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Reactions of 1,1-Bismethylthio-2-nitroethylene. IV.[1] Syntheses and Reactions of 4-Methylthio-2-buten-4-olide Derivatives

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Treatment of methyl 2-cyano-3-methylthio-4-nitrocrotonate with conc. sulfuric acid gave 2-carbamoyl-3-methylthio-2-buten-4-olide (II) in a good yield. This compound (II) was formed easily by the replacement reaction between methylthio group and nucleophilic reagents such as amines or active methylene compounds.

Condensation reaction of II as a nucleophilic reagent with various reagents having a formyl or ketone group gave corresponding condensation products. Reaction of II with quinoline 1-oxide gave 2-carbamoyl-3-methylthio-4,4-bis(2-quinolyl)-2-buten-4-olide (X).

Our previous paper[3] reported that the treatment of methyl 2-cyano-3-methylthio-4-nitrocrotonate (I) in acidic solution afforded pyrroline and maleic anhydride derivatives in a good yield. Substitution of methylthio group in these compounds with nucleophilic reagents such as amines or active methylene was easily carried out and corresponding derivatives were obtained.

The present paper deals with the syntheses of butenolide derivatives and their reactions.

Treatment of I with conc. sulfuric acid gave white crystals (II), mp 243—245°, in a good yield. Elemental analysis of II supported a molecular formula of $C_6H_7O_3NS$. The infrared (IR) spectrum of II showed absorption at 3483 and 3218 cm^{-1} due to NH, and 1720 and 1660 cm^{-1} due to carbonyl groups. The nuclear magnetic resonance (NMR) spectrum of II gave useful information in the structure analysis. This spectrum in trifluoroacetic acid showed signals due to a methylthio proton at 2.70 ppm and a methylene proton a singlet at 5.40 ppm. From these spectral data and elemental analysis, 2-carbamoyl-3-methylthio-2-buten-4-olide was assigned to compound II.

Treatment of II with phosphoryl chloride on a steam bath for 10 min gave white crystals of mp 47—49°, in 60% yield. Elemental analysis of this compound III agreed with a molecular formula of $C_6H_5O_2NS$ and was also supported by mass spectrum (m/e: 155 (M^+)). The ultraviolet (UV) spectrum of III revealed absorption maximum at 292 nm (ε=4.29), which is similar to II. Its IR spectrum showed a new band at 2220 cm^{-1} due to cyano group instead of carbonyl group. From these spectral data and elemental analysis, this compound III was found to be a dehydrated product, 2-cyano-3-methylthio-2-buten-4-olide. This result also suggested that the structure of II was correct. II and III, which had both an active methylthio group and an active methylene system in themselves, were available respectively as neucleophilic and electrophilic reagents.

In a similar reaction of methylthio group, we reported previously that the reaction of 2-cyano-1-(methylthio)pyrano[2,3-*b*]indol-2-one,[4] 3-cyano-4-(methylthio)pyrano[3,2-*b*]indol-

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[1] Part III: M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **93**, 1008 (1973).

[2] Location: *1-14 Bunkyo-machi, Nagasaki.*

[3] M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **21**, 1667 (1973).

[4] G. Kobayashi, S. Furukawa, Y. Matsuda, M. Nakamura, and R. Natsuki, *Yakugaku Zasshi*, **87**, 1044 (1967).

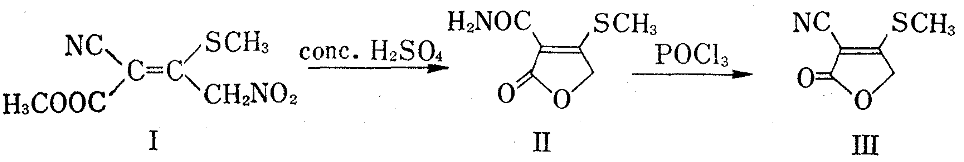

Chart 1

2-one,[5] and 3-cyano-4-(methylthio)coumarine[6] with various nucleophilic reagents (amines, active methylene compounds) resulted in the formation of products by substitution of the methylthio group.

Substitution of methylthio group in compound II as the electrophile with amines (aniline, benzylamine, ethanolamine, cyclohexylamine, aminoacetal, phenylhydrazine, piperidine, morpholine) occurred easily and the corresponding amino derivatives were obtained in a good yield. Physical properties of these compounds are shown in Table I.

Reaction of II with active methylene compounds such as oxindole and 1-methyloxindole in the presence of base gave Va and Vb in 60—70% yield.

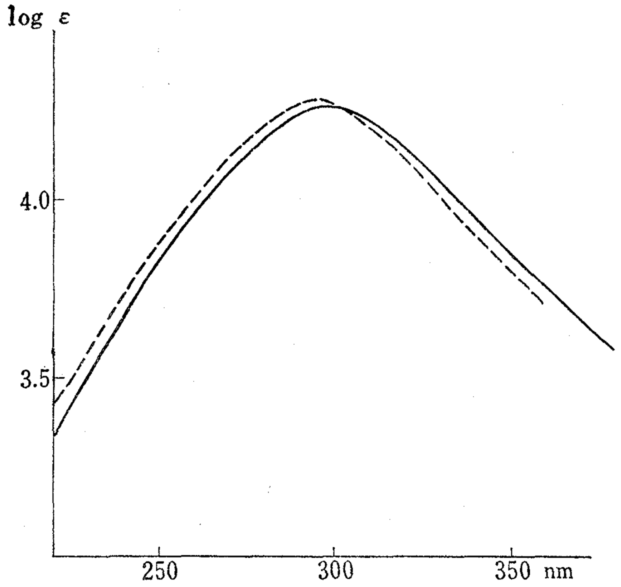

Fig. 1. Ultraviolet Spectra of II and III

——: II ------: III

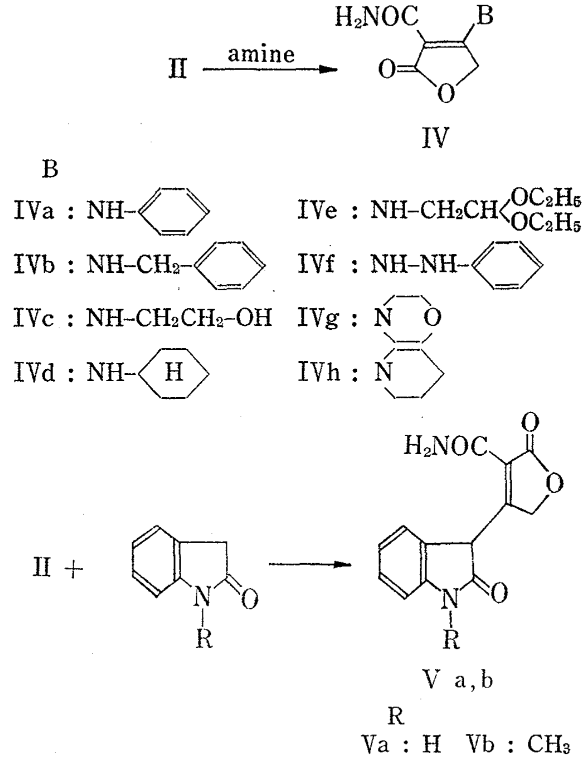

Chart 2

Recently, Corrie[7] reported the reaction of α-(γ-butyrolactonylidene)triphenylphosphorane with aldehyde derivatives (Wittig reaction). We are going to report about the condensation reaction of II as a nucleophile with various reagents having a formyl or ketone group. When II was allowed to react with dimethylformamide and phosphoryl chloride on a steam bath for 4—5 hr, yellow crystals of mp 167° were obtained in 70% yield. Elemental analysis of the compound agreed with $C_9H_{10}O_2N_2S$. The UV spectrum of this compound was not similar to that of the parent compound (II) and its IR spectrum exhibited absorption of a cyano group

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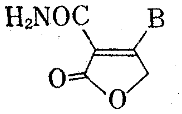
5) G. Kobayashi, Y. Matsuda, R. Natsuki, Y. Tominaga, T. Okamura, and A. Itamura, *Yakugaku Zasshi*, 93, 964 (1973).

6) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, 93, 836 (1973).

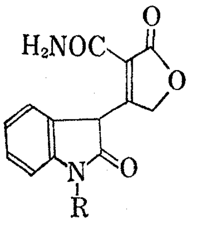
7) J.E.T. Corrie, *Tetrahedron Letters*, 1971, 4873.

TABLE I.



No.	mp (°C)	Yield (%)	B	Formula	Analysis (%) Calcd. (Found) C	H	N	UV λ_{max}^{EtOH} nm (log ε)	IR (KBr) cm⁻¹
IVa	182—184	65	-NH- 	$C_{11}H_{10}O_3N_2$	60.54 (60.33)	4.62 (4.67)	12.84 (12.64)	298 (4.34)	NH; 3480, 3380, 3260 CO; 1720, 1660
IVb	153—155	75	-NH-CH₂- 	$C_{12}H_{12}O_3N_2$	62.06 (61.94)	5.21 (5.37)	12.06 (11.79)	270 (4.42)	NH; 3475, 3360, 3300 CO; 1710, 1655
IVc	162—164	70	-NH-CH₂CH₂OH	$C_7H_{10}O_4N_2$	45.16 (45.08)	5.41 (5.56)	15.05 (14.92)	267 (4.42)	NH; 3480, 3380 CO; 1715, 1655
IVd	203—204	70	-NH- 	$C_{11}H_{16}O_3N_2$	58.91 (59.10)	7.19 (7.29)	12.49 (12.89)	269 (4.41)	NH; 3505, 3480, 3355 CO; 1710, 1655
IVe	101—103	80	$-NH-CH_2CH\langle^{OC_2H_5}_{OC_2H_5}$	$C_{11}H_{18}O_5N_2$	51.15 (51.43)	7.03 (7.12)	10.85 (10.95)	267 (4.39)	NH; 3480, 3340, 3220 CO; 1720, 1660
IVf	241	65	NH-NH- 	$C_{11}H_{11}O_3N_3$	56.65 (56.95)	4.75 (4.76)	18.02 (18.11)	265 (4.33)	NH; 3540, 3400, 3300 CO; 1705, 1650
IVg	203	60	- 	$C_9H_{12}O_4N_2$	50.94 (50.95)	5.70 (5.84)	13.20 (13.30)	282 (4.42)	NH; 3400, 3240 CO; 1700, 1655
IVh	204	65	- 	$C_{10}H_{14}O_3N_2$	57.13 (57.24)	6.71 (7.00)	13.33 (13.36)	282 (4.42)	NH; 3400, 3240 CO; 1700, 1655

TABLE II.



No.	mp (°C)	Yield (%)	R	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	UV λ_{max}^{EtOH} nm (log ε)	IR (KBr) cm⁻¹
Va	232	75	H	$C_{13}H_{10}O_4N_2$	60.46	3.90	10.85	60.61	3.90	10.73	285(4.26) 396(4.56)	NH 3240 3400 CO 1690
Vb	231	65	CH_3	$C_{14}H_{12}O_4N_2$	61.76	4.44	10.37	61.42	4.51	10.29	288(4.22) 396(4.54)	NH 3280 3400 CO 1700

at 2205 cm⁻¹ and a carbonyl group at 1720 cm⁻¹. Its NMR spectrum showed two singlet peaks of methyl protons at 3.38 ppm (6H, s, $-N\langle^{Me}_{Me}$) and 2.81 ppm (3H, s, SMe), and a singlet peak of a proton in double bond at 6.62 ppm (1H, s, C=CH). From these spectral data and elemental analysis, this compound VI was found to be a Vilsmeier reaction product, 2-cyano-4-(N,N-dimethylaminomethylidene)-3-methylthio-2-buten-4-olide (VIa). In a similar manner, the Vilsmeier reaction of II with N-methylpyrrolidone and phosphoryl chloride afforded a Vilsmeier product (VIb) of mp 224°. By the application of this reaction, reaction of II with aldehydes (benzaldehyde, *m*-nitrobenzaldehyde), in the presence of phosphoryl chloride, afforded the condensation products, 4-benzylidene-2-cyano-3-methylthio-2-buten-4-olides (VIIa, b), in a good yield. These compounds, VIa, VIb, and VII having active methylthio group are available as electrophilic reagents. These 3-methylthio-2-buten-4-olides are also useful compounds for the preparation of 3-substituted 4-alkylidene-2-buten-4-olides.

Reaction of VIa with benzylamine afforded two products, 4-(N-benzylaminomethylidene)-2-cyano-3-methylthio-2-buten-4-olide (VIIIa) and 3-benzylamino-4-(N-benzylaminomethylidene)-2-cyano-2-buten-4-olide (IX).

In a similar manner as above, reaction of VIa with morpholine gave 2-cyano-4-(N,N-dimethylaminomethylidene)-3-morpholino-2-buten-4-olide (VIIIb) which was formed by replacement reaction between only one methylthio group and morpholine.

Hamana reported that active methylene compounds of high acidity react with aromatic amine N-oxides in the presence of an acylating agent.[8] As we found that 4-position of the

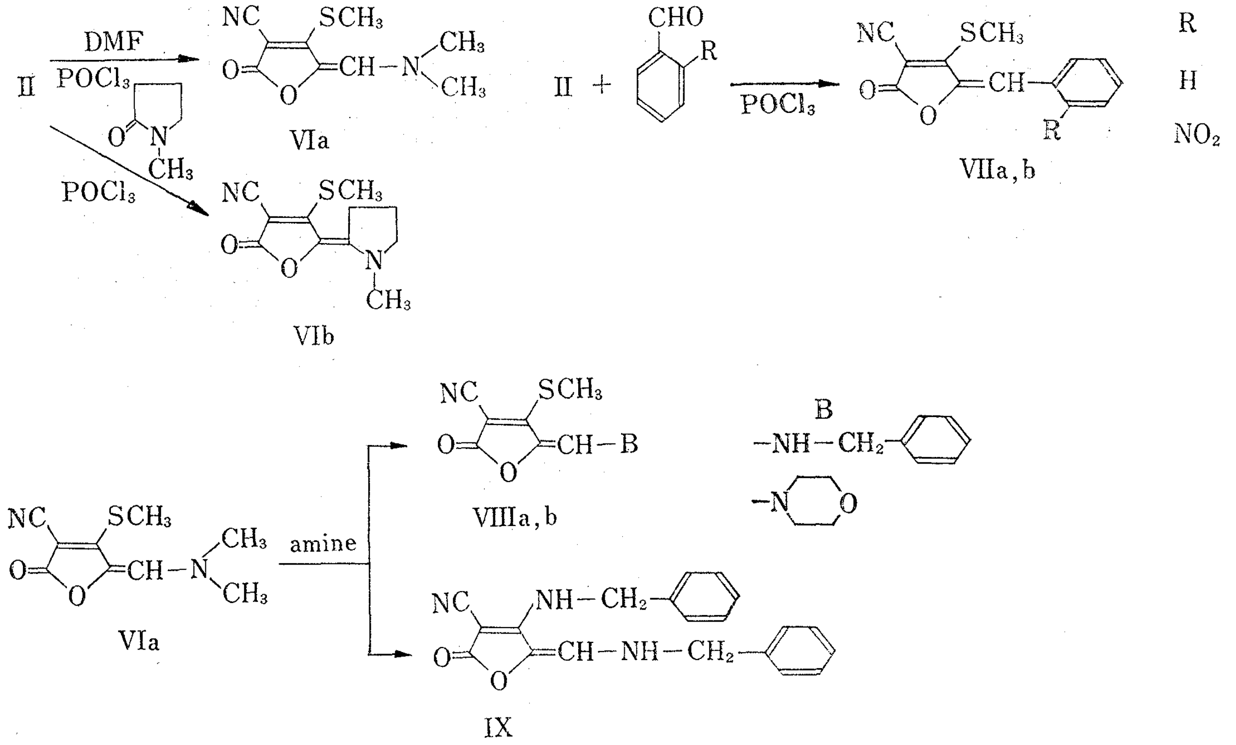
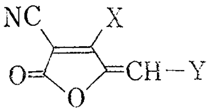
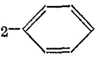
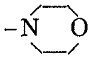
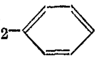
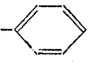


Chart 3

Table III.



No.	mp (°C)	Yield (%)	X	Y	Formula	Analysis (%) Calcd. (Found) C	H	N	UV λ_{max}^{EtOH} nm (log ε)	IR (KBr) cm^{-1}
VIIIa	162	30	SMe	-NH-CH$_2$- 	$C_{14}H_{12}O_2N_2S$	61.76 (61.55)	4.44 (4.39)	10.29 (10.30)	320(3.96) 402(4.76)	NH 3280 CN 2220 CO 1710
VIIIb	187	70	SMe		$C_{11}H_{12}O_3N_2S$	52.38 (52.18)	4.80 (4.77)	11.11 (10.75)	320(4.04) 404(4.70)	CN 2205 CO 1720
IX	205	40	-NHCH$_2$- 	-NHCH$_2$- 	$C_{20}H_{17}O_2N_3$	72.49 (72.04)	5.17 (5.14)	12.68 (12.87)	303(4.15) 350(5.01)	NH 3400 CN 2205 CO 1650

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[8] M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 415 (1963).

2-buten-4-olide derivative (II) behaved as an active methylene, we examined the reaction of II with quinoline 1-oxide.

Reaction of quinoline 1-oxide and 2-buten-4-olide (II) in the presence of acetic anhydride afforded yellow crystals (X) of mp 229°, which had an empirical formula of $C_{24}H_{17}O_3N_3S$ in agreement with bis(quinolyl)-2-buten-4-olide and its mass spectrum showed a molecular ion peak at 427 (M^+). In its NMR spectrum the ratio of numbers of S-methyl protons to those of aromatic ones was found to be 3: 16 and no signal of α-proton of quinoline ring and a methylene proton of butenolide was deteced. From these spectral data and elemental anlysis, this compound (X) was found to be 2-carbamoyl-3-methylthio-4,4-bis(2-quinolyl)-2-buten-4-olide.

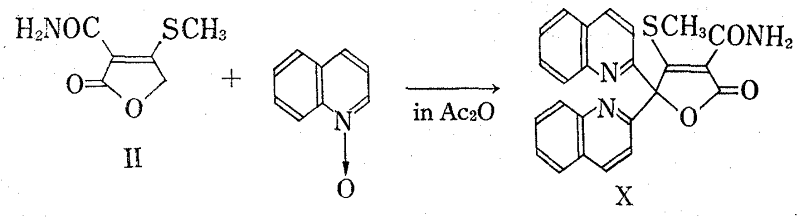

Chart 4

From the results described above it is now shown that these 2-buten-4-olide derivatives have both electrophilic and nucleophilic characters.

Experimental

2-Carbamoyl-3-methylthio-2-buten-4-olide (II)——To 30 ml of conc. H_2SO_4, 5 g of powdered I was added in small portions at 0°. The mixture was stirred at room temperature for 5 hr, poured into 100 ml of ice-water, and then allowed to stand for 2—3 hr. The white yellow crystalline powders that formed were collected on a filter, washed with H_2O, and recrystallized from acetone to give white needles, mp 243—245°, in 55% yield. *Anal.* Calcd. for $C_6H_7O_3N$: C, 41.62; H, 4.08; N, 8.09. Found: C, 41.63; H, 4.08; N, 7.66. IR (KBr) cm^{-1}: 3483, 3218 (NH), 1720, 1660 (C=O). UV λ_{max}^{EtOH} nm (log ε): 293 (4.27). NMR (in CF_3COOH) ppm: 2.70 (3H, s, SMe), 5.40 (2H, s, $-CH_2-$).

2-Cyano-3-methylthio-2-buten-4-olide (III)——A mixture of 0.5 g of II and 10 ml of $POCl_3$ was heated under reflux for 10 min. After the excess of $POCl_3$ was evaporated under reduced pressure, 50 ml of H_2O was added to the residue under cooling (0—5°) and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, the solvent was evaporated, and the residue was washed with ether. The precipitates were collected by filtration, washed with ether to give 0.3 g of white powder. Recrystallization from ether gave white crystals, mp 47—49°. *Anal.* Calcd. for $C_6H_5O_2N$: C, 46.46; H, 3.25; N, 9.03. Found: C, 46.34; H, 3.22; N, 8.63. IR (KBr) cm^{-1}: 2220 (CN), 1762 (C=O). UV λ_{max}^{EtOH} nm (log ε): 292 (4.29).

Reaction of II with Amines——A solution of II (0.01 mole) and an amine (0.02 mole) in 30 ml of MeOH was refluxed for 4 hr. The solvent was evaporated, 50 ml of ice water was added to the residue, and 10% HCl solution was added to remove excess amines. Resulting precipitates were collected and recrystallized from MeOH. These products are shown in Table I.

3-Anilino-2-carbamoyl-2-buten-4-olide (IVa)——A mixture of 1.4 g of II and 1.4 g of aniline was heated at 150° for 1 hr. When cooled, 10 ml of MeOH was added to the reaction mixture and the mixture was allowed to stand for 2—3 hr. The resulting precipitate was collected by filtration and recrystallized from MeOH. The result of this reaction is shown in Table I.

Reaction of II with Oxindoles——To a suspension of 0.72 g (0.015 mole) of NaH in mineral oil in 100 ml of absolute tetrahydrofuran, 0.01 mole of oxindole (oxindole or N-methyloxindole) and 1.4 g of II were added. The mixture was refluxed for 4 hr. After the solvent was evaporated, 100 ml of ice water was added to its residue and stirred until all the solid dissolved. The solvent was acidified with 10% HCl solution, the precipitates were collected by filtration, washed with H_2O, and recrystallized from acetone. The results are shown in Table II.

2-Cyano-4-(N,N-dimethylaminomethylidene)-3-methylthio-2-buten-4-olide (VIa)——To a solution of 5 ml of $POCl_3$ in 20 ml of absolute dimethylformamide, 0.5 g of II was added and the mixture was stirred for 3 hr at room temperature. The reaction mixture was cooled and poured into 50 ml of ice water with vigorous stirring. The precipitates were collected by filtration, washed with H_2O, and recrystallized from MeOH and iso-PrOH to give yellow-green needles, mp 167°, in 75% yield. *Anal.* Calcd. for $C_9H_{10}O_2N_2S$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.60; H, 4.91; N, 12.46. IR (KBr) cm^{-1}: 2205 (CN), 1720 (C=O). UV λ_{max}^{EtOH} nm (log ε): 320 (3.53), 402 (4.44).

2-Cyano-4-(N-methylpyrrolidene-2)-3-methylthio-2-buten-4-olide (VIb)——To a solution of 5 ml of $POCl_3$ in 20 ml of N-methylpyrrolidone, 0.4 g of II was added and stirred for 3 hr. The mixture was treated as in the preparation of VIa. Recrystallization from EtOH gave yellow needles, mp 224°, in 75% yield. *Anal.* Calcd. for $C_{11}H_{12}O_2N_2S$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.82; H, 5.03; N, 11.77. IR (KBr) cm^{-1}: 2200 (C≡N). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε): 310 (3.72), 398 (4.72).

2-Cyano-4-benzylidene-3-methylthio-2-buten-4-olide (VIIa)——A mixture of 1.4 g of II and 1.5 g of benzaldehyde was added to 10 ml of $POCl_3$ and refluxed for 2 hr. After removal of excess $POCl_3$, the residue was cooled and poured into 50 ml of ice water. The precipitates were collected by filtration, washed with H_2O, and recrystallized from benzene and MeOH to give white needles, mp 193—194°, in 80% yield. *Anal.* Calcd. for $C_{13}H_9O_2NS$: C, 64.20; H, 3.73; N, 5.76. Found: C, 64.82, H, 3.71; N, 6.10. IR (KBr) cm^{-1}: 2200 (CN), 1740 (C=O). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε): 230 (3.90), 363 (4.36).

2-Cyano-4-(*m*-nitrobenzylidene)-3-methylthio-2-buten-4-olide (VIIIb)——A mixture of 1.4 g of II and 1.5 g of *m*-nitrobenzaldehyde was added to 10 ml of $POCl_3$ and refluxed for 2 hr. The mixture was treated as in the preparation of VIIIa. Recrystallization from acetone gave yellow needles, mp 240°, in 60% yield. *Anal.* Calcd. for $C_{13}H_8O_4N_2S$: C, 54.14; H, 2.80; N, 9.72. Found: C, 54.02; H, 2.80; N, 9.72. IR (KBr) cm^{-1}: 2220 (CN), 1755 (C=O). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε): 225, 263 (concentration is unknown because of insufficient solubility).

2-Carbamoyl-3-methylthio-4,4-bis(2-quinolyl)-2-buten-4-olide (X)——To a mixture of 0.3 g of quinoline 1-oxide and 20 ml of Ac_2O, 0.35 g of II was added dropwise with stirring and ice-cooling. The mixture was allowed to stand overnight at room temperature, was poured into ice water, and allowed to stand for 6 hr. The precipitates were collected by filtration and recrystallized from MeOH to give white crystals, mp 229°, in 60% yield. *Anal.* Calcd. for $C_{24}H_{17}O_3N_3S$: C, 67.44; H, 4.02; N, 9.83. Found: C, 67.65; H, 4.20; N, 9.51. IR (KBr) cm^{-1}: 3560, 3430 (NH), 1718, 1668 (C=O). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε): 234, 308, 319 (concentration is unknown because of insufficient solubility).

Reaction of VIa with Benzylamine——To a solution of 1.4 g of VIa in 50 ml of MeOH, 1.5 g of benzylamine was added and the mixture was heated under reflux for 30 min. After the solvent was evaporated, 100 ml of ice-water was added to its residue, solution was acidified with 10% HCl solution, and the resultant precipitate was collected by filtration. This precipitate was suspended in $CHCl_3$, insoluble solid was collected by filtration, and washed with $CHCl_3$. The organic filtrate was dried over Na_2SO_4, and evaporation of the solvent and addition of 5 ml of EtOH to the residue gave 0.8 g of VIIIa white crystals. The solid (1.3 g) undissolved in $CHCl_3$ was recrystallized from EtOH to give yellow plates, mp 205°, which was found to be IX. These results are shown in Table III.

2-Cyano-4-(N,N-dimethylaminomethylidene)-3-morpholino-2-buten-4-olide (VIIIb)——A solution of 1.4 g of VIa in 50 ml of MeOH and 0.3 g of morpholine was heated under reflux for 30 min. After the solvent was evaporated, 100 ml of ice water was added to its residue. The precipitates were collected by filtration and recrystallized from EtOH to give VIIIb in 70% yield. This result is shown in Table III.

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