over Na_2SO_4, and evaporated. The residual crude product was purified by recrystallization or distillation.

VIIIa: Colorless sticks, mp 137—138° (aq. EtOH). *Anal.* Calcd. for $C_{16}H_{14}ON_2S$: C, 68.07; H, 5.00; N, 9.92; S, 11.33. Found: C, 68.05; H, 4.99; N, 9.93; S, 11.40. TLC[12] (Al_2O_3, AcOEt): *Rf* 0.83. UV λ_{max}^{EtOH} mμ (log ε): 262 (4.04), 320 (3.86).

VIIIb: Viscous oil. NMR τ: 8.52 (3H,d, J=7.0), 6.46 (3H,s), 5.97 (1H,q, J=7.0), 2.73—2.05 (5H,m). TLC(Al_2O_3, AcOEt): *Rf* 0.82.

VIIIc: Colorless crystals, mp 115—120° (EtOH). *Anal.* Calcd. for $C_{22}H_{18}ON_2S$: C, 73.73; H, 5.06; N, 7.82; S, 8.92. Found: C, 73.52; H, 5.25; N, 7.75; S, 9.10. UV λ_{max}^{EtOH} mμ (log ε): 260 (4.02), 320 (3.86). NMR τ: 5.26 (1H,s), 4.83 (2H,s), 2.83—2.17 (15H,m). TLC (Al_2O_3, AcOEt): *Rf* 0.77.

VIIId: Viscous oil. TLC (Al_2O_3, AcOEt): *Rf* 0.83. NMR τ: 5.35 (1H,d, J=1.7), 4.95 (2H,s), 2.78 (5H,s), 2.75 (5H,s), 2.47 (1H,d, J=1.7).

VIIIe: Viscous oil. TLC (Al_2O_3, AcOEt): *Rf* 0.89. NMR τ: 8.52 (3H,d, J=7.0), 6.44 (1H,q, J=7.0), 4.90 (2H,s), 2.82—2.12 (1OH,m).

10,10a-Dihydro-8-methyl-2-phenyl-5H-pyrimido[4,5-*d*]-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (IX)——To a suspension of 1.95 g of VIIe·HBr in 12 ml of DMF, 1.4 g of Et_3N was added dropwise under ice cooling with stirring. After standing overnight at room temperature, the deposited crystals were collected, washed and dried to give 0.7 g (56.5%) of colorless crystals. Recrystallization from EtOH gave IX as colorless sticks, mp >200°. *Anal.* Calcd. for $C_{14}H_{13}N_5S$: C, 59.35; H, 4.63; N, 24.72; S, 11.30. Found: C, 58.93; H, 4.62; N, 24.56; S, 11.60. UV λ_{max}^{EtOH} mμ (log ε): 241 (4.22), 282 (4.07). NMR τ: 7.43 (CH_3,s), 3.92 (NCH_2,s), 2.80—1.75 (6H, C_6H_5, Py.[13] C_6–H,m), 1.33 $\left(\begin{matrix}N\\N\end{matrix}\!>\!CH\text{–}S,s\right)$.

10a-(1-Dialkylphosphoroyl)benzyl(or ethyl)-10,10a-dihydro-8-methyl-2-phenyl(or unsubstituted)-5H-pyrimido[4,5-*d*]-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (Xa—e)——General Procedure: To a suspension of 8.1 mmole of VIId—e·HBr (dried over P_2O_5 at room temperature *in vacuo*) and 8.4 mmole of IIa—b or IIIa—b in 50 ml of DMF, 24.7 mmole of Et_3N was added dropwise at −50° under N_2 steam. The reaction mixture was stirred for 45 hr at −50——60°. DMF was removed *in vacuo* below 45°. The residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography and recrystallization.

Xa: Colorless crystals, mp 145—147° (decomp.) (acetone). *Anal.* Calcd. for $C_{17}H_{20}O_4N_5SP$: C, 48.45; H, 4.79; N, 16.62; P, 7.36. Found: C, 48.57; H, 4.43; N, 16.56; P, 7.33. NMRτ: 7.52 (3H, CH_3,s), 6.47 (3H, OCH_3,d, J_{PH}=11.3), 6.24 (3H, OCH_3,d, J_{PH}=11.3), 5.52, 5.45 (2H, NCH_2, AB-q, J=16.4), 4.15 (1H, C_6H_5CHOP,d, J_{PH}=9.0), 2.82 (1H, N=CH–S,s), 2.55 (5H, C_6H_5, slightly splitting doublet), 2.02 (1H, Py. C_6–H,s). Yield 29.2%.

Xb: Pale yellow viscous oil. NMR τ: 7.55 (CH_3,s), 6.47 (OCH_3,d, J_{PH}=11.3), 6.20 (OCH_3,d, J_{PH}=11.3), 5.80, 5.28 (NCH_2, AB-q, J=16.4), 4.80 (NH,b), 4.17 (1H, $C_6H_5\overset{|}{C}H$–O–P,d, J_{PH}=9.0), 2.83—2.33 (2×C_6H_5,m), 2.015 (Py. C_6–H,s).

Xc: Colorless prisms, mp 130—132° (acetone). *Anal.* Calcd. for $C_{12}H_{18}O_4N_5SP$: C, 40.10; H, 5.05; N, 19.49; P, 8.16. Found: C, 40.15; H, 5.32; N, 19.45; P, 8.16. IR λ_{max}^{Nujol} cm^{-1}: 3160 (NH), 1286, 1277 (P=O), 1082, 1058, 1035, 1025, 998 (P–O–C). UV λ_{max}^{EtOH} mμ (log ε): 240 (4.08), 2.80 (3.85). NMR τ: 8.42 (CH_3,d, J=6.3), 7.52 (CH_3,s), 6.25 (OCH_3,d, J_{PH}=11.3), 6.23 (OCH_3,d, J_{PH}=11.3), 5.57, 5.37 (NCH_2, AB-q, J=17.0), 5.45 (NH,b), 5.03 ($CH_3\overset{|}{C}HOP$, quint, J=6.3, J_{PH}=7.2), 2.83 (N=CH–S,s), 1.99 (Py. C_6–H,s). Yield 27.2%.

Xd: Viscous oil. NMR τ: 8.35 (CH_3,d, J=6.2), 7.55 (CH_3,s), 6.4—6.1 (6H, 2×OCH_3,m), 6.0—4.8 (3H, NCH_2 and $CH_3\overset{|}{C}HOP$,m), 3.90 (NH,b), 2.8—2.3 (C_6H_5,m), 1.97 (Py. C_6–H,s).

Xe: Colorless powders, mp 110—118°. *Anal.* Calcd. for $C_{19}H_{24}O_4N_5SP$: N, 15.58; P, 6.90. Found: N, 15.37; P, 6.58. IR λ_{max}^{Nujol} cm^{-1}: 1269 (P=O), 1070, 1020, 970 (P–O–C). UV λ_{max}^{EtOH} mμ (log ε): 240 (4.09), 279 (3.88). Yield 20.0%.

Methylcarbomoylation of Xe——To a solution of 278 mg of Xe in 16 ml of DMF, 1.0 g of methyl isocyanate was added. After the reaction mixture had been allowed to stand overnight at room temperature, DMF was removed *in vacuo* below 40° and the residual oil was crystallized from ether slowly. The resulting

12) TLC: thin-layer chromatography.
13) Py.: pyrimidine.

crystals were collected to give 158 mg (50.6%) of crystals, mp 179° (decomp.). Recrystallization from acetone gave yellow prisms, mp 179—180° (decomp.). *Anal.* Calcd. for $C_{21}H_{27}O_5N_6SP$: C, 49.79; H, 5.33; N, 16.59. Found: C, 50.21; H, 5.80; N, 16.65. UV λ_{max}^{EtOH} mμ (log ε): 230 (4.07, shoulder), 295 (4.19). IR λ_{max}^{Nujol} cm^{-1}: 3194 (NH), 1770 (C=O), 1265, 1248 (P=O), 1057, 1029, 992 (P–O–C).

Neutral Hydrolysis of Xa—e——General Procedure: A solution of 0.5 g of Xa—e in 15 g of 50% EtOH was refluxed for 1.5 hr. The solution was concentrated and the residue was extracted with $CHCl_3$. The extract was washed with aq. $NaHCO_3$ and H_2O successively. After drying over Na_2SO_4, $CHCl_3$ was removed and the residual oil was treated with a mixture of acetone and ether to give XIa—d as crystals.

XIa: Colorless sticks, mp 147—149° (EtOH). *Anal.* Calcd. for $C_{15}H_{15}ON_5S$: C, 57.50; H, 4.83; N, 22.34; S, 10.20. Found: C, 57.17; H, 4.91; N, 22.23; S, 10.25. NMR τ: 7.52 (CH_3,s), 5.30 (1H, C_6H_5CH–S,d, J=2.0), 4.15 (NH_2,b), 1.72 (C_6H_5,s), 2.36 (N–CH–S,d, J=2.0), 1.83 (Py. C_6–H,s).

XIb: Colorless needles, mp 205—207° (EtOH). Yield 50%. *Anal.* Calcd. for $C_{21}H_{19}ON_5S$: C, 64.77; H, 4.92; O, 4.11; N, 17.99; S, 8.22. Found: C, 64.76; H, 4.91; O, 4.15; N, 17.90; S, 8.22; UV λ_{max}^{EtOH} mμ (log ε): 230 (4.35), 268 (4.19), 318 (3.93). IR λ_{max}^{Nujol} cm^{-1}: 3372, 3312 (NH_2), 1668 (C–O), 1653 (NH_2). NMR τ: 7.52 (CH_3,s), 5.22 (1H, C_6H_5CH–S,s), 5.18, 4.82 (NCH_2, AB-q, J=15.0), 4.08 (NH_2,b), 2.70 (C_6H_5,s), 2.70—2.12 (C_6H_5,m), 1.716 (Py. C_6–H,s).

XIc: Colorless sticks, mp 128—130° (acetone). *Anal.* Calcd. for $C_{10}H_{13}ON_5S$: C, 47.80; H, 5.22; N, 27.88; S, 12.74. Found: C, 47.68; H, 5.33; N, 27.64; S, 12.57. UV λ_{max}^{EtOH} mμ (log ε): 233 (4.03), 279 (3.83). IR λ_{max}^{Nujol} cm^{-1}: 3364, 3321 (NH_2), 1675 (C=O), 1665 (NH_2). NMR τ: 8.56 (CH_3,d, J=7.0), 7.53 (CH_3,s), 6.46 (1H, CH_3–CH–S, q, (J=7.0) of d (J=1.5)), 5.20 (NCH_2,s), (3.98 (NH_2,b), 2.42 (1H, N=CH–S,d), 1.89 (Py. C_6–H,s).

XId: Pale yellow prisms, mp 145—148° (acetone). *Anal.* Calcd. for $C_{16}H_{17}ON_5S$: C, 58.70; H, 5.23; N, 21.40; S, 9.77. Found: C, 58.55; H, 5.17; N, 21.43; S, 9.88. UV λ_{max}^{EtOH} mμ (log ε): 232.5 (4.56), 276.5 (4.42), 316 (4.18). IR λ_{max}^{Nujol} cm^{-1}: 3388, 3325 (NH_2), 1677 (C=O), 1655 (NH_2). NMR τ: 8.50 (CH_3,d, J=7.0), 7.53 (CH_3,s), 6.40 (1H, CH_3–CH–S,q, J=7.0), 5.09 (NCH_2,s), 4.02 (NH_2,b), 2.67—2.12 (C_6H_5,m), 1.75 (Py. C_6–H,s).

Reaction of VIId·HBr with IIb in the Presence of Pyridine——To a suspension of 5.0 g of VIId·HBr, 3.3 g of IIb in 35 ml of DMF, 3.25 g of pyridine (dried over KOH) was added dropwise under N_2 steam. After stirring for 40 hr at room temperature, DMF was removed *in vacuo* below 42°. To the residue, $CHCl_3$ was added and insoluble crystals were collected to give 1.6 g (30.5%) of starting material VIId·HBr, which proved to be identical with an authentic sample by IR comparison. The filtrate was washed with aq. $NaHCO_3$ and H_2O successively. After drying over Na_2SO_4, $CHCl_3$ was removed by evaporation and the residual oil was treated with ether to give 1.79 g (42.4%) of crystals. Recrystallization from EtOH gave colorless sticks, mp 144—147°, which was proved to be identical with an authentic sample of XIa by IR comparison.

Alkaline Hydrolysis of Xa——To a solution of 300 mg of Xa in 4.0 g of EtOH, 4.0 g of 5% $NaHCO_3$, 1.0 g of aq. saturated Na_2CO_3 and 7.0 g of H_2O were added. After standing overnight at room temperature, the precipitated products were collected to give 34 mg (17.3%) of crystals. Recrystallization from acetone gave XIIa as pale yellow sticks, mp 129—132°. *Anal.* Calcd. for $C_{15}H_{13}N_5S$: C, 61.01; H, 4.44; N, 23.72; S, 10.84. Found: C, 60.64; H, 4.24; N, 23.17; S, 10.88. UV λ_{max}^{EtOH} mμ (log ε): 235 (3.68, shoulder), 372 (3.81). NMR τ: 7.35 (CH_3,s), 5.02 (C_6H_5CH–S,d, J=2.5), 4.97, 4.80 (NCH_2, AB-q, J=14.9), 2.60 (C_6H_5,s), 2.28 (N=CH–S,d, J=2.5), 1.766 (Py. C_6–H,s).

The above filtrate was concentrated under reduced pressure, and the residue was extracted with $CHCl_3$. The extracts were washed with H_2O, dried and evaporated. The residual oil was crystallized from a mixture of ether and acetone to yield 89 mg (42.6%) of pale yellow crystals, mp 137—141°, which were identical with an authentic sample of XIa.

Alkaline Hydrolysis of Xb——A solution of 0.88 g of Xb in 46 g of 50% EtOH and 17 g of 5% $NaHCO_3$ was allowed to stand for 6 hr at room temperature. After evaporation of the EtOH *in vacuo* below 30°. The residue was extracted $CHCl_3$, the extracts were washed with H_2O, dried and evaporated. The residual oil was crystallized from acetone to give 0.45 g (68.5%) of XIIb as yellow crystals, mp 125—127°. *Anal.* Calcd. for $C_{21}H_{17}N_5S$: C, 67.91; H, 4.61; N, 18.86; S, 8.62. Found: C, 67.63; H, 4.62; N, 18.53; S, 8.74. UV λ_{max}^{EtOH} mμ (log ε): 261 (4.08), 387 (4.23). NMR τ: 7.35 (CH_3,s), 4.89, 4.72 (NCH_2, AB-q, J=14.0), 4.87 (1H, C_6H_5–CH–S,s), 2.8—2.0 (2×C_6H_5,m), 1.766 (Py. C_6–H,s).

A trace amount of XIb was obtained further from the filterate of XIIb.

Alkaline Hydrolysis of Xd——Xd was treated as above to give XIId as a yellow viscous oil. UV λ_{max}^{EtOH} mμ: 260 (shoulder), 384. NMR τ: 8.40 (CH_3,d, J=7.3), 7.35 (CH_3,s), 6.12 (1H, CH_3–CH–S,q, J=7.3), 4.83 (NCH_2,s), 2.7—2.1 (C_6H_5,m), 1.78 (Py. C_6–H,s).

Neutral Hydrolysis of XIIa——A solution of 31 mg of XIIa in 10 g of 50% EtOH was refluxed for 6.5 hr. The solution was concentrated, and the residue was added H_2O, and then extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, evaporated *in vacuo*, and the residual oil was crystallized from a mixture of acetone and ether to give 17 mg of colorless crystals. TLC (SiO_2, acetone) of these crystals showed them to be a mixture (ratio 1:1) of XIa and XIIIa. Recrystallization from EtOH gave XIIIa as colorless plates, mp 232—234° (decomp.). *Anal.* Calcd. for $C_{15}H_{13}N_5$: C, 68.42; H, 4.98; N, 26.60; mol. wt., 263.3. Found: C, 68.76; H, 5.21; N, 26.59; mol. wt. (solvent: $CHCl_3$), 274.

Neutral Hydrolysis of XIIb——A solution of 144 mg of XIIb in 16 g of 65% EtOH was refluxed for 40 min. The solution was treated as above to give 116 mg (88%) of XIIIb as colorless plates, mp 264—265° (from $CHCl_3$–EtOH). *Anal.* Calcd. for $C_{21}H_{17}N_5$: C, 74.31; H, 5.05; N, 20.64. Found: C, 74.29; H, 5.04; N, 20.75. UV λ_{max}^{EtOH} mμ (log ε): 245 (4.33), 255 (shoulder), 308 (4.09). IR λ_{max}^{Nujol} cm^{-1}: 3150, 3050, 1613. NMR τ: 7.49 (CH_3,s), 4.59 (NCH_2,s), 2.72 (C_6H_5,s), 2.9—2.4 (C_6H_5,m), 2.32 (NH_2,b), 1.72 (Py. C_6–H,s). Further, the filterate of XIIIb showed the presence of a trace amount of XIb on TLC (SiO_2, acetone).

Pyrolysis of XIIb——4 mg of XIIb was heated at 140—150° for 13 min on a slide-glass. Brownish crystals (4 mg) were obtained, and identified with XIIIb obtained above, by IR comparison.

Reaction of IX with IIb——a) Base Pyridine: To a mixture of 544 mg of IX, 486 mg of IIb and 1.6 g of pyridine in 16 ml of DMF was heated for 18 hr at 105°. After removal of the solvent *in vacuo*, the residue was dissolved in $CHCl_3$, and the $CHCl_3$ solution was successively washed with aq. $NaHCO_3$ and H_2O, dried and evaporated. The residue was treated with ether to give 120 mg (18.8%) of the crystals. Rectystallization from $CHCl_3$ gave 3-(4-amino-2-methyl-5-pyrimidinyl)methyl-5-phenyl-1,3,4-thiadiazoline-2-thione as colorless sticks, mp 258—259°. *Anal.* Calcd. for $C_{14}H_{13}N_5S_2 \cdot H_2O$: C, 50.28; H, 4.54; O, 4.80; N, 21.01; S, 19.24; H_2O, 5.41. Found: C, 50.59; H, 4.09; O, 4.59; N, 20.89; S, 19.27; H_2O, 4.80. UV λ_{max}^{EtOH} mμ (log ε): 224 (5.28), 279 (3.98), 335 (4.16). IR λ_{max}^{Nujol} cm^{-1}: 3360, 3160, 1660. NMR τ: 7.51 (CH_3,s,), 4.60 (NCH_2,s), 4.12 (NH_2,b), 2.7—2.2 (C_6H_5,m), 1.62 (Py. C_6–H,s). After the filtrate of above thione compound had been allowed to stand at room temperature, the deposited crystals were collected and recrystallized from EtOH–$CHCl_3$ to yield 122 mg of colorless plates, mp 264—266°, which were identical with an authentic sample of XIIIb.

b) Base Et_3N: A mixture of 3.1 g of IX, 2.7 g of IIb and 1.15 g of Et_3N in 160 ml of DMF was heated for 17 hr at 90°. After removal of the solvent *in vacuo*, the residue was extracted with $CHCl_3$ and the identified insoluble materials were removed by filtration.

The extract was successively washed with aq. $NaHCO_3$, H_2O, dried, and evaporated. Residual crystals were collected and subjected to silica gel column chromatography. The first fraction gave 70 mg (2.03%) of 3-(4-amino-2-methyl-5-pyrimidinyl)methyl-5-phenyl-1,3,4-thiadiazoline-2-thione, mp 257—259°, shown by IR spectrum to be identical with an authentic sample. The second fraction gave 345 mg (9.3%) of colorless crystals, mp 264—265°, shown by IR spectrum to be identical with an authentic sample of XIIIb.

Treatment of XIb with $POCl_3$——A mixture of 649 mg of XIb and 13.7 g of $POCl_3$ was heated at 110° for 8 hr under N_2. The excess $POCl_3$ was removed by distillation, and the residue was decomposed with crushed ice, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried and evaporated. The residue was subjected to silica gel chromatography to give 349 mg (61.8%) of colorless crystals, mp 261—264°. IR spectrum showed the product to be identical with an authentic sample of XIIIb.

5-Amino-4-phenylpyrazole (XIV)——To a solution of 23 g of 80% $NH_2 \cdot NH_2 \cdot H_2O$ and 38 ml of AcOH in 400 ml of benzene, 44 g of α-formyl phenyl acetonitrile was added and the mixture refluxed with stirring for 4.5 hr. After cooling to room temperature, 55 ml of 17.5% HCl was added with vigorous stirring. The red benzene layer was then separated and further washed with two 25 ml portions of 17.5% HCl. The aqueous solutions were combined. Neutralization with conc. NH_4OH gave 39.8 g (82.5%) of colorless crystals, mp 170—174°. Recrystallization from aq. EtOH yielded colorless plates, mp 177—180°. *Anal.* Calcd. for $C_9H_9N_3$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.99; H, 5.66; N, 26.28.

5-Acetylamido-4-phenylpyrazole (XV)——A suspension of 10 g of XIV in 48 ml of $CHCl_3$ was treated with 6.4 g of Ac_2O. The reaction mixture was left at room temperature for 7 days. A waxy solid was obtained which appeared to be a solvate containing all the $CHCl_3$. The solid was completely dissolved in warm MeOH and then solvent was removed *in vacuo*. The residual oil was again dissolved in 40 ml of MeOH and diluted with 200 ml of H_2O. After cooling the solution, the precipitated crystalline mass was filtered and dried *in vacuo* to a constant weight (9.15 g, 72.4%), mp 144—145°. Recrystallization from aq. MeOH gave colorless crystals, mp 155—158°. *Anal.* Calcd. for $C_{11}H_{11}ON_3$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.92; H, 5.63; N, 21.06.

5-Acetylamindo-(4-amino-2-methyl-5-pyrimidinyl)methyl-4-phenylpyrazole (XVI)——To a suspension of 12.1 g of 4-amino-5-bromomethyl-2-methylpyrimidine·hydrobromide in 96 g of DMF, 8.6 g of XV was added and the mixture was heated for 40 hr at 79°. After removal of the solvent *in vacuo*, the residue was dissolved in H_2O, and neutralized with $NaHCO_3$. The precipitated crystals were collected to give 7.95 g (57.7%) of crystals. Recrystallization from EtOH gave colorless crystals, mp 257—259°. *Anal.* Calcd. for $C_{17}H_{18}ON_6$: C, 63.34; H, 5.63; N, 26.07. Found: C, 63.20; H, 5.61; N, 25.80. UV λ_{max}^{EtOH} mμ (log ε): 239 (4.31), 319 (3.28). NMR (in d_6-DMSO) τ: 7.87 (CH_3,s), 7.68 (CH_3,s), 5.03 (NCH_2,s), 3.30 (NH_2,b), 2.85—2.45 (C_6H_5,m), 2.20 (Py. C_6–H,s), 2.15 (N–N=CH,s), 0.066 (NH,b).

5-Amino-1-(4-amino-2-methyl-5-pyrimidinyl)methyl-4-phenylpyrazole (XVII)——A mixture of 1.9 g of XVI, 40 ml of 10% NaOH and 220 ml of 99% EtOH in a bomb was heated for 10 hr at 105—110°. The solvent was removed *in vacuo*, and residue was acidified and filtered. The filtrate was made alkaline with $NaHCO_3$ and the precipitated crystals were collected and washed with H_2O. Recrystallization from EtOH gave colorless sticks, mp 208—210°. Yield 1.1 g (66.5%). *Anal.* Calcd. for $C_{15}H_{16}N_6$: C, 64.27; H, 5.75;

N, 29.98. Found: C, 64.26; H, 5.78; N, 29.94. UV λ_{max}^{EtOH} mμ (log ε): 233 (4.20), 269 (4.19). NMR τ: 7.53 (CH_3,s), 7.6—6.0 (NCH_2,b), 4.97 (NCH_2,s), 3.92 (NH_2,b), 2.68 (C_6H_5,s), 2.53 (N–N=CH,s), 1.83 (Py. C_6–H,s).

5-Acetylamino-1-(4-hydroxy-2-methyl-5-pyrimidinyl)methyl-4-methylpyrazole (XVIII)——To a suspension of 5 g of 5-bromomethyl-4-hydroxy-2-methylpyrimidine hydrobromide in 36 g of DMF, 3.5 g of XV was added and the mixture was heated for 18 hr at 81—83°. The solvent was removed *in vacuo* and the residue was dissolved in H_2O and then neutralized with $NaHCO_3$. The precipitated crystals were recrystallized from MeOH to yield 2.25 g (40%) of colorless powder, mp 256—257°. *Anal.* Calcd. for $C_{17}H_{17}O_2N_5$: C, 63.14; H, 5.30; N, 21.66. Found: C, 62.76; H, 5.32; N, 21.44. UV λ_{max}^{EtOH} mμ (log ε): 248 (4.23). NMR (in d_6-DMSO) τ: 7.92 (CH_3,s), 7.72 (CH_3,s), 5.10 (NCH_2,s), 2.90—2.35 (C_6H_5, Py. C_6–H,m),s 2.19 (N–N=CH,s), 0.124 (NH,b).

4-Hydroxy-5-amino-1-(4-hydroxy-2-methyl-5-pyrimidinyl)methylpyrazole (XIX)——a) A mixture of 400 mg of XVII and 10 ml of 20% HCl was boiled. After cooling, the solution was neutralized with $NaHCO_3$ and then the precipitated crystals were recrystallized from EtOH to yield 274 mg (68.4%) of colorless needles, mp 249—251°. *Anal.* Clacd. for $C_{15}H_{15}ON_5$: C, 64.04; H, 5.37; N, 24.90. Found: C, 64.12; H, 5.55; N, 24.69. UV λ_{max}^{EtOH} mμ (log ε): 270 (4.22). NMR (in d_6-DMSO) τ: 7.72 (CH_3,s), 5.12 (NCH_2,s), 4.55 (NH_2,b), 2.95—2.55 (C_6H_5,m), 2.54 (N–N=CH,s), 2.39 (Py. C_6–H,s).

b) A mixture of 1 g of XVIII, 20 ml of 10% NaOH and 120 ml of EtOH in a bomb was heated for 10 hr at 104—106°. After removal of EtOH *in vacuo*, the residue was washed with $CHCl_3$. The H_2O layer was acidified and the deposited oil was filtered off. After the neutralization of the filtrate with $NaHCO_3$, an oily product was obtained, which crystallized slowly, this was recrystallized from EtOH to give 0.52 g (59.7%) of XIX as colorless crystals, mp 249—251°. Identity with the sample obtained above was shown by IR comparison.

Treatment of XIX with 20% HCl——A mixture of 200 mg of XIX and 10 ml of 20% HCl was boiled for 2 hr vigorously. After cooling, the reaction mixture was neutralized with $NaHCO_3$. An oily product was obtained, which crystallized slowly. This crystals were washed with $CHCl_3$ and dried to yield 127 mg (63.5%) of crystals, which were identical with starting material XIX by IR comparison. The aqueous filtrate of XIX was extracted with the above $CHCl_3$ and the extract was washed, dried, and evaporated. The residual crystals were collected and recrystallized from EtOH to yield 48 mg (25.6%) of colorless plates, mp 230—234° (decomp.). Identity with XIIIa obtained above was shown by IR and UV spectra comparison.

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