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Synthesis of Pyrazolone Derivatives. XIV.[1] Synthesis of 3-Mercaptomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one Derivatives[2]

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For pharmacological evaluation of new improved antipyretic and analgesic agents, several kinds of 3-mercaptomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one derivatives were synthesized.

The reaction between 2,4-dimethyl-3-mercaptomethyl-1-phenyl-3-pyrazolin-5-one (I) and 2-nitrochlorobenzene (XVIII) in the presence of sodium ethoxide under cooling with ice gave bis(2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)-*trans*-ethylene (XXIV) and 2-nitrobenzenethiol (XXVII) in addition to the objective compound (XXI).

The same reaction under reflux afforded 2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-carboxylic acid (XXX) and bis(2-nitrophenyl) sulfide (XXXII) as by-products. These by-products were proved to be formed by the splitting of XXI in the presence of sodium ethoxide.

The improved synthesis was effected by using dimethylformamide as an aprotic solvent without the formation of undesirable substances.

The authors have synthesized sulfur-containing pyrazolone derivatives for pharmacological evaluation of new improved antipyretic and analgesic agents, and the synthesis of 4-substituted-3-mercaptomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one[4] (I,II) was reported previously. In the present paper the synthesis of 3-mercaptomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one derivatives and the by-products formed by cleavage of sulfur-containing ylide-type pyrazolone derivatives are described.

As shown in Chart 1, condensation of I or II with aliphatic halogen compounds such as ethyl chloroacetate, ethyl bromide, and allyl bromide was carried out in the presence of sodium ethoxide in absolute ethanol to form the corresponding ethyl (4-substituted-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methylthioacetate (III, IV) and 3-substitutedthiomethyl-4-substituted-2-methyl-1-phenyl-3-pyrazolin-5-one (V, VI, VII). Then, III and IV were hydrolysed with ethanolic potassium hydroxide to (4-substituted-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methylthioacetic acids (VIII, IX), which were derived to the corresponding acid chlorides

1) Part XIII: I. Ito and S. Nagai, *Chem. Pharm. Bull.* (Tokyo), **17**, 490 (1969).
2) This work was presented at the 88th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1968.
3) Location: *Tanabe-dori, Mizuho-ku, Nagoya.*
4) I. Ito and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **14**, 1237 (1966).

(X, XI) with thionyl chloride, and reacted with methanol, isopropanol, isobutanol, and dimethylaminoethanol to give the corresponding esters (XII, XIII, XIV, XV).

Conversion of III or IV to (4-substituted-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)-methylthioacetohydrazide (XVI, XVII) was effected with 80% hydrazine hydrate in 75% yield.

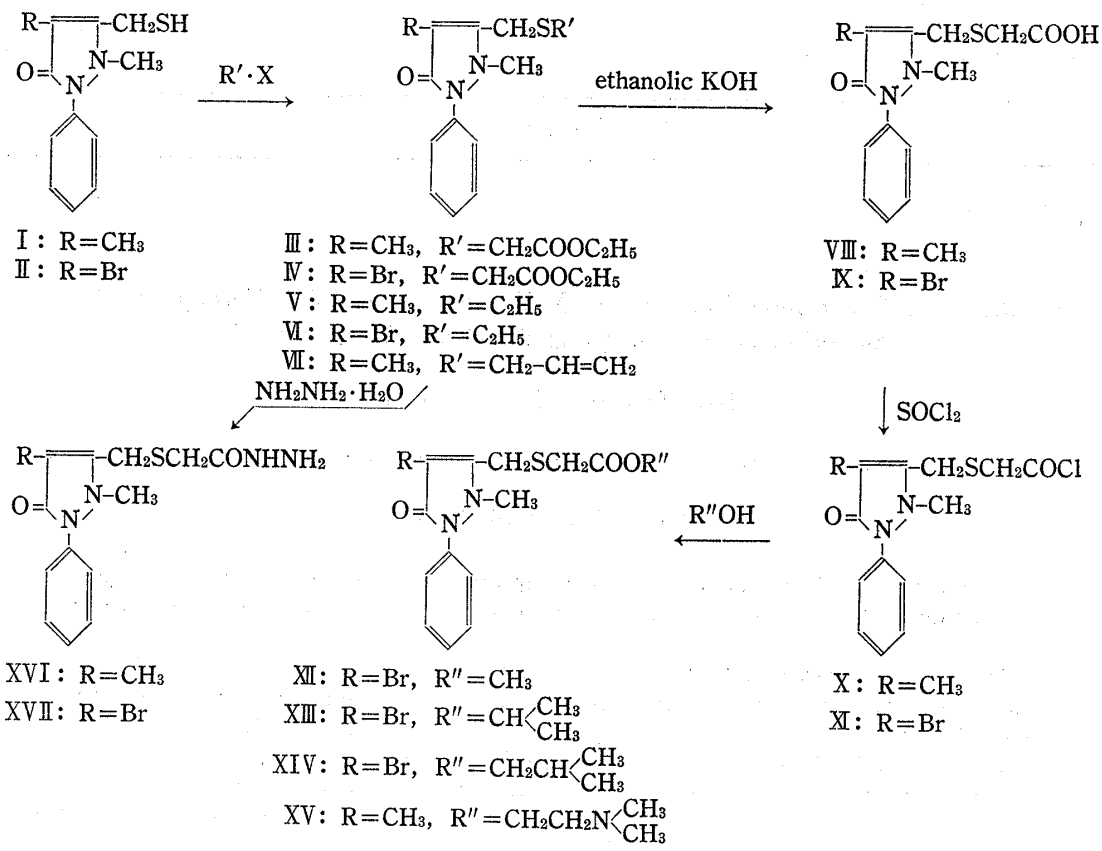


Chart 1

On the other hand, the reaction between I and aromatic halogen compound such as 2-nitrochlorobenzene (XVIII) as listed on Chart 2, in the presence of sodium ethoxide in absolute ethanol and cooling with ice (0—5°) (method A) resulted in a poor yield of the objective 2-(2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methylthionitrobenzene (XXI), and unexpected 2-nitrobenzenethiol (XXVII) and a trace of yellow needles (XXIV) of mp 245—246° were isolated. XXVII was converted into the corresponding bis(2-nitrophenyl) disulfide[5] and was identified with the authentic sample.

XXIV did not contain sulfur or halogen atom in its molecule. Its infrared (IR) spectrum, elemental analysis, and high melting point suggested a bispyrazolone structure. Its ultraviolet (UV) absorption maximum at 318 mμ indicated the presence of a conjugated double bond. Therefore, it was hydrogenated over Raney nickel to colorless prisms (XXV) of mp 214—215°, whose absorption maximum at 278 mμ was in a considerably shorter wave length and of lower intensity than that of XXIV.

XXV was identified with the sample synthesized by the Ullmann reaction from 3-bromomethyl-2,4-dimethyl-1-phenyl-3-pyrazolin-5-one[6] (XXVI). These experiments confirmed XXV to be bis(2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)ethane, and XXIV must be bis(2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)-*trans*-ethylene. Considering of steric hin-

5) J.J. Blanksma, *Rec. Trav. Chim.*, **20**, 127 (1901); M.T. Bogert and A. Stull, "Organic Syntheses," Coll. Vol. I, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, N.Y., 1956, p. 220.
6) Höchst Farbwerke, Ger. Patent 206637 (1907) [*Chem. Zntr.*, **80**, 806 (1906)].

drance only the *trans* isomer will have a plane conjugated structure. The observation of the molecular model of XXIV supports this fact. Moreover, the absorption band at 990 cm^{-1} in the IR spectrum of XXIV suggests the trans form.[7]

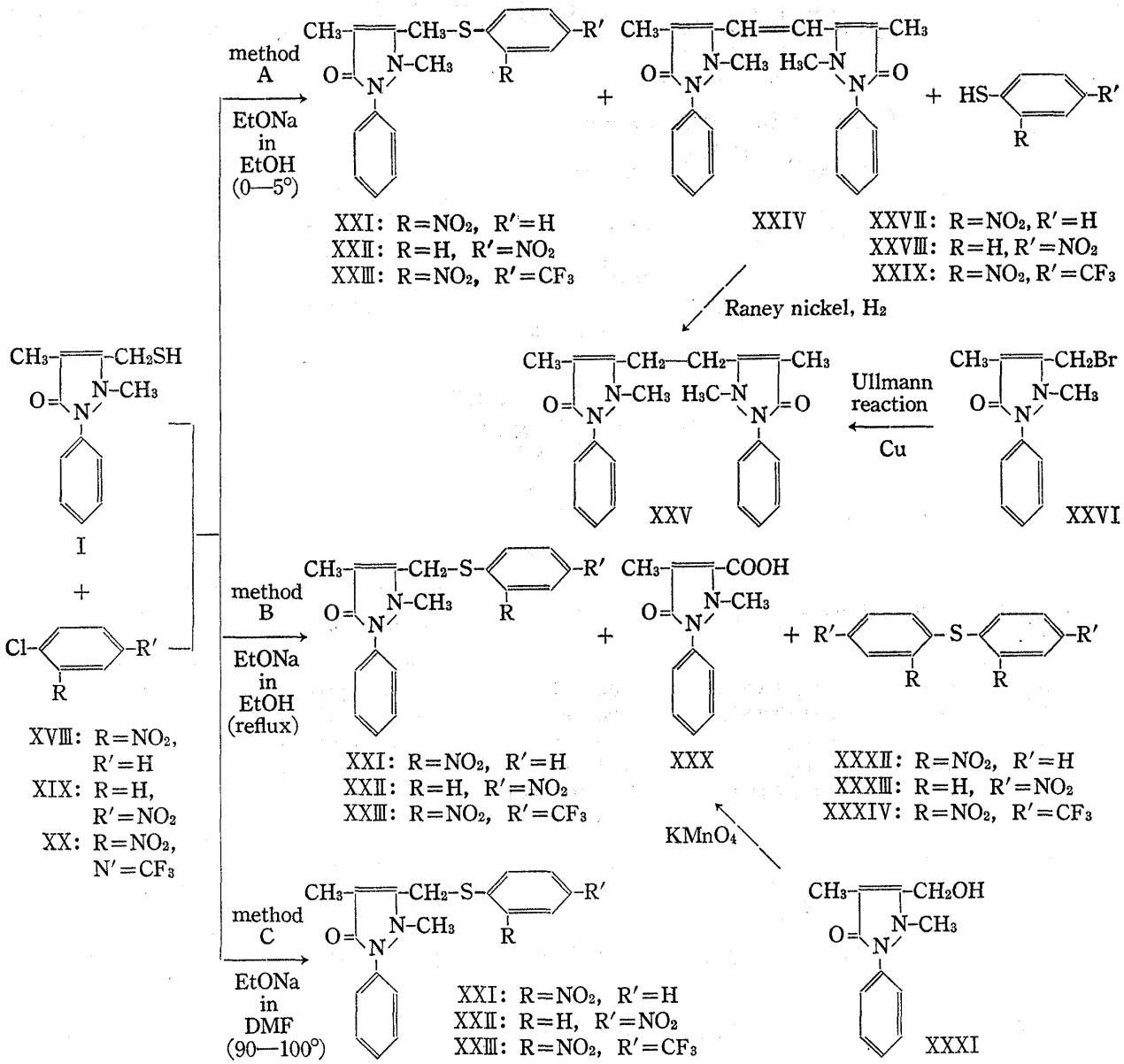
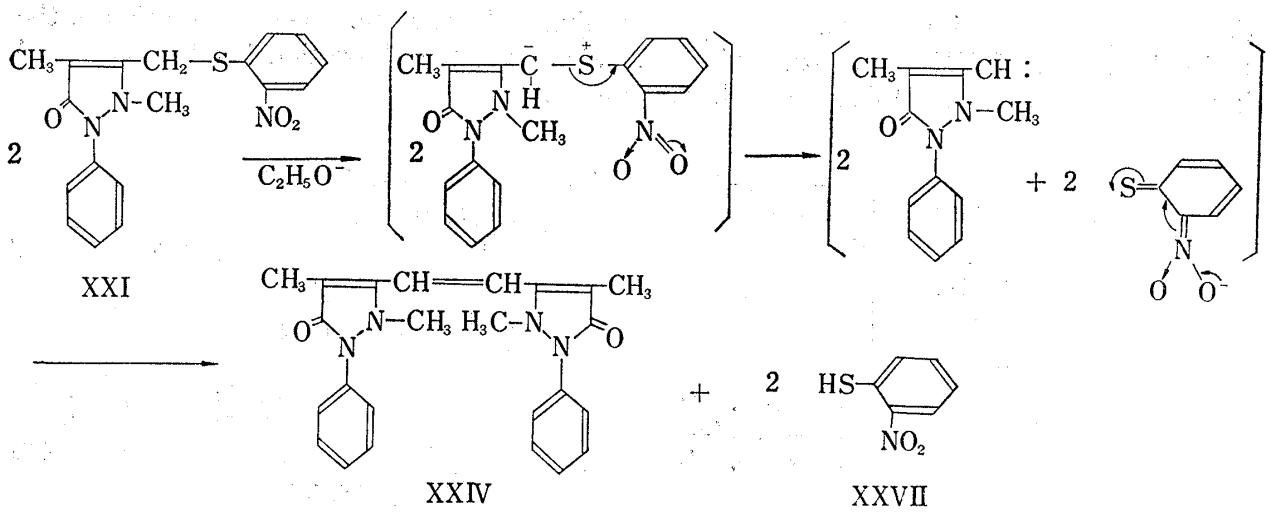


Chart 2

The same reaction under reflux (method B), however, gave colorless prisms (XXX) of mp 216—218° and bis(2-nitrophenyl)sulfide[8] (XXXII) in addition to the objective compound (XXI). XXX did not contain sulfur or halogen atom in the molecule. The strong absorption band at 1720 cm^{-1} and characteristic small absorption bands in the region of 3000—2500 cm^{-1} in its IR spectrum suggested a carboxylic acid, and XXX was identified with the sample prepared by the oxidation of 2,4-dimethyl-3-hydroxymethyl-1-phenyl-3-pyrazolin-5-one[6] (XXXI). Thus XXX was assigned as 2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-carboxylic acid.

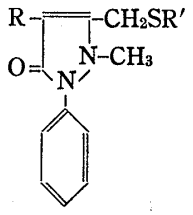
7) E.L. Eliel, "Stereochemistry of Carbon Compounds," ed. by Mcgraw-Hill Book Company, Inc., New York, 1962, p. 335.
8) R. Nietzk and H. Bothof, *Chem. Ber.*, **29**, 2774 (1896).

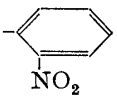
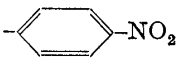
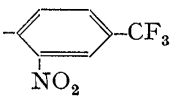


XXI XXIV XXVII

Chart 3

TABLE I.



Compd. No.	Substituents R	R′	mp (°C)	Appearance	Yield (%)
III	$-CH_3$	$-CH_2COOC_2H_5$	65—67	colorless prisms	80
IV	–Br	$-CH_2COOC_2H_5$	94—95	colorless prisms	80
V	$-CH_3$	$-C_2H_5$	55—56	colorless prisms	80
VI	–Br	$-C_2H_5$	103—105	colorless prisms	80
VII	$-CH_3$	$-CH_2-CH=CH_2$	bp 140—145 (4 mmHg)	pale yellow oil	80
XXI	$-CH_3$		165—166	yellow prisms	method A 50 method B 50 method C 80
XXII	$-CH_3$		172—174	yellow prisms	method A 50 method B 50 method C 80
XXIII	$-CH_3$		169—171	yellow prisms	method A 50 method B 50 method C 80

Compd. No.	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
III	$C_{16}H_{20}O_3N_2S$	59.99	6.29	8.75	59.76	5.93	9.01
IV	$C_{15}H_{17}O_3N_2SBr$	46.75	4.42	7.27	47.03	4.50	7.48
V	$C_{14}H_{18}ON_2S$	64.10	6.92	10.68	64.05	6.87	10.42
VI	$C_{13}H_{15}ON_2SBr$	47.71	4.59	8.56	47.94	5.06	8.54
VII	$C_{15}H_{18}ON_2S$	65.67	6.61	10.21	65.42	6.95	10.12
XXI	$C_{18}H_{17}O_3N_3S$	60.84	4.82	11.83	61.09	5.04	11.96
XXII	$C_{18}H_{17}O_3N_3S$	60.84	4.82	11.83	61.00	5.09	12.02
XXIII	$C_{19}H_{16}O_3N_3SF_3$	53.90	3.78	9.93	54.15	3.99	9.86

These by-products were also produced from XXI in the presence of sodium ethoxide in absolute ethanol. The mechanism of the formation of these by-products is assumed as shown in Chart 3.

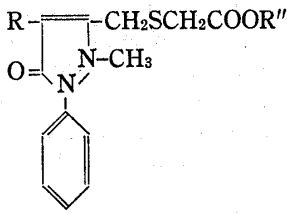
Because of the deficiency of electron density due to electron-attracting property of carbonyl in XXI, the methylene group is probably attacked and a proton is expelled by an ethoxide anion.

On the other hand, the strong electron-attracting property of the nitro group produces a positive charge on the sulfur atom, and this perhaps momentarily performs an ylide-type, which is decomposed to carbene and thiol. Two moles of carbene will afford ethylene. Trost[9] reported carbene mechanism by the decomposition of sulfur-ylide. Trippett[10] and Franzen, *et al.*[11] explained the stilbene synthesis by the carbene mechanism.

The improved procedure (method C) for the synthesis of XXI was investigated by using aprotic solvent such as dimethylformamide (DMF) instead of ethanol and 80% yield of XXI was obtained.

The reaction of I and 4-nitrochlorobenzene (XIX) or 2-nitro-4-trifluoromethyl-chlorobenzene (XX) was carried out similary by the above-mentioned methods (A, B, and C).

Table II.



Compd. No.	Substituents R	Substituents R''	mp (°C)	Appearance	Yield (%)
XII	-Br	$-CH_3$	139—140	colorless needles	80
XIII	-Br	$-CH<^{CH_3}_{CH_3}$	96—97	colorless needles	70
XIV	-Br	$-CH_2CH<^{CH_3}_{CH_3}$	77—78	colorless needles	70
XV	$-CH_3$	$-CH_2CH_2N<^{CH_3}_{CH_3}$	bp 190—195 (0.2 mmHg)	pale yellow oil	60

Compd. No.	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XII	$C_{14}H_{15}O_3N_2SBr$	45.28	4.04	7.55	44.81	4.33	7.77
XIII	$C_{16}H_{19}O_3N_2SBr$	48.12	4.76	7.02	48.33	5.08	7.50
XIV	$C_{17}H_{21}O_3N_2SBr$	49.39	5.08	6.78	49.11	5.29	7.18
XV	$C_{18}H_{25}O_3N_3S$	59.49	6.93	11.56	59.30	6.54	11.84

9) B.M. Trost, *J. Am. Chem. Soc.*, **88**, 1587 (1966).
10) S. Trippett, *Proc. Chem. Soc.*, **1963**, 19.
11) V. Franzen, H.J. Schmidt, and C. Mertz, *Chem. Ber.*, **94**, 2942 (1961).

Experimental[12)]

Ethyl (4-Substituted-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methylthioacetate (III, IV) (Table I)——To a solution of 0.23 g of sodium in 10 ml of absolute ethanol, was added 0.01 mole of I or II in 10 ml of absolute ethanol, followed by 0.01 mole of ethyl chloroacetate, and the mixture was stood overnight at room temperature. The solvent was removed, the residue was poured into water, and extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated. The residue was recrystallized from ethanol.

3-Substitutedthiomethyl-4-substituted-2-methyl-1-phenyl-3-pyrazolin-5-one (V, VI, VII) (Table I)——To a solution of 0.23 g of sodium in 10 ml of absolute ethanol was added 0.01 mole of I or II in 10 ml of absolute ethanol, followed by 0.01 mole of ethyl bromide or allyl bromide, and the solution was treated similary as for III or IV.

(2,4-Dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methylthioacetic Acid (VIII)——A solution of 1.6 g (0.005 mole) of III dissolved in 5 ml of ethanolic potassium hydroxide was heated at 70° for 1 hr. The solvent was evaporated to dryness, water was added to the residue and filtered. The filtrate was neutralized with 15% sulfuric acid. The resulting precipitate was collected and recrystallized from ethanol to 1.24 g (85%) of colorless prisms, mp 178—180°. IR cm^{-1}: ν_{OH} 3000—2500, $\nu_{C=O}$ 1710 (KBr). *Anal.* Calcd. for $C_{14}H_{16}O_3N_2S$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.28; H, 5.30; N, 9.61.

(4-Bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methylthioacetic Acid (IX)——The same procedure as for VIII gave colorless prisms (from ethanol), mp 189—191°. IR cm^{-1}: ν_{OH} 3000—2500, $\nu_{C=O}$ 1710 (KBr). *Anal.* Calcd. for $C_{13}H_{13}O_3N_2SBr$: C, 43.70; H, 3.64; N, 7.84. Found: C, 44.04; H, 3.91; N, 7.74.

Isobutyl (4-Bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methylthioacetate (XIV)——To 0.01 mole of IX in 20 ml of dry chloroform was added 0.02 mole of thionyl chloride with mechanical stirring. The mixture was warmed on a water bath for 1 hr. Distillation of chloroform left a crude acid chloride (XI) to which excess isobutanol was added and warmed on a water bath for 1 hr. After evaporation of the solvent, the residue was recrystallized from corresponding alcohol.

XII and XIII were similary prepared from XI and methanol or isopropanol, and their analytical data are summarized in Table II.

Dimethylaminoethyl (2,4-Dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methylthioacetate (XV)——To the acid chloride (X) prepared from 0.01 mole of VIII and 0.02 mole of thionyl chloride, excess dimethylaminoethanol in 10 ml of dry benzene was added under cooling with ice. The benzene layer was separated and evaporated, and the residue was subjected to distillation, bp 190—195° (0.2 mmHg).

This compound was also formed directly by refluxing a mixture of VIII (0.01 mole) and dimethylaminoethanol (0.02 mole) in xylene for 24 hr. Xylene was distilled and the residue was extracted with ether. The extract was dried over anhydrous sodium sulfate. By evaporation of ether and distillation of the residue, XV was obtained in 60% yield. Analytical data are summarized in Table II.

(2,4-Dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methylthioacetohydrazide (XVI)——A solution of 1.6 g (0.05 mole) of III dissolved in 10 ml of 80% hydrazine hydrate was stood overnight at room temperature. Resulting white crystals were collected by filtration, and recrystallized from ethanol to 1.15 g (75%) of colorless prisms, mp 166—167°. IR cm^{-1}: ν_{NH} 3300, 3220, 3080; $\nu_{C=O}$ 1675, 1630 (KBr). *Anal.* Calcd. for $C_{14}H_{18}O_2N_4S$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.85; H, 6.33; N, 18.44.

(4-Bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methylthioacetohydrazide (XVII)——The same procedure as for XVI gave colorless prisms (from ethanol), mp 156—158°. IR cm^{-1}: ν_{NH} 3280, 3220, 3060; $\nu_{C=O}$ 1680, 1640 (KBr). *Anal.* Calcd. for $C_{13}H_{15}O_2N_4SBr$: C, 42.05; H, 4.04; N, 15.09. Found: C, 42.01; H, 4.37; N, 15.03.

Reaction of I with 2-Nitrochlorobenzene——Method A. The Reaction under Cooled Condition (Sodium Ethoxide in Ethanol): To 0.01 mole of I dissolved in a solution of 0.23 g of sodium in 10 ml of absolute ethanol, 0.01 mole of 2-nitrochlorobenzene (XVIII) in 10 ml of absolute ethanol was added under cooling with ice (0—5°), and the mixture was stood overnight in nitrogen atmosphere. After the reaction, the solvent was distilled under reduced pressure, water was added to the residue, and extracted with chloroform, separated into the organic layer (fraction a) and an aqueous layer (fraction b).

Fraction a. Evaporation of the dried organic layer, left a yellow oil, which was washed with ether (fraction c) to give a crude 2-(2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methylthionitrobenzene (XXI). Recrystallization from ethanol afforded yellow prisms of mp 165—166° in 50% yield. IR cm^{-1}: ν_{NO_2} 1560, 1340, 860; $\nu_{C=O}$ 1650 (KBr). Analytical data are summarized in Table I.

Fraction b. The aqueous layer was acidified with 10% hydrochloric acid and extracted with chloroform. The extract was dried over anhydrous sodium sulfate and evaporated. The residual liquid solidified

12) All melting points were determined on a Yanagimoto Micro-Melting Point apparatus and are uncorrected. The ultraviolet absorption spectra were taken with a Hitachi Recording Spectrophotometer EPS-3T. The nuclear magnetic resonance (NMR) spectra were measured with a Varian A-60 Spectrophotometer in deuteriochloroform or dimethyl sulfoxide, and tetramethylsilane was used as an internal reference.

on standing. Recrystallization from ethanol gave yellow prisms, mp 192—193°, in 5% yield. This compound was identified as bis(2-nitrophenyl)disulfide from the comparison of IR spectra and mixed melting points with the authentic sample.

Fraction c. From the above-mentioned ether-soluble fraction, a trace of bis(2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)-*trans*-ethylene (XXIV) was obtained as pale yellow needles (from ethanol) of mp 246—247°. This compound showed negative Beilstein test and negative sulfur test. IR cm^{-1}: $\nu_{C=O}$ 1650, δ_{C-H} (out-of-plane) 990 (KBr). UV λ_{max}^{EtOH} mμ (log ε): 225 (4.30), 318 (4.35). *Anal.* Calcd. for $C_{24}H_{24}O_2N_4$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.97; H, 6.07; N, 13.72.

Method B. The Reaction under Refluxed Condition (Sodium Ethoxide in Ethanol): To 0.01 mole of I dissolved in a solution of 0.23 g of sodium in 10 ml of absolute ethanol, 0.01 mole of XVIII in 10 ml of absolute ethanol was added, and the mixture was refluxed on a water bath for 1 hr. After the solvent was distilled off, water was added to the residue, extracted with chloroform and separated into the organic layer (fraction d) and aqueous layer (fraction e).

Fraction d. Evaporation of the dried organic layer left a yellow oil, which was submitted to silica gel column chromatography (chloroform). From the first eluate, yellow prisms of mp 122—123° were obtained in 5% yield and this was identified as bis(2-nitrophenyl)sulfide (XXXII) from the comparison of IR spectra and the mixed melting point with the authentic sample.

From the second eluate, XXI was obtained in 50% yield.

Fraction e. The aqueous layer was neutralized with 10% hydrochloric acid and extracted with chloroform. The extract was dried and evaporated to obtain a white powder, which was recrystallized from ethanol to afford 2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-carboxylic acid (XXX) as colorless prisms of mp 216—218° in 5% yield. This compound showed negative Beilstein test and negative sulfur test, and was identified with sample prepared from XXXI (cited below) from the mixed melting point and the comparison of IR spectra.

Method C. The Reaction in the Presence of Sodium Ethoxide in Dimethylformamide (DMF): To a solution of 0.1 g of sodium in 5 ml of absolute ethanol was added 1.2 g of I in 5 ml of DMF, and ethanol was distilled off under a reduced pressure. To this residue 0.7 g of XVIII in 5 ml of DMF was added and the mixture was heated on a water bath (90—100°) for 1 hr. The resulting precipitate (sodium chloride) was filtered off and the filtrate was concentrated. When cooled, yellow crystalline product appeared which was collected by filtration and recrystallized from ethanol to yellow prisms (XXI) of mp 165—166°. Yield, 1.42 g (80%).

2,4-Dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-carboxylic Acid (XXX)——To a solution of 20 ml of 1% potassium hydroxide, 10 ml of 10% sodium carbonate, 2 g of XXXI, and 20 ml of 10% potassium permanganate were added and the mixture was warmed on a water bath for a while and stood overnight at room temperature. The separated manganese dioxide was filtered off and the filtrate was neutralized with 10% hydrochloric acid to obtain a white powder. Recrystallization from ethanol gave colorless prisms of mp 216—218°. Yield, 1.5 g. IR cm^{-1}: ν_{OH} 3000—2500, $\nu_{C=O}$ 1720, 1650 (KBr). *Anal.* Calcd. for $C_{12}H_{12}O_3N_2$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.90; H, 5.59; N, 12.27. NMR (DMSO) τ: 7.79 (3H, singlet, $=\!\!-C\underline{H}_3$), 6.81 (3H, singlet, N–C$\underline{H}_3$), 2.52 (5H, singlet, –C$_6\underline{H}_5$).

Bis(2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)ethane (XXV)——(a) A mixture of 0.1 g of XXIV in 20 ml of ethanol and Raney nickel catalyst, prepared from 0.5 g of alloy was agitated in hydrogen stream for 5 hr. The catalyst was filtered off and the filtrate was evaporated to dryness. The white crystals so obtained were recrystallized from ethanol to 70 mg of colorless prisms, mp 214—215°. *Anal.* Calcd. for $C_{24}H_{26}O_2N_4$: C, 71.62; H, 6.51; N, 13.92. Found: C, 71.64; H, 6.63; N, 13.55. IR cm^{-1}: $\nu_{C=O}$ 1650 (KBr). UV λ_{max}^{EtOH} mμ (log ε): 249 (4.29), 278 (4.27). NMR ($CDCl_3$) τ: 8.10 (3H, singlet, $=\!\!-C\underline{H}_3$), 7.11 (2H, singlet, –C$\underline{H}_2$–), 7.01 (3H, singlet, N–C$\underline{H}_3$), 2.61 (5H, singlet, –C$_6\underline{H}_5$).

(b) A mixture of 2.0 g of XXVI, 0.5 g of copper, 1 g of anhydrous potassium carbonate, and 10 ml of DMF was heated on an oil bath (150—160°) for 10 hr with mechanical stirring. The organic solvent was distilled off, the residue was poured into water and extracted with chloroform. Evaporation of chloroform left a brown powder. Recrystallization from ethanol afforded 1.0 g of colorless prisms, mp 213—215°. This compound was the same as that prepared by (a), from the mixed melting point and the comparison of IR spectra.

Acknowledgement The authors express their deep gratitude to Miss T. Yamagishi of this Faculty for carrying out the microanalyses.