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168. Isoo Ito and Taisei Ueda: Synthesis of Pyrazolone Derivatives. XII.*1 Synthesis of 3-Mercaptomethyl-2-methyl-4-substituted-1-phenyl-3-pyrazolin-5-one.*2

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In order to search for new improved antipyretic and analgestic agents, synthesis of a series of pyrazolopyridine and synthesis of 2,4,6-trioxohexahydro-5-pyrimidinyl derivatives have been reported in the previous papers.[1~5] The present paper is concerned with the synthesis of 3-mercaptomethyl-2-methyl-4-substituted-1-phenyl-3-pyrazolin-5-one (F), which have not been described previously in the literature.

Although there are various methods of mercaptan synthesis, some convenient and successful ones applied in our laboratory were the following, *i.e.*, the alkaline treatment followed the reaction of halogen compounds with thiourea, the reduction of disulfides and thiocyanates. Other unsuccessful attempts to introduce mercapto group into the 3-position of pyrazolone derivatives were made by the treatment with thioacetic acid, and by the reduction of xanthates (G) with lithium aluminum hydride.

It is known that halogen alkyl reacts with thiourea to isothiouronium halide and its alkaline treatment affords mercaptan.[6] Thus, starting compounds, 3-bromomethyl-2,4-dimethyl-1-phenyl-3-pyrazolin-5-one (I)[7] and 4-bromo-3-bromomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one (II)[8] were reacted with the equivalent amount of thiourea in alcohol to give isothiouronium bromides (B), which were treated with alkaline to objective mercaptans, 2,4-dimethyl-3-mercaptomethyl-1-phenyl-3-pyrazolin-5-one (XI) and 4-bromo-3-mercaptomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one (XII), respectively, together with a small amount of disulfides (VII, VIII) as by-products. The disulfides obtained here were identical with those obtained by the reaction with compounds (A) and sodium disulfide. Reduction of 2-(4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl isothiouronium bromide (IV) by Raney nickel in the presence of sodium bicarbonate gave 2-(2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl isothiourea (XVII).

The mercaptans could be easily oxidized to disulfides by hydrogen peroxide or even by air. Although compound (XI) was obtained as colorless prisms of m.p. 83~85°, compound (XII) was pale yellow viscous oil, which could not be crystallized. Thus, it was oxidized with hydrogen peroxide to disulfide (VIII) and assigned to be identical with the compound obtained by the reaction of compound (II) and sodium disulfide from the comparison of the infrared spectrum and the mixed melting point determination.

Reduction of 1,1-bis(2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl disulfide (VII) with zinc dust in glacial acetic acid afforded corresponding mercaptan (XI). However, in case of 1,1-bis(4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl disulfide (VIII), bromo atom of the 4-position was also reduced to dehalogenated mercaptan

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*1 Part XI. I. Ito, N. Oda: This Bulletin, **14**, 297 (1966).

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1) I. Ito: Yakugaku Zasshi, **81**, 1730 (1961).
2) *Idem*: *Ibid.*, **81**, 1735 (1961).
3) *Idem*: *Ibid.*, **81**, 1738 (1961).
4) I. Ito, T. Ueda, E. Kurokawa: This Bulletin, **14**, 207 (1966).
5) I. Ito, N. Oda: *Ibid.*, **14**, 297 (1966).
6) Organic Synthesis Coll. Vol. **3**, 363 (1955).
7) Höchst Farbwerke: Chem. Zntr., **1909**, **I**, 806.
8) H. Graef, J. Ledrut, G. Combes: Bull. soc. chim. Belges, **61**, 331 (1952) (C. A., **47**, 12363 (1953)).

(XIII) as colorless viscous oil having characteristic odor. Since this could not be induced to crystal, it was oxidized with hydrogenperoxide to crystalline disulfide (XIV). The characteristic -SH absorption band of 2500 cm^{-1}, which appeared in the compound (XIII), was disappeared in this disulfide and its analytical data was satisfactory.

An equivalent amount of potassiumthiocyanate was reacted with the compound (A) in alcohol to give (2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methylthiocyanate (IX) and (4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methylthiocyanate (X). Reduction of thiocyanate (IX) with sodium sulfide and potassium hydroxide gave corresponding mercaptan (XI). However the same procedure on thiocyanate (X) resulted no mercaptan but 4-bromo antipyrine. Reduction under rather mild condition without potassium hydroxide at 70~80° afforded desired mercaptan (XII). The mercaptans obtained here were identical with those obtained by the alkaline treatment of thiouronium bromide (B).

Reaction of compounds (A) and potassium ethylxanthate, according to the method of Djerassi *et al.*[9] gave ethyl (2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl xanthate (XV) and ethyl (4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl xanthate (XVI). However, attempt to obtain mercaptans by the reduction of these compounds (XV, XVI) with lithium aluminum hydride was unsuccessful.

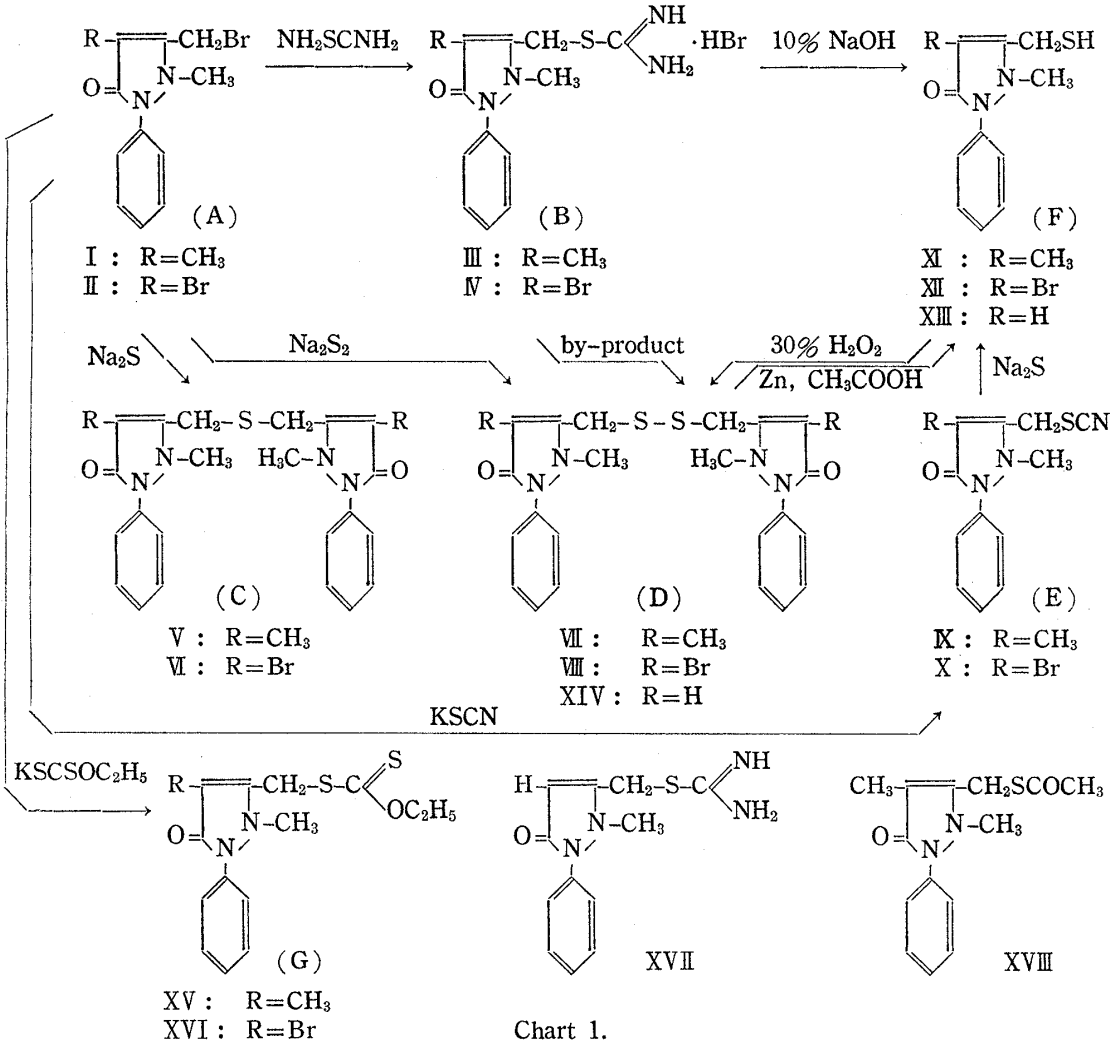

Chart 1.

9) C. Djerassi, M. Gorman, F. X. Markler, E. B. Oldenburg : J. A. C. S., **77**, 568 (1955).

It is well known that thioacetic acid has acetylating and thiating properties.[10] Thus, the compound (I) was reacted with thioacetic acid according to the method of Giner-Sorolla *et al.*[10] to yield 3-acetylthiomethyl-2,4-dimethyl-1-phenyl-3-pyrazolin-5-one (XVIII). Treatment of compound (II) with thioacetic acid failed to give the desired thiated product. Attempt to yield mercaptan by the reaction of compound (XVIII) with conc. ammonia according to the method of Giner-Sorolla *et al.* resulted in recovery of compound (XVIII) and a small amount of disulfide (VII).

Experimental*4

3-Bromomethyl-2,4-dimethyl-1-phenyl-3-pyrazolin-5-one (I)[7]——To a solution of 20 g. of 2,3,4-trimethyl-1-phenyl-3-pyrazolin-5-one in 30 ml. of $CHCl_3$, a solution of 16 g. of bromine in 30 ml. of $CHCl_3$ was added and stirred for 1 hr., neutrized with 10% Na_2CO_3, $CHCl_3$ layer was separated, dried over anhyd. Na_2SO_4, $CHCl_3$ was distilled out by reduced pressure to obtain colorless crystals. Needles (from EtOH), m.p. 111~112°(lit.[7] m.p. 113°). Yield 20 g. (90%).

4-Bromo-3-bromomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one (II)[8]——To a stirred solution of 100 g. of 4-bromoantipyrine in 700 ml. of CCl_4, 70 g. of powdered NBS was added in small portions over a period of 3 hr. under refluxing. Stirring and refluxing were continued for additional 4 hr. The reaction mixture was filtered, and the solid was extracted with 1000 ml. of hot CCl_4. The filtrate and the extract were evaporated, and the residue was crystallized from EtOH to colorless prisms, m.p. 135~136°. Yield 80.5 g. (62.1%).

2-(2,4-Dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl Isothiouronium Bromide (III)——A mixture of 1.4 g. (0.005 mole) of compound (I) in 10 ml. of EtOH and 0.38 g. (0.005 mole) of thiourea in 5 ml. of EtOH was refluxed on a water bath for 1 hr. After cooling the resulting crystals were collected by filtration and recrystallized from EtOH. Colorless prisms, m.p. 205~207°(decomp.). Yield 1.6 g. (90%). *Anal.* Calcd. for $C_{13}H_{17}ON_4SBr_2$: C, 43.70; H, 4.76; N, 15.68. Found: C, 43.98; H, 5.01; N, 15.97. IR ν_{N-H} cm^{-1}: 3300 (KBr).

2-(4-Bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl Isothiouronium Bromide (IV)——Same procedure as compound (III). Colorless prisms (from EtOH), m.p. 201~202° (decomp.). *Anal.* Calcd. for $C_{12}H_{14}ON_4SBr_2$: C, 34.12; H, 3.32; N, 13.27. Found: C, 34.36; H, 3.38; N, 13.58. IR ν_{N-H} cm^{-1}: 3300 (KBr).

1,1-Bis(2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl Sulfide (V)——To a solution of 1.4 g. (0.005 mole) of compound (I) in 10 ml. of 95% EtOH, a solution of 0.6 g. of $Na_2S \cdot 9H_2O$ in 10 ml. of 95% EtOH was added and refluxed on a water bath for 2 hr. The reaction mixture was filtered and the filtrate was condensed to a crude crystalline product, which was washed with a little water and dried. Colorless prisms (from EtOH), m.p. 134.5~136°. Yield 0.9 g. (87%). *Anal.* Calcd. for $C_{24}H_{26}O_2N_4S$: C, 66.34; H, 6.03; N, 12.90. Found: C, 66.78; H, 6.10; N, 13.01.

1,1-Bis(4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl Sulfide (VI)——Same procedure as compound (V), colorless prisms (from EtOH), m.p. 187~188°. *Anal.* Calcd. for $C_{22}H_{20}O_2N_4SBr_2$: C, 46.81; H, 3.57; N, 9.93. Found: C, 47.09; H, 3.47; N, 9.48.

1,1-Bis(2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl Disulfide (VII)——To a solution of 1.4 g. (0.005 mole) of compound (I) in 10 ml. of 95% EtOH, a solution of 0.6 g. of $Na_2S \cdot 9H_2O$ and 0.08 g. of sulfur in 10 ml. of 95% EtOH was added and refluxed on a water bath for 2 hr. The reaction mixture was filtered and the filtrate was condensed to obtain crude crystalline product, which was washed with water and dried. Recrystallization from EtOH afforded colorless needles, m.p. 192~193°(decomp.). Yield 0.9 g. (81%). *Anal.* Calcd. for $C_{24}H_{26}O_2N_4S_2$: C, 61.79; H, 5.62; N, 12.01. Found: C, 61.69; H, 5.38; N, 12.28.

1,1-Bis(4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl Disulfide (VIII)——Same procedure as compound (VII), colorless needles, m.p. 205~206°(decomp.). *Anal.* Calcd. for $C_{22}H_{20}O_2N_4S_2Br_2$: C, 44.30; H, 3.35; N, 9.40. Found: C, 44.33; H, 3.51; N, 9.63.

(2,4-Dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl Thiocyanate (IX)——To a solution of 2.8 g. (0.01 mole) of compound (I) in 20 ml. of 95% EtOH, 1.0 g. (0.01 mole) of KSCN was dissolved and heated on a water bath (at 70~80°) for 1 hr. The resulting precipitate was removed by filtration and the filtrate was condensed to obtain a crude crystalline product, which was washed with a little water and dried. Recrystallization from EtOH afforded colorless pillars, m.p. 140~141.5°, yield 2.4 g. (92%). *Anal.* Calcd. for $C_{13}H_{13}ON_3S$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.32; H, 5.14; N, 16.57. IR ν_{SCN} cm^{-1}: 2150 (KBr).

(4-Bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl Thiocyanate (X)——Same procedure as compound (IX). Colorless pillars (from EtOH), m.p. 155~156°. *Anal.* Calcd. for $C_{12}H_{10}ON_3SBr$: C, 44.44; H, 3.09; N, 12.96. Found: C, 44.54; H, 3.17; N, 13.08. IR ν_{SCN} cm^{-1}: 2150 (KBr).

*4 All melting points are uncorrected.

10) A. Giner-Sorolla, A. Bendich: J. Med. Chem., 8, 667 (1965).

3-Mercaptomethyl-2,4-dimethyl-1-phenyl-3-pyrazolin-5-one (XI) Method A Reaction of Compound (III) and 10% NaOH——To 10 ml. of 10% NaOH, 1.8 g. (0.005 mole) of compound (III) was dissolved and heated on a water bath for 2 hr. After cooling the reaction mixture was neutralized with 10% H_2SO_4 cooling with ice water. The resulting yellow oil was extracted with $CHCl_3$, the extract was washed with water, dried over anhyd. Na_2SO_4 and evaporated under reduced pressure to a viscous oil, which was extracted with ether and condensed to obtain colorless prisms, m.p. 83~85°. Yield 0.6 g. (51%). *Anal.* Calcd. for $C_{12}H_{14}ON_2S$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.74; H, 6.21; N, 12.00. IR ν_{SH} cm^{-1}: 2500 (KBr). A small amount of insoluble substance in ether was recrystallized from EtOH to obtain colorless needles, m.p. 191~192° (decomp.). This compound was confirmed to be disulfide (VII) from the comparison of the IR spectrum and the mixed melting point determination.

Method B Reduction of Disulfide (VII) with Zinc in Acetic Acid——A mixture of 2.4 g. (0.005 mole) of disulfide (VII) and 2.8 g. of zinc dust in 40 ml. of glacial acetic acid was refluxed on a water bath under mechanical stirring for 5 hr. After the reduction was complete, the mixture was cooled and filtered with suction. The filter cake was washed once with water, and then the cake was suspended in 100 ml. of water, and the suspension was heated to boiling. The hot solution was made strongly alkaline, and alkaline solution was boiled for about 20 min. to ensure complete extraction of the product from the filter cake, filtered from the insoluble material. By the addition of sufficient conc. HCl, white precipitate appeared and the addition of excess conc. HCl, the precipitate disappeared. The solution was extracted with benzene, dried over anhyd. Na_2SO_4, and distilled to obtain viscous oil, which was recrystallized from ether to give colorless prisms, m.p. 80~82°. Yield 0.9 g. (38%). IR ν_{SH} cm^{-1}: 2500 (KBr). The IR spectrum of this compound was identical with that of the compound obtained by the method A, and the mixed metling point of this compound and the compound obtained by the method A showed no depression.

Method C Reduction of Thiocyanate (IX) with Sodium Sulfide——To 30 ml. of 95% EtOH, 1.3g. (0.005 mole) of thiocyanate (IX), 2.3 g. of $Na_2S \cdot 9H_2O$ and 0.35 g. of KOH were dissolved and heated on a water bath for 4 hr. under nitrogen gas atmosphere. After cooling solvent was distilled under reduced pressure, ice water and 5 g. of NH_4Cl were added to the residue and extracted with benzene, dried over anhyd. Na_2SO_4, benzene was distilled to obtain pale yellow solid, recrystallized from ether to obtain colorless prisms, m.p. 82~84°. Yield 0.8 g. (68%). IR ν cm^{-1}: 2500 (KBr). This compound was assigned to be identical with those obtained by the method A and B from the comparison of the IR spectrum and the determination of mixed melting point.

4-Bromo-3-mercaptomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one (XII). Method A——Same procedure as method A of compound (XI). Pale yellow viscous oil. *Anal.* Calcd. for $C_{11}H_{11}ON_2SBr$: C, 44.14; H, 3.68; N, 9.33. Found: C, 44.43; H, 3.97; N, 9.65. IR ν_{SH} cm^{-1}: 2500. This compound was dipped in 30% H_2O_2 and stood overnight at 5~10°, the resulting solid was confirmed to be identical with disulfide (VIII) from the comparison of the IR spectrum and the mixed melting point determination.

Method B——To 30 ml. of 95% EtOH, 1.6 g. (0.005 mole) of thiocyanate (X) and 2.3 g. of $Na_2S \cdot 9H_2O$ were dissolved and warmed on a water bath (70~80°) for 2 hr. under nitrogen gas atmosphere. After cooling solvent was distilled out under reduced pressure, ice water and 5 g. of NH_4Cl were added to the residue and extracted with $CHCl_3$, dried over anhyd. Na_2SO_4. $CHCl_3$ was distilled to pale yellow viscous oil, yield 0.1 g. (6%). The IR spectrum of this compound was identical with that of compound obtained by the method A. This compound was also introduced to disulfide (VIII).

2-Methyl-3-mercaptomethyl-1-phenyl-3-pyrazolin-5-one (XIII)——Reduction of disulfide (VIII) with zinc dust in acetic acid. Same procedure as method B of compound (XI). Colorless viscous oil, negative Beilstein test. *Anal.* Calcd. for $C_{11}H_{12}ON_2S$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.21; H, 5.78; N, 13.03. IR ν_{SH} cm^{-1}: 2500.

1,1-Bis(2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl Disulfide (XIV)——The compound (XIII) was dipped in 30% H_2O_2 and stood overnight at 5~10°, the resulting solid was washed with water and ether. Colorless needles (from EtOH), m.p. 163~165°. *Anal.* Calcd. for $C_{22}H_{22}O_2N_4S_2$: C, 60.27; H, 5.06; N, 12.78. Found: C, 60.54; H, 5.31; N, 12.53.

Ethyl (2,4-Dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl Xanthate (XV)——To a solution of 1.4 g. (0.005 mole) of compound (I) in 50 ml. of acetone, a solution of 0.8 g. of commercial potassium ethyl xanthate in 50 ml. of acetone was added with good agitation over a period of 1 hr. After filtration of potassium bromide and removal of acetone, chloroform was added, the solution was washed well with water, dried and the solvent was removed under diminished pressure, m.p. 119~120°. Colorless needles (from EtOH), yield 1.3 g. (81%). *Anal.* Calcd. for $C_{15}H_{18}O_2N_2S_2$: C, 55.89; H, 5.63; N, 8.69. Found: C, 56.05; H, 5.84; N, 8.88.

Ethyl (4-Bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl Xanthate (XVI)——Same procedure as compound (XV), colorless needles, m.p. 107~108° (from EtOH). *Anal.* Calcd. for $C_{14}H_{15}O_2N_2S_2Br$: C, 43.41; H, 3.88; N, 7.24. Found: C, 43.11; H, 4.09; N, 7.49.

2-(2-Methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl Isothiourea (XVII)——One gram of compound (IV) was reduced in a mixture of 50 ml. of EtOH, 5 ml. of H_2O and 0.44 g. of $NaHCO_3$ at atmospheric pressure in the presence of Raney-Ni catalyst prepared from 1.5 g. of Ni-Al alloy. Catalyst was removed by filtration.

Filtrate was evaporated to obtain a crude crystalline product. Recrystallization from EtOH afforded colorless prisms, m.p. 169~171°. Yield 0.6 g. (80%). *Anal.* Calcd. for $C_{12}H_{14}ON_4S$: C, 54.95; H, 5.38; N, 21.37. Found: C, 55.17; H, 5.36; N, 21.44. IR ν_{NH} cm^{-1}: 3300 (KBr).

3-Acetylthiomethyl-2,4-dimethyl-1-phenyl-3-pyrazolin-5-one (XVIII)——A solution of 2.8 g. (0.01 mole) of compound (I) in 3 ml. of thioacetic acid was refluxed for 1 hr. on an oil bath. After cooling ether was added to obtain white solid, m.p. 156~158°, colorless needles (from EtOH-ether (1:1)). Then this was dissolved in water, extracted with benzene, dried over anhyd. Na_2SO_4, benzene was evaporated to obtain colorless needles (from ether), m.p. 81~82°, yield 2.6 g. (94%). *Anal.* Calcd. for $C_{14}H_{16}O_2N_2S$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.15; H, 5.93; N, 10.43. IR $\nu_{C=O}$ cm^{-1}: 1690 (KBr).

Reaction of Compound (XVIII) and Concentrated Ammonia——To 10 ml. of conc. NH_3(25%) 0.5 g. of compound (XVIII) was dissolved and the solution was kept at room temp. for 1 hr. in a nitrogen atmosphere. White flocky substance which appeared was removed by filtration. The filtrate was concentrated under reduced pressure, water was added and this operation was repeated three times. The resulting crystalline product was extracted with ether, dried over anhyd. Na_2SO_4. By distilling ether white solid was obtained, m.p. 82~84° (0.3 g.). The IR spectrum of this compound was identical with that of starting material (XVIII) and the mixed melting point of this substance and the compound (XVIII) showed no depression. The small amount of flocky substance which was obtained in the above procedure was confirmed to be disulfide (VII) from the comparison of the IR spectrum and the mixed melting point determination.

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Summary

As a part of studies on syntheses of pyrazolone derivatives, 3-mercaptomethyl-2-methyl-4-substituted-1-phenyl-3-pyrazolin-5-one were prepared by the reaction of 3-bromomethyl-2-methyl-4-substituted-1-phenyl-3-pyrazolin-5-one with thiourea and alkaline treatment, the reduction of 1,1-bis(2-methyl-4-substituted-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl disulfide and (2-methyl-4-substituted-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl thiocyanate.

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169. Hiroshi Hikino, Kanji Meguro, Yojiro Sakurai, and Tsunematsu Takemoto: Structure of Curcumol.*1

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The rhizome of zedoary (*Curcuma zedoaria* Roscoe (Zingiberaceae)) has been used medicinally since olden times. Although investigations directed towards a study of its composition have spread over many years, knowledge concerning the nature of its constituents has remained scanty.[1] We have undertaken an analysis of it and, by chromatography of the extract, isolated a new sesquiterpenoid, curcumol. A

*1 This paper is Part V in the series on Sesquiterpenoids. Preceding paper, Part IV, H. Hikino, K. Aota, T. Takemoto: This Bulletin, **14**, 890 (1966).

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1) For a historical background of early works, see E. Gildemeister, F. Hoffmann: Die Ätherischen Öle," Vol. IV, 477 (1956), Akademie Verlag, Berlin.