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Reaction of 1-Nitro-2,2-bis(methylthio)ethylene. II.[1] Synthesis of 2-Hydroxyimino-3-methylthio-5-oxopyrroline Derivatives

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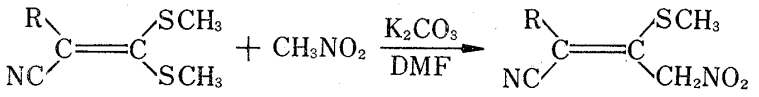
Methyl 1-cyano-2-methylthio-3-nitrocrotonate, 1-phenyl-2-methylthio-3-nitrocrotonitrile, and 1-cyano-2-methylthio-3-nitrocrotonamide, which contain cyano and nitro group at 1- and 3-position, were refluxed in MeOH or EtOH to give 2-hydroxy-3-methylthio-5-oxopyrroline derivatives, with ring closure between cyano and nitro group. The reaction of methyl 1-cyano-2-methylthio-3-nitrocrotonate with equimolar amount of amine gave methyl 2-hydroxy-3-amino-5-oxopyrroline-4-carboxylate which was replaced methylthio with amino group and with ring closure. However, with excess amine gave amine salt of nitro group, and also replaced with methylthio group. The reaction of pyrroline derivatives with active methylene compounds gave the corresponding substituted compounds.

In the previous paper[1] we reported the reaction of 1-nitro-2,2-bismethylthioethylene with various active methylene compounds, and the reaction was carried out in dimethyl sulfoxide (DMSO) or dimethyl formamide (DMF) with powdered sodium hydroxide. Under these conditions one methylthio group of 1-nitro-2,2-bismethylthioethylene was substituted with active methylene compound. It is commonyl known that nitro compounds are quite reactive. For example in acid solution a protonated nitro compound undergoes addition of nucleophiles such as halide[3] and hydroxide ion[4] and the nitro group becomes a nitroso in the product which occasionaly forms an isonitroso compound[5] or a dimer.[6] Michael addition[7] of cyclohexane-1,3-dione to ω-nitrostyrene, which produced an abnormal adduct, is one of the examples of intermolecular addition to nitro compound. The structure of this abnormal adduct was confirmed by X-ray crystallography to be 2-hydroxyimino-6,7-dihydro-3-phenyl-4(5H)-benzofuranone.[8] Nitro compounds are paticularly interesting in the reaction. Now we found that nitro compounds, 1-cyano-2-methylthio-3-nitrocrotonate derivatives (IIa, b) and 1-phenyl-2-methylthio-3-nitrocrotonate derivatives (IIa, b) and 1-phenyl-2-methylthio-3-nitrocrotonitrile (IIc), synthesized previously, which contain cyano and nitro group at 1- and 2- position, when refluxed in methanol or ethanol, give 2-hydroxyimino-3-methylthio-5-oxopyrroline derivatives (IIIa, b, c). In this paper, we report the structure of IIIa, b, c and the substitution reaction of methylthio group with amines and active methylene compounds.

1) Part I: G. Kobayashi, Y. Matsuda, R. Natsuki, Y. Tominaga, and M. Sone, *Yakugaku Zasshi*, **93**, 612 (1973).
2) Location: *1-14, Bunkyo-machi, Nagasaki, 852, Japan.*
3) W.E. Noland and R. Libers, *Tetrahedrone*, **19**, Suppl., 23 (1963).
4) E. Bamberger and E. Rust, *Chem. Ber.*, **35**, 45 (1902).
5) *a*) A. Hassner and J. Larkin, *J. Am. Chem. Soc.*, **85**, 2181 (1963); *b*) O. Piloty and H. Steinbock, *Chem. Ber.*, **35**, 3101 (1902); *c*) G. Casnati and A. Ricca, *Tetrahedron Letters*, **1967**, 327.
6) *a*) A.T. Nielsen, *J. Org. Chem.*, **27**, 1993, (1962); *b*) O. Piloty and H. Steinbock, *Chem. Ber.*, **35**, 3101 (1902).
7) H. Stetter and K. Hoehne, *Chem. Ber.*, **91**, 1344 (1958).
8) G.B. Ansell, D.W. Moore and A.T. Nielsen, *Chem. Commun.*, **1970**, 1602; *b*) S.J. Dominianni, M.O. Chaney and N.D. Jones, *Tetrahedron Letters*, **1970**, 4735.

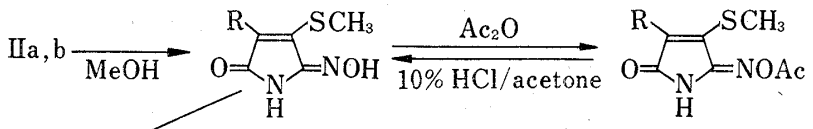
IIa and c were synthesized according to the previously described procedure. The reaction of nitromethane with 1-cyano-2,2-bis(methylthio)acrylate or 1-cyano-2,2-bis(methylthio)acrylamide in DMF in the presence of potassium carbonate gave IIa (mp 95—97°) or IIb in 85—90% yield. The melting point and infrared (IR) and ultraviolet (UV) spectra of IIa agreed completely with IIa synthesized by the previously described procedure. IIc did not crystallize, and it was confirmed by leading to IIIc by refluxing in ethanol. IIa was refluxed in methanol to give the yellow crystals (IIIa) in 50% yield. IIIa dissolved in aqueous 10% potassium carbonate. The molecular formula $C_7H_8O_4N_2S$ was given to IIIa from elemental analysis and mass spectrum (M^+, 216). IR spectrum of IIIa showed the presence of NH and OH, strong and broad absorptions at 3270 cm^{-1}, carbonyl absorptions at 1715 and 1695 cm^{-1}, and C=N- at 1661 cm^{-1} but the cyano absorption had disappeared. Nuclear magnetic resonance (NMR) spectrum of IIIa in CF_3COOH showed two singlets at 3.05 ppm (3H, s, $-SCH_3$) and 4.10 ppm (3H, s, $-COOCH_3$), and methylene signal had disappeared. In DMSO instead of CF_3COOH a broad singlet appeared at 11.45 ppm (2H, NH and OH). From these spectroscopic data and elemental analysis, this compound IIIa was found to be a cyclized product, methyl 2-hydroxyimino-3-methylthio-5-oxopyrroline-4-carboxylate. The structure of IIIa was confirmed by alkylation, hydrolysis and catalytic reduction.

Monoacetyl compound (IV) was formed from IIIa by refluxing in Ac_2O or under Schotten-Baumann condition with Ac_2O. IV came out as yellow crystals and its IR spectrum showed a new band at 1786 cm^{-1} for carbonyl in the acetoxy group and NH absorption at 3220 cm^{-1}.



Ia : R=—$COOCH_3$
Ib : R=—$CONH_2$

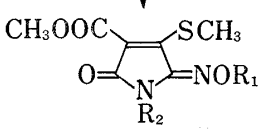
IIa : R=—$COOCH_3$
IIb : R=—$CONH_2$
IIc : R=—C$_6$H$_5$



IV : R=—$COOCH_3$

IIIa : R=—$COOCH_3$
IIIb : R=—$CONH_2$
IIIc : R=—C$_6$H$_5$

RX



V	a	b	c	d	e	f
R_1	CH_3	Ts	Ms	$CH_2C_6H_5$	$CH_2C_6H_5$	CH_2COOEt
R_2	CH_3	H	H	H	$CH_2C_6H_5$	H

Ts : p-$CH_3 \cdot C_6H_4 \cdot SO_2$—
Ms : CH_3SO_2—

Va—f

Chart 1

TABLE I

	Yield (%)	R	Formula	Analysis (%) Calcd. (Found) C	H	N	NMR ppm (TFAA)	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} mμ (log ε)
IIb	85	$CONH_2$	$C_6H_7O_3N_3S$	35.83 (35.94)	3.51 (3.52)	20.89 (18.82)	—	NH 3490, 3380 CN 2215 CO 1660	323 (4.07)
IIIa	50	$COOCH_3$	$C_7H_8O_4N_2S$	38.89 (39.00)	3.73 (3.82)	12.96 (12.94)	OCH_3 4.10 SCH_3 3.05	OH NH 3270 C=N 1661 CO 1715, 1695	359[a]
IIIb	51	$CONH_2$	$C_6H_7O_3N_3S$	35.83 (35.73)	3.51 (3.70)	20.89 (20.40)	—	NH 3500, 3360 OH 3250 CO 1710	362 (4.13)
IIIc	58		$C_{11}H_{10}O_2N_2S$	56.41 (56.40)	4.30 (4.42)	11.96 (11.44)	—	NH 3430 OH 3250 CO 1680, 1650	246 (3.89) 306 (4.03)
IV	85	$COOCH_3$	$C_9H_{10}O_5N_2S$	41.86 (42.07)	3.90 (4.01)	10.85 (9.80)	OCH_3 4.05 SCH_3 2.98 $COCH_3$ 2.42	NH 3220 CO 1786, 1717, 1676	310 (4.04)

a) Concentration is unknown because of being insoluble.

This indicated that the acetyl group was attached to a hydroxyl group. Mono- or di- alkylated compounds (IVa—f) were similarly obtained from IIIa by treating with alkylating reagents such as dimethyl sulfate, benzyl chloride, *etc.*, under the Schotten-Baumann condition in DMF or pyridine. It seemed that alkylation reaction proceeded similarly to acylation, so that the monoalkyl group must be attached to the hydroxyimino group. IR spectra of Vb, c, d, f showed NH absorption at about 3200 cm^{-1}. Hydrolysis of Vf with an acid, which will be described later, proved distinctly because hydroxyimino group being attached with alkyl group was hydrolyzed. Their IR, UV, and NMR spectra are summarized in Table I.

Hydrolysis of IV with 10% HCl in acetone gave IIIa which was recovered in a satisfactory yield. Hydrolysis of IIIa with 6N HCl in methylcellosolve refluxing for about 15 min gave methyl 3-methylthio-2,5-dioxopyrroline-4-carboxylate(VI). The same product VI was obtained by hydrolysis of Vf with 6N HCl. IR spectrum of VI showed a carbonyl bands at 1755, 1718, and 1670 cm^{-1} and NH band at 3230 and 3080 cm^{-1}. On the other hand hydrolysis of IIIa with aqueous 10% NaOH solution at room temperature gave 2-hydroxyimino-3-methylthio-5-oxopyrroline-4-carboxylic acid (VII).

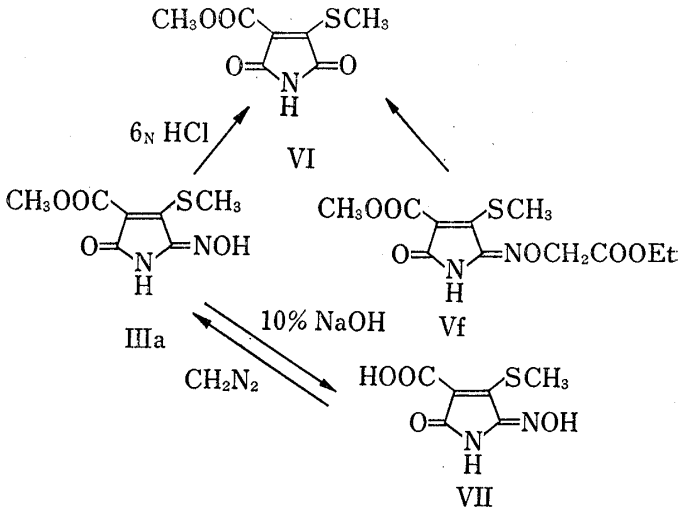


Chart 2

Alkylation of VII with diazomethane in ether gave IIIa. A. Foucaud, *et al.*[9] reported that 3,3-disubstituted 2-hydroxyimino-4-cyano-5-pyrrolidinone was hydrolyzed with sodium hydroxide solution to 3,3-disubstituted 2-hydroxyimino-5-pyrrolidinone-4-carboxylic acid, only the cyano group being hydrolyzed and that 3,3-disubstituted 1-hydroxy-2-imino-5-pyrrolidinone was changed to 3,3-disubstituted 2-hydroxyimino-5-pyrrotidinone by sodium hydroxide. This indicated that hydroxy group of IIIa was attached to imino group which was 2- position of IIIa.

Next, we examined the substituted reaction of amines and active methylene compounds with methylthio group of IIa, IIIa, and V.

The reaction of IIa with equimolar amount of an amine gave pyrroline derivatives (VIIIa—f) in which methylthio group was replaced with amino group with simultaneous ring closure. The reaction of IIIa with excess amine also gave VIII. These two products showed no depression of mp in admixture and their IR and UV spectra were identical. Reaction of IIa with excess benzylamine gave benzylamine salt of nitro group (IX) in which the methylthio group was also replaced with amine. IX was treated with 98% HCOOH at 100° and gave VIII in low yield. Type of compound V also gave substituted X when treated with an amine in methanol. Physical constants are summarized in Table II and III.

Reaction of Va with active methylene compound such as malononitrile, ethyl cyanoacetate, *etc.*, gave ordinary substituted compound XIa—c, and ethyl pyridine-2-acetate and 3,4-dihy-

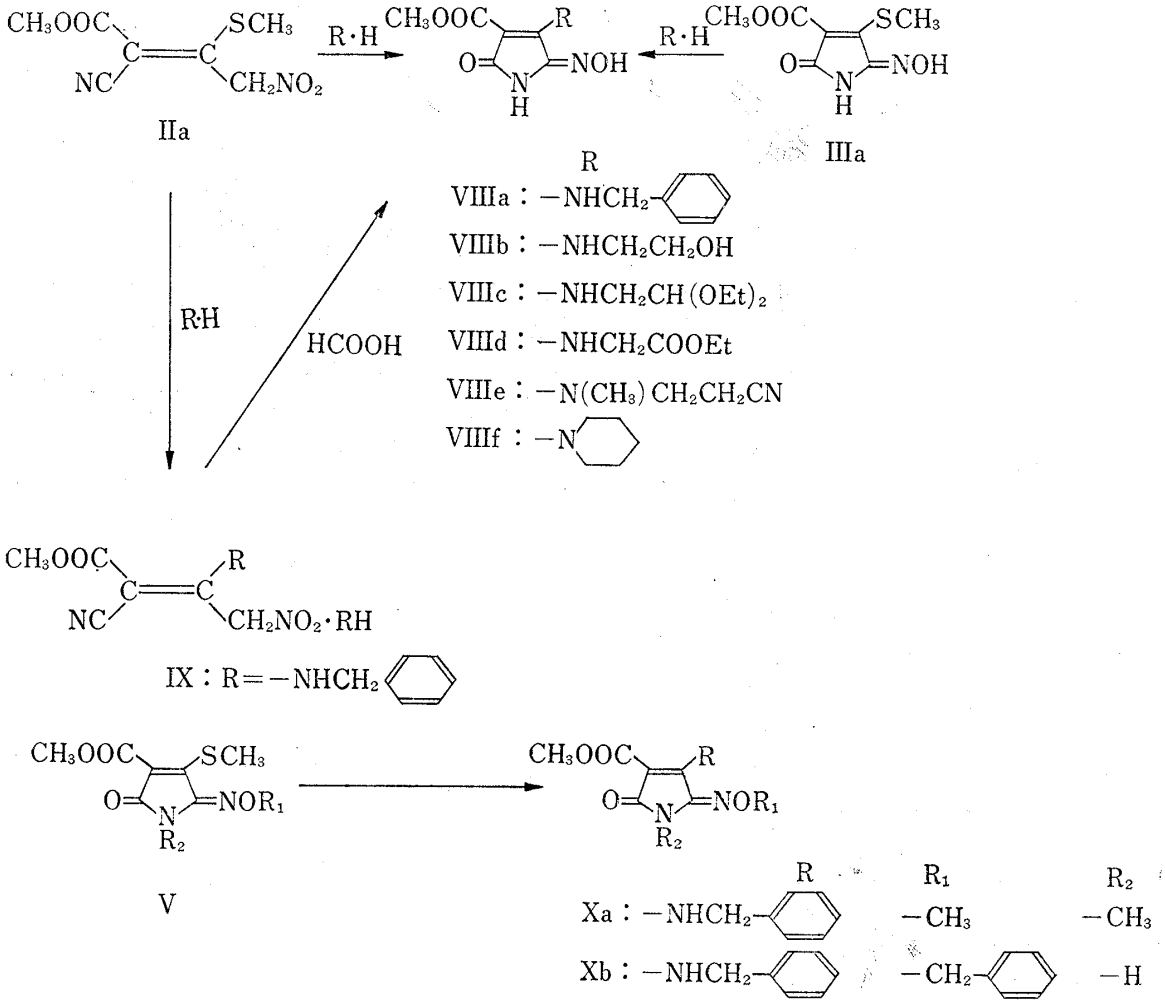


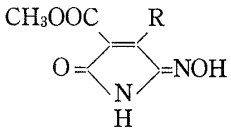
Chart 3

9) A. Foucaud and C. Gadreau, *Bull. Soc. Chim. France*, **1966**, 995.

droisoquinoline-1-acetonotrile gave XII and XIII respectively, in which the methylthio group of Va was substituted with an active methylene compound and an ester of Va cyclized with nitrogene of pyridine or isoquinoline.

Catalytic reduction of Xa in ethanol over Pd-C gave methyl 2-imino-3-dicyanomethyl-5-oxopyrroline-4-carboxylate (XIV), absorbing one molar equivalent of hydrogen. IR spe-

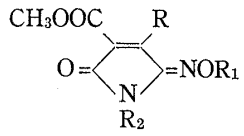
TABLE II.



	R	mp	Formula	Analysis (%) Calcd. (Found) C	H	N	IR (KBr) (cm^{-1})	UV λ_{max}^{EtOH} mμ (log ε)
VIIIa	-NHCH$_2$-⟨⟩	255	$C_{13}H_{13}O_4N_3$	56.72 (56.83)	4.76 (4.98)	15.27 (14.84)	NH 3360, 3240; CO 1711, 1660	365 (4.31)
VIIIb	-NHCH$_2$CH$_2$OH	232	$C_8H_{11}O_5N_3$	41.92 (42.20)	4.84 (5.03)	18.34 (17.67)	NH 3360; OH 3500, 3220; CO 1718, 1653	359 (4.09)
VIIIc	-NHCH$_2$CH(OEt)$_2$	222—223	$C_{12}H_{19}O_6N_3$	47.83 (47.28)	6.36 (6.37)	13.95 (13.43)	NH 3280; CO 1713, 1673	363[a]
VIIId	-NHCH$_2$CO$_2$Et	244—245	$C_{10}H_{13}O_6N_3$	44.28 (44.67)	4.83 (5.00)	15.49 (14.67)	NH 3310; CO 1712, 1670	356 (4.17)
VIIIe	CH$_3$ | -NCH$_2$CH$_2$CN	219—220	$C_{10}H_{12}O_4N_4$	47.62 (47.56)	4.80 (5.01)	22.22 (21.40)	NH 3210; CN 2233; CO 1695	357 (4.09)
VIIIf	-N⟨ ⟩O	247—248	$C_{10}H_{13}O_5N_3$	47.06 (46.93)	5.13 (5.27)	16.47 (16.46)	NH 3260; CO 1712, 1680	374 (4.03)
IX	-NHCH$_2$-⟨⟩	127.5—128.5	$C_{20}H_{22}O_4N_4$	62.81 (63.03)	5.80 (6.00)	14.65 (14.27)	NH 3345; CN 2200; CO 1650	312 (4.43), 378 (4.55)

a) Concentration is unknown because of being insoluble.

TABLE III.



	R	R_1	R_2	mp (°C)	Formula	Analysis (%) Calcd. (Forund) C	H	N	IR (KBr) (cm^{-1})	UV λ_{max}^{EtOH} mμ (log ε)
Xa	NHCH$_2$-⟨⟩	CH$_3$	CH$_3$	111—113	$C_{15}H_{17}O_4N_3$	59.39 (59.43)	5.65 (5.70)	13.86 (13.32)	NH 3360; CO 1704, 1658	347 (4.12), 243 (3.92)
Xb	NHCH$_2$-⟨⟩	CH$_2$-⟨⟩	H	139—140	$C_{20}H_{19}O_4N_3$	65.74 (66.05)	5.24 (5.63)	11.50 (10.32)	NH 3380, 3250; CO 1723, 1679	350 (4.01)

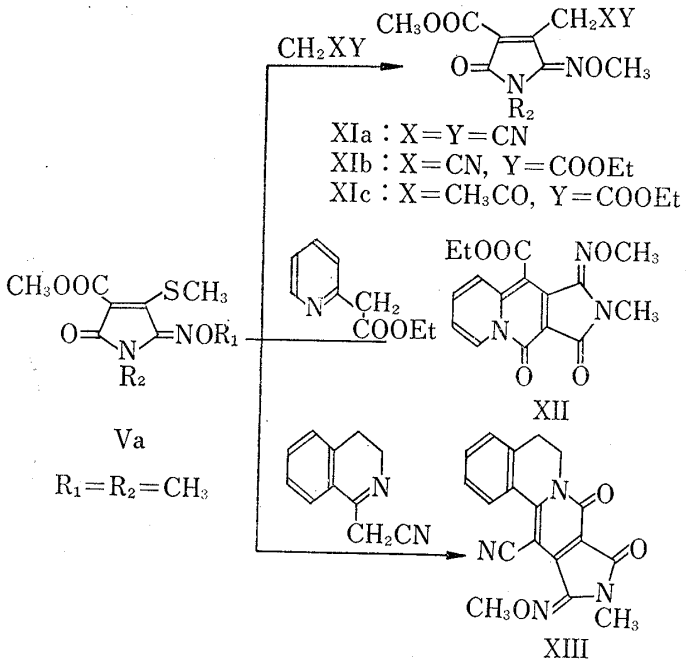


Chart 4

ctrum of XIV exhibited absorption of NH at 3360 cm^{-1}. Reduction of XII was carried out under a similar condition and the corresponding compound XV was formed. NMR spectrum of XII showed absorption of $-OCH_3$ at 4.10 ppm, but this absorption had disappeared in XV.

Hydrolysis of XII by refluxing in 50% H_2SO_4 at 120° gave XVI which was hydrolyzed of methoxyimino group and methoxycarbonyl group to decarboxylate. Hydrolysis of XII with 10% NaOH in methanol gave XVII which was only hydrolyzed methoxycarbonyl group to free carboxylic acid.

Table IV

	Yield (%)	X	Y	Formula	Analysis (%) Calcd. (Found) C	H	N	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} mμ (log ε)	NMR ppm ($CDCl_3$)
XIa	80	CN	CN	$C_{11}H_{10}O_4N_4$	50.38 (50.47)	3.84 (3.88)	21.37 (20.10)	C N 2200 C O 1742 1660	322 (3.80) 433 (4.33)	—
XIb	70	CN	COOEt	$C_{13}H_{15}O_6N_3$	50.48 (50.32)	4.89 (4.83)	13.59 (12.63)	C N 2219 C O 1755 1710 1655	322 (3.73) 440 (4.09)	CH 5.35 OCH_3 4.00 3.85 NCH_3 3.35
XIc	80	CH_3C(=O)	COOEt	$C_{14}H_{18}O_7N_2$	51.53 (51.67)	5.56 (5.48)	8.59 (7.82)	C O 1730 1710 1640	258 (4.10) 330 (4.05)	—
XII	75	—	—	$C_{16}H_{15}O_5N_3$	58.35 (58.46)	4.59 (4.82)	12.76 (12.22)	C O 1720 1700 1685	273 (4.09) 435 (4.28) 460 (4.43)	OCH_3 4.10 NCH_3 3.66
XIII	85	—	—	$C_{18}H_{14}O_3N_4$	64.66 (64.67)	4.22 (4.21)	16.76 (16.30)	C N 2219 C O 1720 1680	408 (4.32) 398 (4.30)	OCH_3 4.13 NCH_3 3.65

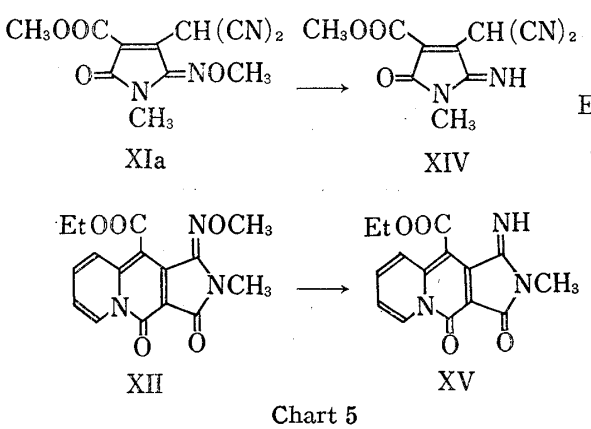


Chart 5

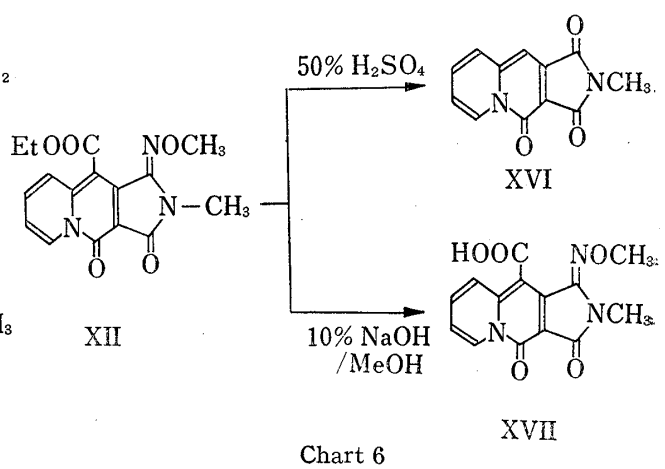


Chart 6

Experimental[10]

Methyl 1-Cyano-2-methylthio-3-nitrocrotonate (IIa)——To a solution of methyl 1-cyano-2,2-bis(methylthio)acrylate (50 g) and nitromethane (15 g) in DMF was added anhyd. K_2CO_3 (60 g). The mixture was stirred for 4 hr at room temperature. The reaction mixture turned reddish brown. Ice was added to the reaction mixture which was acidified with 10% HCl, the resulting precipitate was collected by filtration, and washed with H_2O. IIa was unstable when heated, so purification was performed at room temperature. IIa was dissolved in a small amount of acetone and petr. benzine was added slowly by which white crystals precipitated, mp 95—97°. The crude material was used for the next reaction. Color of IIa changed into reddish brown during storage but its purity did not chang.

1-Cyano-2-methylthio-3-nitrocrotonamide (IIb)——A solution of 1-cyano-2,2-bis(methylthio)acrylamide (0.1 mole), nitromethane (0.12 mole) and anhyd. K_2CO_3 (0.2 mole) in DMF was treated in a manner similar to IIa. IIb was also unstable when heated and its purification was performed at room temperature same as IIa, mp 132°.

1-Phenyl-2-methylthio-3-nitrocrotonitrile (IIc)——To a solution of phenylacetonitrile (0.012 mole) and 1-nitro-2,2-bis(methylthio)ethylene (0.01 mole) was added powdered NaOH (0.022 mole). The mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into ice water and acidified with 10% HCl and an oily product precipitated. This product was taken out by decantation and used for the next reaction.

Methyl 2-Hydroxyimino-3-methylthio-5-oxopyrroline-4-carboxylate (IIIa, b, c)——A solution of IIa (10 g) in MeOH (100 ml) was refluxed for 30 min. The reaction mixture turned reddish brown and after about 5 min, yellow crystals precipitated which were collected and washed with MeOH. Recrystallization of IIIa from methylcellosolve afforded a yellow powder, mp 268—270 (decomp.). IIIb,c were synthesized from IIb, c to treat samely as IIIa and condense the reaction mixture. IIIb and c were recrystallized from MeOH–iso-PrOH to yellow crystals; IIIb, mp 257° (decomp.) and IIIc, 228—230°.

Methyl 2-Acetoxyimino-3-methylthio-5-oxopyrroline-4-carboxylate (IV)——a) A solution of IIIa (0.3 g) in Ac_2O (10 ml) was refluxed for 6 hr and cooled. The yellow crystals that appeared were recrystallized from acetone to a yellow powder, mp 229—231° (decomp.), in 65% yield.

b) To a solution of IIIa (0.3 g) in 10% NaOH Ac_2O was added dropwise. The yellow crystals that appeared were collected, washed with H_2O, dried in vacuo, and recrystallized from acetone mp 229—230° (decomp.). These crystals were identical with the above compound IV.

Reaction of IIIa with Alkyl Reagents (Va—f)——a) Va: To a solution of IIIa (5 g) and 10% NaOH (20 ml) in DMSO (50 ml) was added dropwise 5 ml of Me_2SO_4 under stirring at 5°. After 1 hr, the reaction mixture was poured into ice-water, the resulting white precipitate was dissolved in benzene, washed two times with dil. NaOH solution, and then with water. Benzene solution was dried over anhyd. Na_2SO_4 and evaporated, the residue was recrystallized from petr. benzine to white needles, mp 71—73°, in 70% yield.

b) Vb: To a solution of IIIa (1 g) in pyridine (50 ml), TsCl (1.1 g) was added under ice cooling. The reaction mixture was allowed to stand for 1 day and poured into ice–water. The resulting crystals were collected and recrystallized from MeOH to yellow crystals, mp 198—200°, in 20% yield. Crystals insoluble in MeOH were the parent compound IIIa (0.4 g).

c) Vc: To a suspension of NaH (0.012 mole) in DMF IIIa (0.01 mole) was added under ice cooling. $MeSO_2Cl$ (0.012 mole) was added to the reaction mixture and stirred at room temperature for 1 hr. The mixture was poured into ice–water, the resulting precipitate was collected, dried *in vacuo*, and recrystallized from MeOH–iso-PrOH to yellow crystals, mp 206°, in 20% yield.

d) Vd and Ve: Alkylation of IIIa made use of C_6H_5Cl. The reaction was similar to c). The reaction mixture was poured into ice–water, a little 10% NaOH was added to this mixture and the resulting presipitate Ve was recrystallized from petr. benzine, mp 111—113°, in 25% yield. The filtrate was acidified with 10% HCl, Vd precipitated, which was recrystallized from benzene to pale yellow needles, mp 175—177°, in 30% yield.

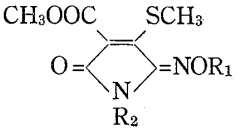
e) Vf: Alkylation of IIIa made use of ethyl α-bromoacetate. The reaction manner was similar to c). Vf was recrystallized from EtOH to white needles, mp 166—167°, in 72% yield. IR, UV, and NMR spectra of Va—f are summarized in Table V.

Hydrolysis of IV: IV (0.3 g) was dissolved in acetone (50 ml) and 10% HCl (1 ml) was added, and refluxed on a boiling water bath for 20 min. After about 5 min, yellow crystals (IIIa) began to precipitate, which were recrystallized from Methylcellosolve. This melting point and its IR and UV spectra agreed with IIIa completly.

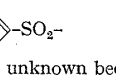
Hydrolysis of IIIa and Vf——a) IIIa with 6N HCl: A solution of IIIa (1 g) and 6N HCl (10 ml) in methylcellosolve (80 ml) was refluxed for 15 min and the solvent was evaporated to dryness. The residue

10) All melting point are uncorrected. IR spectra were measured with Nihon Bunko Mode DS-301 spectrophotometer. NMR spectra were measured with a Hitachi H 60 spectrometer operating at 60 MHz, using tetramethylsilane as an internal standard.

TABLE V.



	R_1	R_2	Formula	Analysis (%) Calcd. (Found) C	H	N	NMR ppm (TFAA)		IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} mμ (log ε)
Va	CH_3	CH_3	$C_9H_{12}O_4N_2S$	44.26 (44.67)	4.95 (5.13)	11.47 (11.14)	OCH_3	4.30	C O 1705	340 (4.07)
								4.12	1690	
							NCH_3	3.70		
							SCH_3	3.10		
Vb	Ts[a]	H	$C_{14}H_{14}O_6N_2S_2$	45.41 (45.39)	3.81 (3.65)	7.57 (7.66)	—		N H 3300	226[b]
									C O 1740	302[b]
									1700	365[b]
Vc	Ms[c]	H	$C_8H_{10}O_6N_2S_2$	31.17 (31.84)	3.57 (3.34)	9.09 (8.62)	OCH_3	4.10	N H 3260	302 (4.01)
							SO_2CH_3	3.40	C O 1727	360 (3.91)
							SCH_3	2.95	1683	
Vd	CH_2-C_6H_5	H	$C_{14}H_{14}O_4N_2S$	54.90 (54.71)	4.61 (4.59)	9.15 (8.81)	$-CH_2-$	5.41	N H 3220	364 (4.23)
							OCH_3	4.11	C O 1720	
							SCH_3	3.10	1688	
Ve	CH_2-C_6H_5	CH_2-C_6H_5	$C_{21}H_{20}O_4N_2S$	63.63 (63.00)	5.09 (4.87)	7.07 (7.01)	Ⓓ[d] $-CH_2-$	5.05	C O 1706	340 (4.18)
								5.12	1691	
							OCH_3	3.90		
							SCH_3	2.79		
Vf	CH_2COOEt	H	$C_{11}H_{14}O_6N_2S$	43.71 (43.73)	4.67 (4.47)	9.27 (8.63)	OCH_3	3.80	N H 3205	360 (4.12)
							SCH_3	2.88	C O 1735	
									1720	

a) Ts: CH_3-  -SO_2-

b) Concentration is unknown because of being insoluble.
c) Ms: CH_3SO_2-
d) D: $CDCl_3$

was washed with a little water and dried *in vacuo*. VI was obtained in 40% yield, which was recrystallized from iso-PrOH to yellow crystals, mp 196.5—197.5°. *Anal.* Calcd. for $C_7H_7O_4NS$: C, 41.80; H, 3.51; N, 6.96. Found: C, 41.78; H, 3.43; N, 6.40. IR (KBr cm^{-1}); 3080, 3230; NH, 1755, 1718, 1670; C=O. UV λ_{max}^{EtOH} nm(log ε): 265 (4.84), 375 (4.79).

b) Vf with 6N HCl: A solution of Vf (0.7 g) in 6N HCl (9 ml) was boiled. Crystals easily dissolved and about 5 min later, yellow crystals appeared and then the mixture was cooled instantly to avoid futher heating. The resulting precipitate was collected, dried *in vacuo*, and recrystallized from iso-PrOH, mp 196—198°. Yield, 0.2 g of VI. The melting point and IR and UV spectra of this compound were completely agreed with those of VI.

c) IIIa with 10% NaOH: IIIa (1 g) was dissolved in 12 ml of 10% NaOH and 40 ml of water and the solution was stirred for 13 hr. This mixture was acidified with 10% HCl. The resulting precipitate (VII) was collected, dried *in vacuo*, and recrystallized from iso-PrOH, mp 227—228°, in 60% yield. *Anal.* Calcd. for $C_6H_6O_4N_2S$: C, 35.65; H, 2.99; N, 13.86. Found: C, 35.79; H, 3.03; N, 13.64. IR (KBr cm^{-1}); 3200 (broad); NH, 1722; C=O. UV λ_{max}^{EtOH} nm(log ε); 340 (4.08).

Methylation of VII with Diazomethane: VII (0.5 g) was dissolved in ether and CH_2N_2 was passed and yellow crystals appeared instantly. The precipitate was collected and recrystalized from methylcellosolve to yellow powder, mp 268° (decomp.), in 54% yield, which was identical with IIIa.

General Procedure for Methyl 2-Hydroxyimino-3-amino-5-oxopyrroline-4-carboxylate (VIIIa—f)——IIa and equimolar amount of the amine was refluxed in MeOH for 30 min. The color of the reaction mixture turened to reddish brown and then yellow crystals appeared, which were collected, washed with MeOH and recrystallized from methylcellosolve or MeOH–iso-PrOH. Details of the data are summarized in Table II.

Reaction of IIIa with Morpholine——IIIa and morpholine was refluxed in EtOH for 8 hr. EtOH was evaporated and the recidue was recrystallized from methylcellosolve to yellow powder, mp 246—247°. This melting point and its IR and UV spectra were identical with those of Ve.

Reaction of IIa with Excess Benzylamine——A solution of IIa (0.5 g) and 1 ml of benzylamine in 30 ml of MeOH was stirred at room temperature for 4 hr, crystals (IX) that precipitate were collected by filtration and recrystalized from EtOH to white crystals, mp 127.5—128.5°, in 80% yield.

Reaction of IX with HCOOH: IX (0.5 g) and 10 ml of 98% HCOOH were heated in a boiling water-bath for 5 hr. HCOOH was evaporated to dryness and the residue was washed with water, dried *in vacuo*, and recrystallized from methylcellosolve, mp 251—253° (decomp.). This melting point and its IR and UV spectra were identical with those of VIIa.

Reaction of Va, c with Amines: A solution of V (0.02 mole) and amines (0.024 mole) in MeOH was refluxed for 1.5—2 hr. MeOH was evaporated, ice-water was added to the residue, and 10% HCl was added to remove excess amine. Resulting precipitate (Xa—c) was collected, dried, and recrystallized from petr. benzine. Details are summarized in Table III.

Reaction of Va with Active Methylene Compounds: a) To a solution of Va (0.02 mole) and active methylene compounds (0.024 mole) in DMF anhyd. K_2CO_3 (0.04 mole) was added. The reaction mixture was heated on a boiling water bath for 4—6 hr and poured into ice-water. The solution was acidified with 10% HCl, the resulting precipitate was collected, washed with water, and dried *in vacuo*. XIa was recrystallized from acetone, mp 210—212°, XIb from petr. benzine, mp 116—118°, XII from acetone, mp 198—200°, XIII from acetone and $CHCl_3$, mp 291—292°.

b) To a solution of Va (0.02 mole) and ethyl acetoacetate (0.024 mole) in DMF anhyd. K_2CO_3 (0.04 mole) was added. The reaction mixture was stirred at room temperature for 12 hr, and treated in a similar manner as in a). Recrystallization from hexane gave white needles, mp 116—117.5°.

Catalytic Reduction of XIa and XII: A solution of XIa or XII (0.5 g) in EtOH was shaken in H_2 stream over 5% Pd-C (0.5 g). The reaction stopped after absorption of calc. 1 mole of H_2. The catalyst was filtered off, the solvent was evaporated, and the residue was recrystallized from acetone (XIV), mp 290° (decomp.), or from EtOH (XV), mp 211—213°, in 80% yield. *Anal.* Calcd. for $C_{10}H_8O_3N_4$ (XIV): C, 51.72; H, 3.47; N, 24.13. Found: C, 51.61; H, 3.62; N, 21.91. IR (KBr cm^{-1}): 2208; C≡N, 1750, 1650; C=O. UV λ_{max}^{EtOH} nm (insoluble): 267, 453. *Anal.* Calcd. for $C_{15}H_{13}O_4N_3$ (XV): C, 60.30; H, 4.38; N, 14.04. Found: C, 60.30; H, 4.43; N, 13.74. IR (KBr cm^{-1}): 1734 (shoulder), 1705, 1675; C=O. UV λ_{max}^{EtOH} nm(log ε); 265 (4.19), 450 (4.34). NMR ($CDCl_3$) ppm: 1.52 (–CCH_3, t), 3.40 (–SCH_3, s), 4.62 (–OCH_2–, q).

Hydrolysis of XII: a) XII with 50% H_2SO_4: A solution of XII (0.5 g) in 50% H_2SO_4 was refluxed at 120° for 1.5 hr. The solution was poured into ice-water. Resulting precipitate was filtered, washed with water, and dried. Recrystallization from methylcellosolve gave orange crystals, mp 290°. *Anal.* Calcd. for $C_{12}H_8O_3N_2$; C, 63.16; H, 3.58; N, 12.28. Found: C, 63.04; H, 3.49; N, 12.64. IR (KBr cm^{-1}): 1754, 1700, 1660; C=O. UV λ_{max}^{EtOH} nm (insoluble): 232, 310, 460.

b) XII with 10% NaOH in MeOH (10 ml) was refluxed for 3.5 hr. Solvents were evaporated, the residue was dissolved in water and acidified with 10% HCl. The resulting precipitate was collected and recrystallized from dioxan, mp 264—266° (decomp.). *Anal.* Calcd. for $C_{14}H_{11}O_5N_3$; C, 55.81; H, 3.68; N, 13.95. Found: C, 55.96; H, 3.67; N, 12.98. IR (KBr cm^{-1}): 3440; NH, 1720, 1672; C=O. UV λ_{max}^{EtOH} nm (insoluble); 272.5, 467.

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