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Addition Reactions of Heterocumulenes. III.[1] Reaction of Diketene with Formamidine Derivatives

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Reaction of several conjugated C–N double bond compounds with diketene was carried out with a view to establishing the structure-reactivity relationship of the 1,3-diaza-1,3-butadiene system. Formamidine derivatives (IIIa—h) reacted with diketene in benzene to form the products (Va—h) through 1,4-dipolar cycloaddition with the elimination of dimethylamine, respectively.

Similarly, reaction of diketene with 2-(*p*-dimethylaminobenzylideneamino)benzothiazole (IXa) and 2-(*p*-dimethylaminobenzylideneamino)benzimidazole (IXb) respectively afforded 3-acetyl-2-(*p*-dimethylaminophenyl)-2,3-dihydro-4-oxo-4H-pyrimido[2,1-*b*]benzothiazole (Xa) and 3-acetyl-2-(*p*-dimethylaminophenyl)-2,3-dihydro-4-oxo-4H-pyrimido-[1,2-*a*]benzimidazole (Xb).

Keywords——1,4-dipolar cycloaddition; diketene; 1,3-diaza-1,3-diene; pyrimidine derivatives; formamidine derivatives; heterodiene

Cycloaddition reactions of diketene with azadienes would be expected to be applicable to the synthesis of heterocyclic compounds containing one or more heteroatoms. Recently, Kato, *et al.*[3,4] reported 1,4-dipolar cycloaddition reactions of diketene with azadienes containing one or two nitrogen atoms. On the other hand, Matsuda, *et al.*[5] reported that N-diphenylmethylene-N′-methylbenzamidine (I) reacted with diketene to give a different type of heterocyclic compound, 1,3-oxazine (II).

It has been also reported[6] that N′-2-benzothiazolyl-N,N-dimethylformamidine (IIIa) reacts with phenyl isocyanate to give 3-phenyl-2H-s-triazino[2,1-*b*]benzothiazol-2,4(3H)-dione (IV).

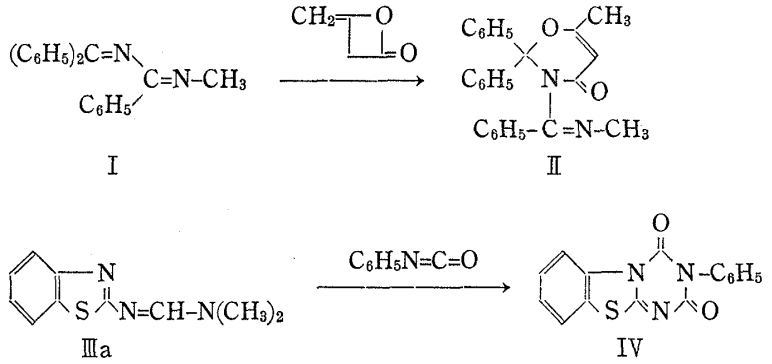


Chart 1

1) Part II: M. Sakamoto, K. Miyazawa, and Y. Tomimatsu, *Chem. Pharm. Bull.* (Tokyo), **24**, 2532 (1976).
2) Location: *35–23, Nozawa 1-chome, Setagaya-ku, Tokyo, 154, Japan.*
3) T. Kato and T. Chiba, *Yakugaku Zasshi*, **89**, 1464 (1969); T. Kato, T. Chiba, and S. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **22**, 744 (1974); T. Kato and S. Masuda, *Chem. Pharm. Bull.* (Tokyo), **22**, 1542 (1974).
4) T. Kato and S. Masuda, *Chem. Pharm. Bull.* (Tokyo), **23**, 2251 (1975).
5) I. Matsuda, S. Yamamoto, and Y. Ishii, *J. Chem. Soc. Perkin I*, **1976**, 1528.
6) R. Richter and H. Ulrich, *Chem. Ber.*, **103**, 3525 (1970).

$$Ar\text{-}NH_2 + (CH_3)_2NCH(OCH_3)_2 \longrightarrow ArN{=}CH\text{-}N(CH_3)_2$$

IIIa—h

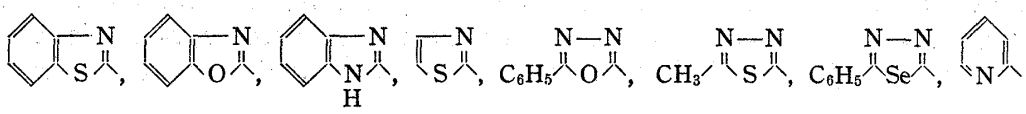
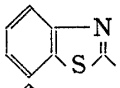
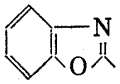
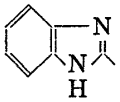
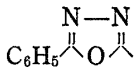
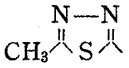
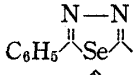
Ar: 

Chart 2

TABLE I. $ArN{=}CH\text{-}N(CH_3)_2$

Compd. No.	Ar	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIIa		103—104[a]	$C_{10}H_{11}N_3S$	58.53	5.40	20.48	58.43	5.45	20.76
IIIb		144—145	$C_{10}H_{11}N_3O$	63.47	5.86	22.21	63.75	5.91	22.34
IIIc		225—228	$C_{10}H_{12}N_4$	63.81	6.43	29.77	64.01	6.47	30.22
IIId		32—34[b]	$C_6H_9N_3S$	46.44	5.85	27.08	46.68	5.90	27.35
IIIe		149—150[c]	$C_{11}H_{12}N_4O$	61.09	5.59	25.91	61.06	5.52	26.45
IIIf		79—80	$C_6H_{10}N_4S$	42.35	5.92	32.93	42.21	5.87	33.05
IIIg		180—181	$C_{11}H_{12}N_4Se$	47.32	4.32	20.06	47.47	4.24	20.21
IIIh		Viscous oil[d]	$C_8H_{11}N_3$	64.40	7.43	28.17	63.96	7.57	28.19

a) mp 98—100°: reported.[6]
b) mp 35—38°: CIBA Ltd., Belg. Pat. 636256 (1964) [*C. A.*, **61**, 13314*e* (1964)].
c) mp 146—147°: P. Henklein and G. Westphal, *Z. Chem.*, **12**, 103 (1972).
d) mp 34—36°: H. Bredereck, F. Effenberger, and A. Hoffmann, *Chem. Ber.*, **97**, 61 (1964).

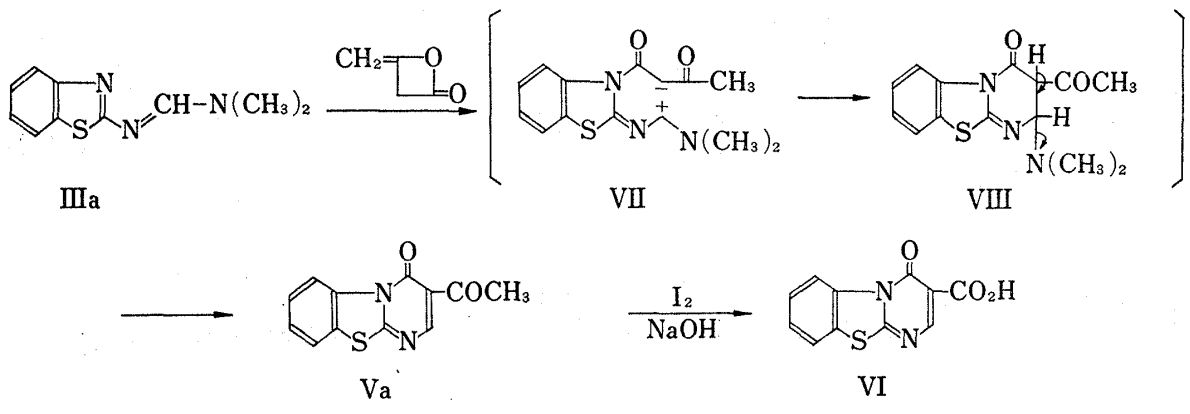


Chart 3

In this paper the authors wish to report the 1,4-dipolar cycloaddition reactions of diketene with the N=C–N=C linkage in the formamidine derivatives.

According to the scheme in Chart 2, we first synthesized new formamidine derivatives, having the N=C–N=C linkage. Here, one of the carbon-nitrogen bonds is a part of the aromatic system. The physical constants of formamidine derivatives are shown in Table I.

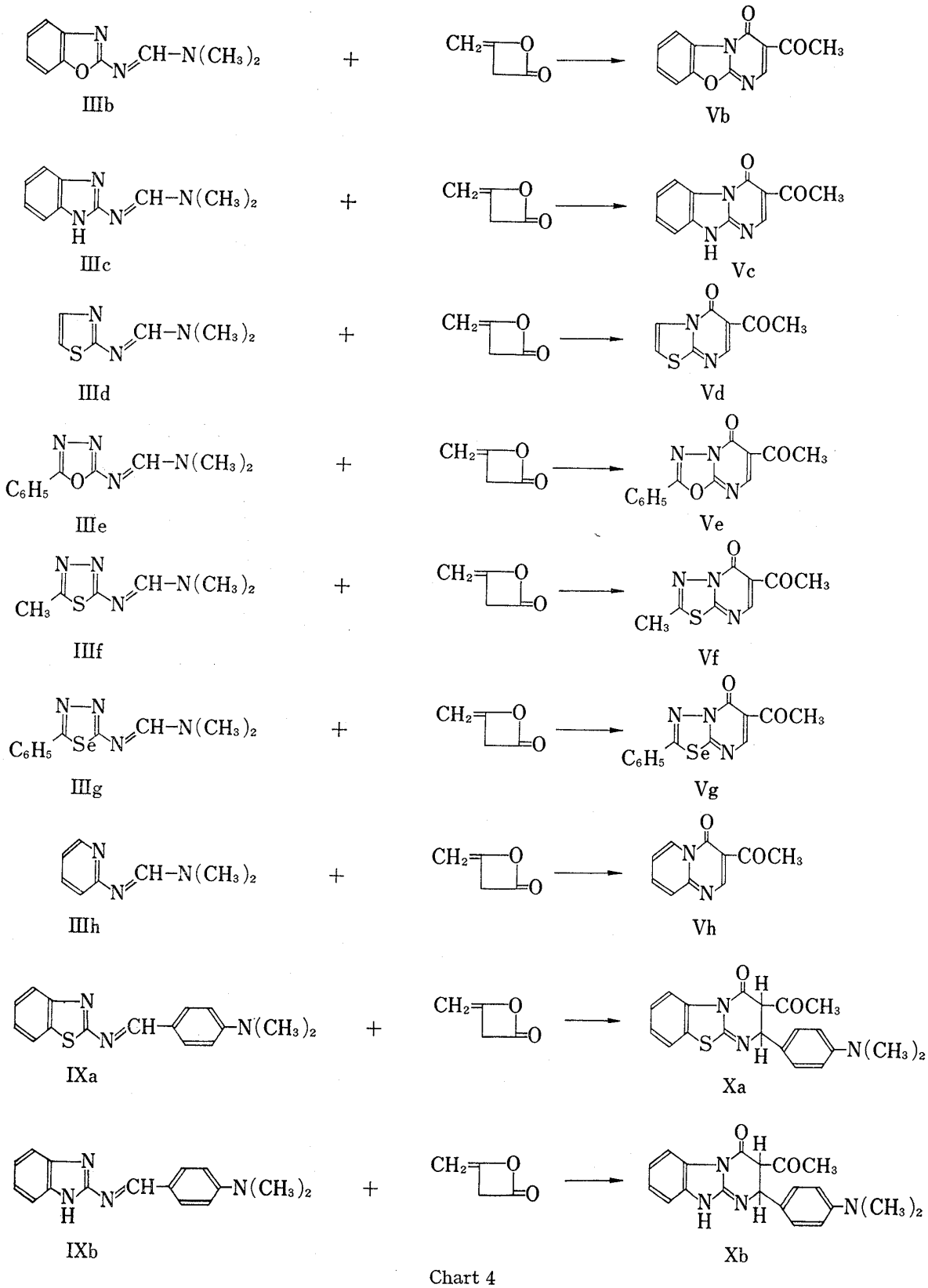


Chart 4

Refluxing a solution of IIIa and diketene in dry benzene for 6 hr gave a crystalline compound Va, mp 202—203°, in 74% yield. The elemental analysis and molecular weight (M^+ 244) provided its empirical formula being $C_{12}H_8O_2N_2S$, the condensation product of one mole of IIIa and one mole of diketene by the elimination of one mole of dimethylamine. The infrared (IR) spectrum indicated the absence of imine absorption and the presence of a carbonyl group at 1675 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum showed two signals due to an acetyl group (δ 3.03, singlet) and a ring proton (δ 8.98, singlet, C_2-H). These observations suggest that this product is 3-acetyl-4H-pyrimido[2,1-*b*]benzothiazol-4-one(Va).

In order to obtain further evidence for its structure, the haloform reaction of Va in the presence of iodine was attempted. As expected, the known compound,[7] 4-oxo-4H-pyrimido-[2,1-*b*]benzothiazole-3-carboxylic acid (VI) (mp 260—262°, lit. mp 260—262°) was obtained.

The pathway[4] of the formation of Va could be explained as an electrophilic addition of the carbonyl carbon of diketene to the ring nitrogen of IIIa, forming the dipolar intermediate VII. Cyclization of VII would then give the dihydropyrimido[2,1-*b*]benzothiazole intermediate VIII, followed by the elimination of dimethylamine to give Va.

Similar reactions of formamidines (IIIb—h) with diketene yielded the corresponding products (Vb—h). The elemental analyses and physical properties are summarized in Table II.

Table II. Physical Properties of V

Compd. No.	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR (KBr) cm^{-1} C=O	NMR δ (in $CDCl_3$)[a] $-CH_3$	$=N-CH=$	UV λ_{max}^{EtOH} nm (log ε)
Va	202—203	$C_{12}H_8N_2O_2S$	59.02 (59.09)	3.30 (3.33)	11.47 (11.84)	1675	3.03 (s)	8.98 (s)	248, 280, 358 (4.05, 3.37, 4.27)
Vb	179—180	$C_{12}H_8N_2O_3$	63.16 (62.96)	3.53 (3.54)	12.28 (12.41)	1692 1667	2.75 (s)	8.73 (s)	232, 269.5, 329 (4.07, 3.10, 4.17)
Vc	276—278	$C_{12}H_9N_3O_2$	63.43 (63.32)	3.99 (3.95)	18.49 (18.70)	1690	2.61 (s)	8.54 (s)	248.5, 271, 344 (4.21, 3.57, 4.32)
Vd	170—171	$C_8H_6N_2O_2S$	49.47 (49.49)	3.12 (3.14)	14.43 (14.36)	1680 1657	2.66 (s)	8.76 (s)	245.5, 260, 351.5 (3.70, 3.70, 4.25)
Ve	211—212.5	$C_{13}H_9N_3O_3$	61.17 (61.08)	3.55 (3.59)	16.47 (16.73)	1711 1679	2.71 (s)	8.65 (s)	241.5, 314 (4.22, 4.19)
Vf	178—180	$C_8H_7N_3O_2S$	45.94 (45.91)	3.37 (3.28)	20.09 (20.35)	1694 1669	2.81 (s)	8.61 (s)	220.5, 255, 335.5 (3.93, 3.57, 4.15)
Vg	226—227	$C_{13}H_9N_3O_2Se$	49.07 (49.11)	2.84 (2.82)	13.20 (13.32)	1691	2.74 (s)	8.52 (s)	231.5, 278, 351.5 (4.25, 4.09, 4.28)
Vh	161—162	$C_{10}H_8N_2O_2$	63.82 (63.68)	4.29 (4.26)	14.89 (14.88)	1698 1663	2.78 (s)	8.98 (s)	254, 305, 370.5 (3.91, 3.57, 4.23)

a) Vc: d_6-DMSO.

Reaction of 2-(*p*-dimethylaminobenzylideneamino)benzothiazole (IXa) with diketene in dry benzene afforded the 1:1 adduct (Xa). From the characteristic carbonyl stretching band[1] at about 1685 cm^{-1} and 1640 cm^{-1}, the structure of Xa was assigned as 3-acetyl-2-(*p*-dimethylaminophenyl)-2,3-dihydro-4-oxo-4H-pyrimido[2,1-*b*]benzothiazole.

A similar reaction of 2-(*p*-dimethylaminobenzylideneamino)benzimidazole (IXb) with diketene gave the 1:1 adduct, 3-acetyl-2-(*p*-dimethylaminophenyl)-2,3-dihydro-4-oxo-4H-pyrimido[1,2-*a*]benzimidazole (Xb).

7) D.W. Dunwell and D. Evans, *J. Chem. Soc.* (*C*), **1971**, 2094.

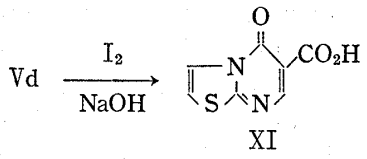


Chart 5

On the other hand, haloform reaction of Vd in the presence of iodine was attempted. As expected, the known compound,[7] 5-oxo-5H-thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid (XI) was obtained.

Lastly, reaction of 2-(*p*-nitrobenzylideneamino)benzothiazole with diketene in dry benzene resulted in recovery of the starting materials.

Experimental

All melting points were measured with a Yanagimoto micro melting points apparatus and are uncorrected. NMR spectra were measured with Japan Electron Optics Co., Model PS-100 (100 MHz) spectrometer with tetramethylsilane as an internal reference. Abbreviation used s=singlet, d=doublet, m=multiplet, b=broad. Mass spectra were taken on a Japan Electron Optics Co., JMS-OISG-2 spectrometer. IR absorption spectra were measured on a Nihon Bunko Jasco DS-701G spectrometer. Ultraviolet (UV) absorption spectra were obtained with a Hitachi Model 124 spectrometer.

Reaction of 2-Aminobenzothiazole with N,N-Dimethylformamide Dimethylacetal——General Procedure: A mixture of 3 g of 2-aminobenzothiazole and one molar equivalent of N,N-dimethylformamide dimethylacetal in 100 ml absolute EtOH was refluxed for 6 hr, and the reaction mixture was condensed *in vacuo* to give a crystalline substance. Recrystallization from ether gave N′-2-benzothiazolyl-N,N-dimethylformamidine (IIIa), as colorless crystals, mp 103—104°, Yield 3.7 g (90%). The other compounds (IIIb—h) were prepared by the same procedure and these data were summarized in Table I.

Reaction of Diketene with N′-2-Benzothiazolyl-N,N-dimethylformamidine (IIIa)——A mixture of 0.5 g of IIIa and two molar equivalent of diketene in 5 ml of dry benzene was refluxed for 6 hr. After cooling, crystals separated were collected by filtration. The filtrate was condensed *in vacuo*, and the residue was purified by preparative TLC ($CHCl_3$: acetone, 20: 1) to give crystals. All crystals thus obtained was combined and purified by recrystallization from acetone to give 0.44 g (74%) of 3-acetyl-4H-pyrimido[2,1-*b*]benzothiazol-4-one (Va) as pale yellow prisms. MS *m/e*: 244 (M^+). The results are shown in Table II.

Reaction of Diketene with N′-2-Benzoxazolyl-N,N-dimethylformamidine (IIIb)——A mixture of 0.5 g of IIIb and two molar equivalent of diketene in 5 ml of dry benzene was refluxed for 6 hr. After cooling, crystals separated were collected by filtration. The filtrate was condensed *in vacuo*, and the residue was purified by silica gel column chromatography (chloroform) to give crystals. All crystals thus obtained were combined and purified by recrystallization from EtOH to give 0.34 g (57%) of 3-acetyl-4H-pyrimido[2,1-*b*]-benzoxazol-4-one (Vb) as pale yellow needles. MS *m/e*: 228 (M^+). The results are shown in Table II.

Reaction of Diketene with N′-2-Benzimidazolyl-N,N-dimethylformamidine (IIIc)——A mixture of 0.5 g of IIIc and two molar equivalent of diketene in 20 ml of dry benzene was refluxed for 4 hr. After cooling, the precipitate was collected by filtration and recrystallized from EtOH to give 0.55 g (91%) of 3-acetyl-4H-pyrimido[1,2-*a*]benzimidazol-4-one (Vc) as colorless needles. MS *m/e*: 227 (M^+). The results are shown in Table II.

Reaction of Diketene with N′-2-Thiazolyl-N,N-dimethylformamidine (IIId)——Using a procedure similar to that described for the synthesis of Vc, IIId (1 g) was treated with two molar equivalent of diketene in 10 ml of dry benzene to give 1 g (71%) of 6-acetyl-5H-thiazolo[3,2-*a*]pyrimidin-5-one (Vd) as colorless needles. MS *m/e*: 194 (M^+). The results are shown in Table II.

Reaction of Diketene with N′-2-(5-Phenyl-1,3,4-oxadiazolyl)-N,N-dimethylformamidine (IIIe)——Using a procedure similar to that described for the synthesis of Vc, IIIe (0.5 g) was treated with two molar equivalent of diketene in 15 ml of dry benzene to give 0.16 g (27%) of 6-acetyl-2-phenyl-5H-1,3,4-oxadiazolo[3,2-*a*]-pyrimidin-5-one (Ve) as pale yellow scales. MS *m/e*: 255 (M^+). The results are shown in Table II.

Reaction of Diketene with N′-2-(5-Methyl-1,3,4-thiadiazolyl)-N,N-dimethylformamidine (IIIf)——A mixture of 0.5 g of IIIf and two molar equivalent of diketene in 10 ml of dry benzene was refluxed for 8 hr, and the reaction mixture was condensed *in vacuo*, and the residue was washed with ether. Recrystallization from EtOH gave 0.44 g (72%) of 6-acetyl-2-methyl-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (Vf) as colorless plates. MS *m/e*: 209 (M^+). The results are shown in Table II.

Reaction of Diketene with N′-2-(5-Phenyl-1,3,4-selenadiazolyl)-N,N-dimethylformamidine (IIIg)——A mixture of 0.5 g of IIIg and two molar equivalent of diketene in 25 ml of dry benzene was refluxed for 7 hr. After cooling, crystals separated were collected by filtration. The filtrate was condensed *in vacuo*, and the residue was purified by preparative TLC ($CHCl_3$: acetone, 20: 1) to give crystals. All crystals thus obtained were combined and purified by recrystallization from EtOH to give 0.51 g (90%) of 6-acetyl-2-phenyl-5H-1,3,4-selenadiazolo[3,2-*a*]pyrimidin-5-one (Vg) as colorless fine needles. MS *m/e*: 319 ($M^+ + 1$). The results are shown in Table II.

Reaction of Diketene with N′-2-Pyridinyl-N,N-dimethylformamidine (IIIh)——A mixture of 1 g of IIIh and two molar equivalent of diketene in 10 ml of dry benzene was heated at 50° for 20 hr, and the reaction

mixture was condensed *in vacuo*, and the residue was washed with ether. Recrystallization from H_2O gave 0.13 g (10%) of 3-acetyl-4H-pyrido[1,2-*a*]pyrimidin-4-one (Vh) as colorless needles. MS *m/e*: 188 (M^+). The results are shown in Table II.

Haloform Reaction of Va——To a solution of 1 g of Va in 40 ml of dioxane and 20 ml of 10% sodium hydroxide was added potassium iodide-iodine reagent dropwise with stirring at room temperature until a definite dark color of iodine persists (*ca.* 70 ml), and the mixture was stirred for 30 min. After the reaction mixture was diluted with 70 ml of water and allow to stand for 1 hr, the precipitate was filtered off, and filtrate was concentrated to 50 ml under reduced pressure. The resulting aqueous layer was acidified with 10% HCl solution and extracted with AcOEt. The extract was washed with an aqueous solution of $NaHSO_3$, water, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was washed with EtOH, and recrystallized from dimethylformamide–EtOH to give 0.04 g of 4-oxo-4H-pyrimido[2,1-*b*]benzothiazole-3-carboxylic acid (VI) as colorless crystals, mp 260—262° (lit.[7] mp 260—262°). MS *m/e*: 246 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1731, 1639 (C=O). NMR (in d_6-DMSO) δ: 7.22—8.00 (4H, m, aromatic protons), 8.57 (1H, s, =N–CH=), 12.39 (1H, b, –COOH). The signal of δ 12.39 is disappeared upon addition of D_2O.

Reaction of Diketene with 2-(*p*-Dimethylaminobenzylideneamino)benzothiazole (IXa)——A mixture of 0.5 g of IXa and two molar equivalent of diketene in 5 ml of dry benzene was refluxed for 5 hr, and the reaction mixture was condensed *in vacuo*, and the residue was washed with ether. Recrystallization from EtOH gave 0.43 g (66%) of 3-acetyl-2-(*p*-dimethylaminophenyl)-2,3-dihydro-4-oxo-4H-pyrimido[2,1-*b*]-benzothiazole (Xa) as yellow needles, mp 205—207°. MS *m/e*: 365 (M^+). *Anal.* Calcd. for $C_{20}H_{19}N_3O_2S$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.36; H, 5.50; N, 11.14. IR ν_{max}^{KBr} cm^{-1}: 1685, 1640 (C=O), 1610 (C=N). NMR (in $CDCl_3$) δ: 2.11 (3H, s, $-COCH_3$), 2.98 (6H, s, $-N(CH_3)_2$).

Reaction of Diketene with 2-(*p*-Dimethylaminobenzylideneamino)benzimidazole (IXb)——Using a procedure similar to that described for the synthesis of Xa, IXb (0.5 g) was treated with two molar equivalent of diketene in 20 ml of dry benzene to give 0.44 g (66%) of 3-acetyl-2-(*p*-dimethylaminophenyl)-2,3-dihydro-4-oxo-4H-pyrimido[1,2-*a*]benzimidazole (Xb) as colorless fine needles, mp 233—235°. MS *m/e*: 348 (M^+). *Anal.* Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.85; H, 5.65; N, 15.92. IR ν_{max}^{KBr} cm^{-1}: 1729, 1715, 1657 (C=O), 1611 (C=N). NMR (in CF_3COOH) δ: 2.14 (3H, s, $-COCH_3$), 3.50 (6H, s, $-N(CH_3)_2$).

Haloform Reaction of Vd——Using a procedure similar to that described for the synthesis of VI, 5-oxo-5H-thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid (XI) was obtained from Vd. Recrystallization from dimethylformamide–EtOH gave colorless crystals (0.07 g), mp 282—284° (dec.). [lit.[7] mp 277° (dec.)]. MS *m/e*: 196 (M^+). *Anal.* Calcd. for $C_7H_4N_2O_3S$: C, 42.87; H, 2.06; N, 14.29. Found: C, 42.60; H, 2.00; N, 14.41. IR ν_{max}^{KBr} cm^{-1}: 1717, 1636 (C=O). NMR (in d_6-DMSO) δ: 7.75, 8.23 (each 1H, d, J=4.0 Hz, –N–CH=CH–S–), 8.67 (1H, s, =N–CH=), 12.48 (1H, b, –COOH). The signal of δ 12.48 is disappeared upon addition of D_2O.

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