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Synthesis of Pyrazolone Derivatives. XVI.[1] Synthesis of Pyrazolo[3,4-*c*][1,5]-benzothiazepines and 3-(2-Benzothiazolyl)-3-pyrazolin-5-ones

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The Ullmann reaction of 1-phenyl-2-methyl-3-(2-aminophenyl)thiomethyl-4-bromo-3-pyrazolin-5-one (VII) in the solvent of xylene gave 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*][1,5]benzothiazepin-3-one (XI).

However, the same reaction in the solvent of dimethylformamide afforded 1-phenyl-2-methyl-3-(2-benzothiazolyl)-3-pyrazolin-5-one (X).

Similarly, 1-phenyl-2-methyl-3-(5-substituted-2-benzothiazolyl)-4-substituted-3-pyrazolin-5-one (XXIV, XXV, XXVI) were synthesized.

As potential psychotropic agents, the synthesis of pyrazolo[3,4-*c*][1]benzothiepin derivatives was reported in a preceeding paper.[1] In continuation of this work, it appeared that an investigation of pyrazolo[3,4-*c*][1,5]benzothiazepines which comprize structurally related component to the antidepressant, thiazesim[3] might lead to the compounds with useful pharmacological properties. Moreover, in the course of synthesis of pyrazolo[3,4-*c*][1,5]-benzothiazepines, the reaction to form 3-(2-benzothiazolyl)-3-pyrazolin-5-ones in which the cyclization occured predominantly to the allylic methylene at 3-position of pyrazolone instead of the ring closure to 4-position was presented.

The preparation of 1-phenyl-2-methyl-3-(2-aminophenyl)thiomethyl-4-bromo-3-pyrazolin-5-one (VII), which was an intermediate of cyclized compound 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*][1,5]benzothiazepin-3-one (XI), was carried out as shown in Chart 1.

The condensation of 1-phenyl-2-methyl-3-mercaptomethyl-4-bromo-3-pyrazolin-5-one[4] (I) with 2-nitrochlorobenzene gave 1-phenyl-2-methyl-3-(2-nitrophenyl)thiomethyl-4-bromo-3-pyrazolin-5-one (II). However, the reduction of II with stannous chloride did not gave VII, but 1-phenyl-2-methyl-3-(2-aminophenyl)thiomethyl-3-pyrazolin-5-one (III). Thus, an alternate preparation of VII was carried out from 1-phenyl-2-methyl-3-bromomethyl-4-bromo-3-pyrazolin-5-one[5] (V) and 2-aminothiophenol in the presence of sodium ethoxide in fairly good yield.

Ring closure of VII to the compound having seven membered ring system was attempted in the presence of anhydrous potassium carbonate, copper powder, and dry dimethylformamide (DMF). However, no objective compound (XI) was isolated, but unexpected compound (X) of mp 165—167° was obtained. X did not show any absorption in the region of 4000—3000 cm^{-1} in the infrared (IR) spectrum. Its ultraviolet (UV) absorption maximum at 308 mμ indicated the formation of a new conjugated system. In the nuclear magnetic resonance (NMR) spectrum one singlet peak at 6.20 ppm suggested the presence of an olefin proton. Elemental analysis and molecular ion peak of mass spectrum agreed with the formula of $C_{17}H_{13}ON_3S$. These experiments confirmed X to be 1-phenyl-2-methyl-3-(2-benzothiazolyl)-3-pyrazolin-5-

1) Part XV: I. Ito and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **18**, 1994 (1970).
2) Location: *Tanabe-dōri, Mizuho-ku, Nagoya.*
3) 5-(2-Dimethylaminoethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one (J. Krapcho, E.R. Spitzmiller, and C.F. Turk, *J. Med. Chem.*, **6**, 544 (1963); J. Krapcho, U.S. Patent 3075967).
4) I. Ito and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **14**, 1237 (1966).
5) H. Graef, J. Ledrut, and G. Combes, *Bull. Soc. Chim. Belges*, **61**, 331 (1952) [*C.A.*, **47**, 12363 (1953)].

one. X was also obtained from 1-phenyl-2-methyl-3-(2-formamidophenyl)thiomethyl-4-bromo-3-pyrazolin-5-one (VIII) or 1-phenyl-2-methyl-3-(2-acetamidophenyl)thiomethyl-4-bromo-3-pyrazolin-5-one (IX) in the similar manner.

Although the Ullmann reaction[6] of VII in the presence of anhydrous potassium carbonate, copper powder, and dry DMF did not gave XI, the reaction in the dry xylene and the presence of a small amount of pyridine or dimethylaniline gave XI. The IR spectrum of XI showed a band at 3200 cm^{-1} due to secondary amine. Elemental analysis and molecular ion peak of mass spectrum agreed with the formula of $C_{17}H_{15}ON_3S$. Moreover, the NMR spectrum gave data in agreement with the assigned structure. Formylation of XI was effected with 99% formic acid to give 1-methyl-2-phenyl-4-formyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*]-[1,5]benzothiazepin-3-one (XII). Its IR spectrum and elemental analysis agreed with the assigned structure.

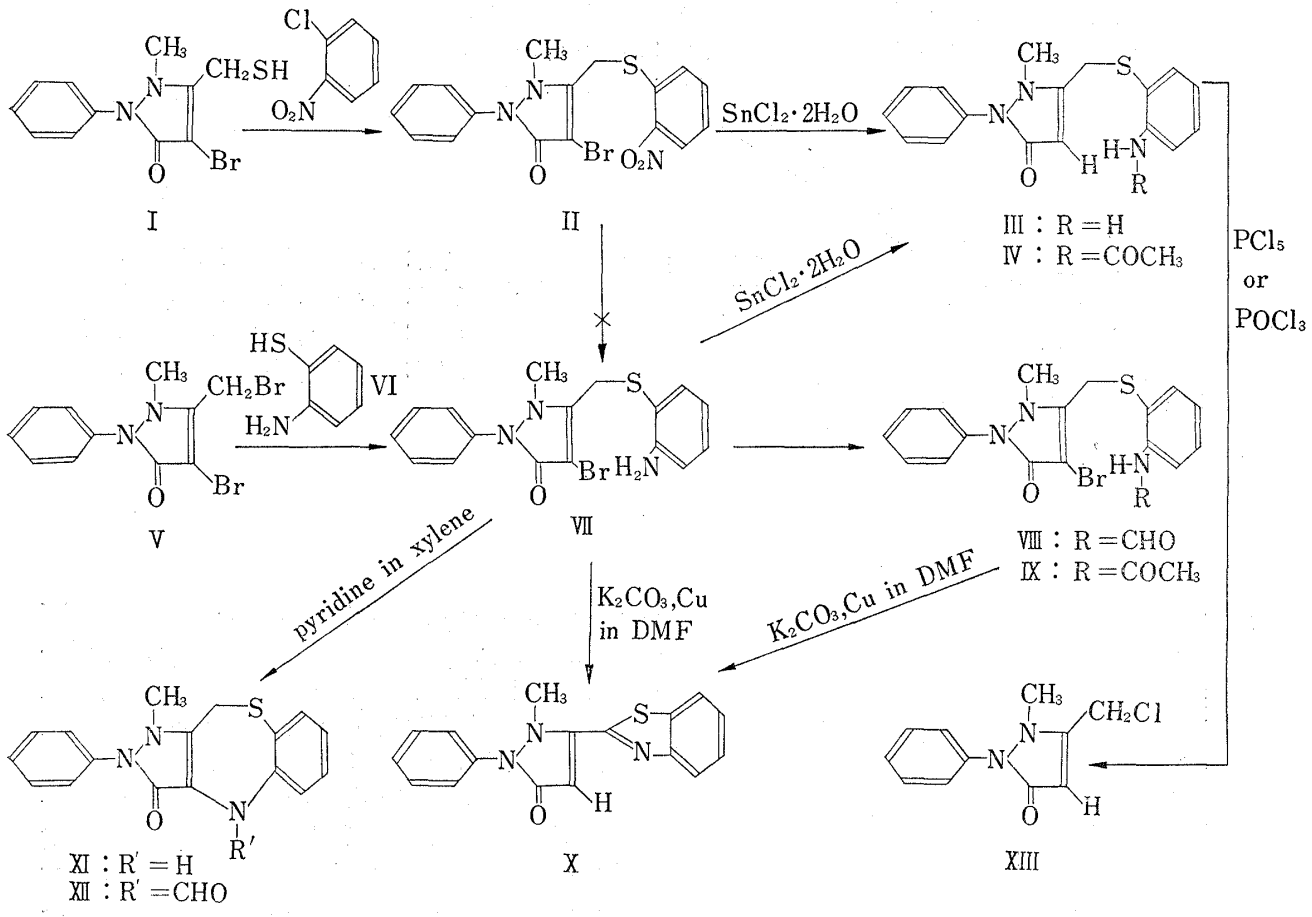


Chart 1

Attempted cyclization of 1-phenyl-2-methyl-3-(2-acetamidophenyl)thiomethyl-3-pyrazolin-5-one (IV) to eight membered ring system by means of Bischler-Napieralski reaction[7] using phosphorus pentachloride or phosphorus oxychloride resulted to yield 1-phenyl-2-methyl-3-chloromethyl-3-pyrazolin-5-one (XIII). XIII did not contain sulfur in its molecule and showed positive Beilstein reaction for halogen. Its elemental analysis, IR spectrum, and NMR spectrum agreed with the assigned structure. Moreover, XIII was identified with the compound[1] obtained by the chlorination of 1-phenyl-2-methyl-3-hydroxymethyl-3-pyrazolin-5-

6) F. Ullmann, *Chem. Ber.*, **36**, 2382 (1903); **37**, 2001 (1904).
7) A. Bischler and B. Napieralski, *Chem. Ber.*, **26**, 1903 (1893).

one[8] with phosphorus pentachloride by the comparison of the IR spectra and the mixture melting point.

In view of the formation of X from VII, it appeared that 1-phenyl-2,4-dimethyl-3-(2-aminophenyl)thiomethyl-3-pyrazolin-5-one (XVII) which was obtained by the condensation of 1-phenyl-2,4-dimethyl-3-bromomethyl-3-pyrazolin-5-one[9] (XIV) and 2-aminothiophenol (VI) might also give rise to the corresponding benzothiazol ring, 1-phenyl-2,4-dimethyl-3-(2-benzothiazolyl)-3-pyrazolin-5-one (XXIV). Therefore, cyclization of XVII was carried

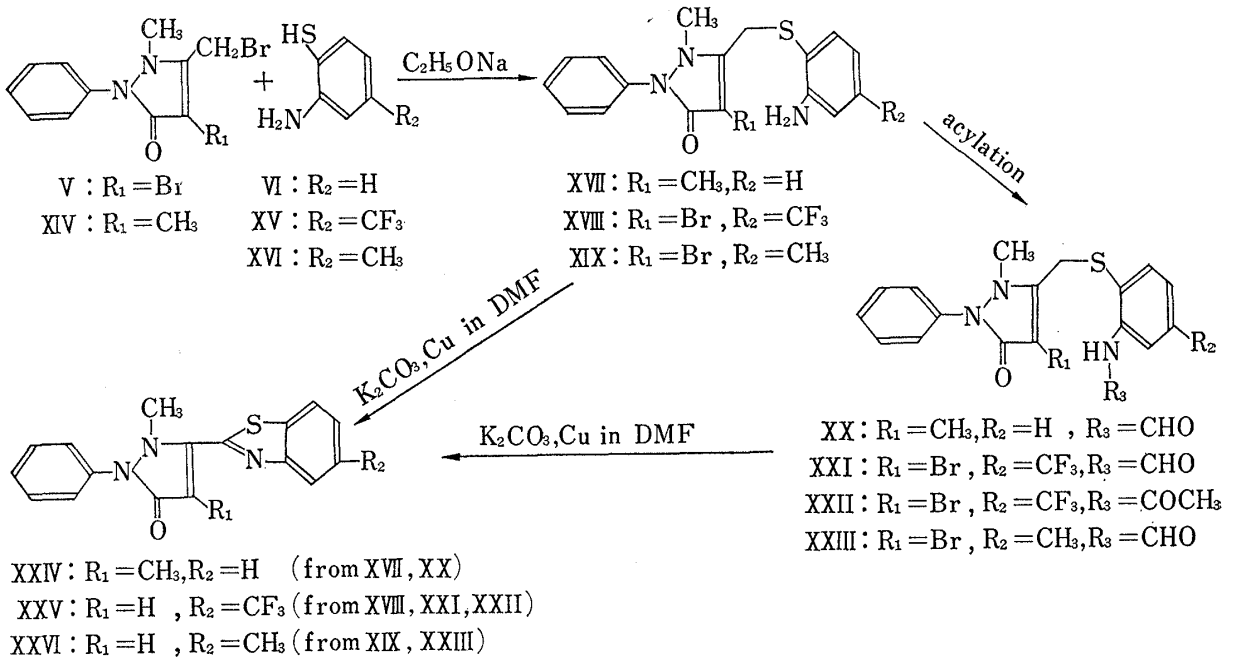


Chart 2

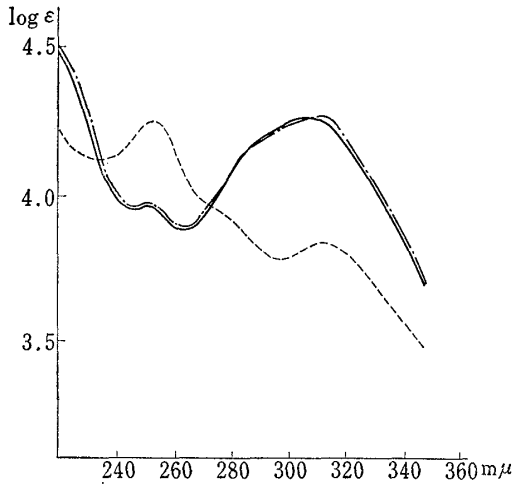


Fig. 1. Ultraviolet Absorption Spectra (in Ethanol)

——: X, ·····: XI, —·—·: XXIV

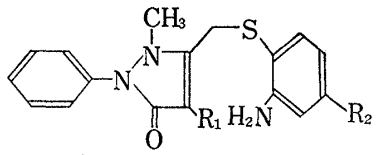
out by the same procedure as for X. The UV spectrum (Fig. 1) of XXIV was closely resemble to that of X. Its elemental analysis, IR spectrum, and NMR spectrum gave data in agreement with the assigned structure.

In order to examine the relationships between the formation of the benzothiazol ring and the substituents at *para*-position for sulfur atom on benzene ring, 1-phenyl-2-methyl-3-(2-amino-4-trifluoromethylphenyl) thiomethyl-4-bromo-3-pyrazolin-5-one (XVIII) which contains electron-withdrawing trifluoromethyl group and 1-phenyl-2-methyl-3-(2-amino-4-methylphenyl)thiomethyl-4-bromo-3-pyrazolin-5-one (XIX) which has electron-donating methyl group were subjected to the Ullmann reaction in DMF. Both XVIII and XIX gave benzothiazol rings 1-phenyl-2-methyl-3-(5-trifluoromethyl-2-

8) I. Ito, *Yakugaku Zasshi*, **76**, 822 (1956).
9) Höchst Farbwerke, Ger. Patent, 206637 (1907) [*Chem. Zntr.*, **80**, 806 (1906)].

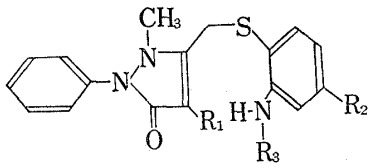
benzothiazolyl)-3-pyrazolin-5-one (XXV) and 1-phenyl-2-methyl-3-(5-methyl-2-benzothiazolyl)-3-pyrazolin-5-one (XXVI) respectively, and their physical data are listed in Table III.

Table I. 1-Phenyl-2-methyl-3-(2-amino-4-substitutedphenyl)thiomethyl-4-substituted-3-pyrazolin-5-ones



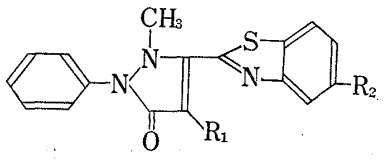
Compd. No.	Substituents R_1	Substituents R_2	mp (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
III	H	H	172—173	colorless needles	$C_{17}H_{17}ON_3S$	65.57	5.50	13.49	65.65	5.66	13.50
VII	Br	H	149—150	colorless prisms	$C_{17}H_{16}ON_3SBr$	52.31	4.13	10.77	52.53	4.27	11.01
XVII	CH_3	H	103—105	colorless prisms	$C_{18}H_{19}ON_3S$	66.43	5.89	12.91	66.74	6.13	13.18
XVIII	Br	CF_3	154—155	colorless prisms	$C_{18}H_{15}ON_3SBrF_3$	47.17	3.30	9.17	47.22	3.54	9.40
XIX	Br	CH_3	148—150	colorless prisms	$C_{18}H_{18}ON_3SBr$	53.47	4.49	10.39	53.33	4.55	10.66

Table II. 1-Phenyl-2-methyl-3-(2-acylamido-4-substitutedphenyl)thiomethyl-4-substituted-3-pyrazolin-5-ones

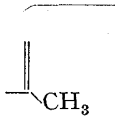
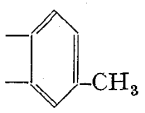
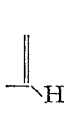


Compd. No.	Substituents R_1	Substituents R_2	Substituents R_3	mp (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IV	H	H	$COCH_3$	147—148	colorless prisms	$C_{19}H_{19}O_2N_3S$	64.57	5.42	11.89	64.80	5.57	11.93
VIII	Br	H	CHO	157—158	colorless prisms	$C_{18}H_{16}O_2N_3SBr$	51.68	3.86	10.05	51.81	3.99	10.31
IX	Br	H	$COCH_3$	135—136	colorless prisms	$C_{19}H_{18}O_2N_3SBr$	52.78	4.20	9.72	52.77	4.24	9.86
XX	CH_3	H	CHO	126—127	colorless prisms	$C_{19}H_{19}O_2N_3S$	64.57	5.42	11.89	64.32	5.48	11.61
XXI	Br	CF_3	CHO	198—199	colorless prisms	$C_{19}H_{15}O_2N_3SBrF_3$	46.93	3.08	8.64	46.85	3.40	8.91
XXII	Br	CF_3	$COCH_3$	143—144	colorless prisms	$C_{20}H_{17}O_2N_3SBrF_3$	48.01	3.42	8.40	48.31	3.32	8.63
XXIII	Br	CH_3	CHO	167—168	colorless prisms	$C_{19}H_{18}O_2N_3SBr$	52.78	4.20	9.72	52.73	4.01	9.51

Table III. 1-Phenyl-2-methyl-3-(5-substituted-2-benzothiazolyl)-4-substituted-3-pyrazolin-5-ones



Compd. No.	Substituents R_1	Substituents R_2	mp (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
X	H	H	165—167	tann prisms	$C_{17}H_{13}ON_3S$	66.43	4.26	13.67	66.39	4.43	13.97
XXIV	CH_3	H	145—147	colorless needles	$C_{18}H_{15}ON_3S$	67.27	4.70	13.07	67.13	5.00	13.13
XXV	H	CF_3	196—197	colorless prisms	$C_{18}H_{12}ON_3SF_3$	57.60	3.22	11.19	57.81	3.27	10.90
XXVI	H	CH_3	145—147	colorless prisms	$C_{18}H_{15}ON_3S$	67.27	4.70	13.07	67.43	5.00	13.18

Compd. No.	NMR ($CDCl_3$) ppm: 		N–CH_3		Aromatic protons	UV λ_{max}^{EtOH} mμ (log ε)	
X			3.53 (3H, singlet)	6.20 (1H, singlet)	7.27—8.25 (9H, multiplet)	254 (3.96)	308 (4.29)
XXIV	2.29 (3H, singlet)		3.25 (3H, singlet)		7.26—7.61 (9H, multiplet)	253 (3.97)	313 (4.33)
XXV			3.64 (3H, singlet)	6.32 (1H, singlet)	7.34—8.50 (8H, multiplet)	256 (4.16)	307 (4.41)
XXVI		2.54 (3H, singlet)	3.54 (3H, singlet)	6.20 (1H, singlet)	7.20—7.98 (8H, multiplet)	254 (4.01)	309 (4.35)

Experimental[10]

1-Phenyl-2-methyl-3-(2-nitrophenyl)thiomethyl-4-bromo-3-pyrazolin-5-one (II)——To a solution of 0.1 g of sodium in 5 ml of absolute ethanol, was added 1.2 g of 1-phenyl-2-methyl-3-mercaptomethyl-4-bromo-3-pyrazolin-5-one[4] (I) in 5 ml of dimethylformamide. Ethanol was distilled off under reduced pressure and 0.7 g of 2-nitrochlorobenzene in 5 ml of dimethylformamide was added. The mixture was heated on a steam-bath (80—100°) for 1 hr in nitrogen. Dimethylformamide was removed by distillation, and the residue was extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to obtain brown solid. Crystallization from ethanol provided analytical sample as yellow prisms of mp 165—168°. Yield 0.6 g. IR ν_{max}^{KBr} cm^{-1}: 1650 (C=O), 1550, 1330, 855 (NO_2). *Anal.* Calcd. for $C_{17}H_{14}O_3N_3SBr$: C, 48.58; H, 3.36; N, 10.00. Found: C, 48.89; H, 3.56; N, 10.32.

1-Phenyl-2-methyl-3-(2-aminophenyl)thiomethyl-3-pyrazolin-5-one (III) (Table I)——To a mixture of 2 g of stannous chloride dihydrate in 3 ml of hydrochloric acid, 1 g of II in 5 ml of ethanol was added with stirring. The mixture was refluxed on a steam-bath for 3 hr. After cooling the mixture was strongly alkalized with 40% sodium hydroxide and extracted with benzene. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated to give white crystals of mp 165—170°. Yield 0.6 g. Recrystallization from ethanol provided analytical sample as colorless prisms of mp 172—173°. Negative Beilstein test. IR ν_{max}^{KBr} cm^{-1}: 3300, 3400 (NH_2), 1650 (C=O).

10) All melting points were determined on a Yanagimoto Micro-Melting Point apparatus and were uncorrected. The UV absorption spectra were taken with a Hitachi Recording Spectrophotometer EPS-3T, and the IR absorption spectra were measured with a Nihon Bunko Spectroscopic Co. Ltd. Model IR-S. The NMR spectra were measured with a Varian A-60 spectrophotometer in deuteriochloroform and tetramethylsilane was used as an internal reference.

This compound was also prepared from VII (described below) by the same procedure as described above.

1-Phenyl-2-methyl-3-(2-acetamidophenyl)thiomethyl-3-pyrazolin-5-one (IV) (Table II)——To a mixture of 10 ml of acetic anhydride and 10 ml of gracial acetic acid, was added 5 g of III. The mixture was stood overnight at room temperature and diluted with water to obtain white crystalline powder, which was collected by filtration, washed with water and dried. Yield 5.1 g. Recrystallization from ethanol provided analytical sample as colorless prisms of mp 147—148°. IR ν_{max}^{KBr} cm^{-1}: 3240 (NH), 1690, 1630 (C=O).

IX and XXII were prepared by the same procedure as for IV.

1-Phenyl-2-methyl-3-(2-aminophenyl)thiomethyl-4-bromo-3-pyrazolin-5-one (VII) (Table I)——To a solution of 1.2 g of sodium in 100 ml of absolute ethanol, 6.3 g (0.05 mole) of 2-aminothiophenol (VI) was added under mechanical stirring and ice-cooling. Then, 17.3 g (0.05 mole) of 1-phenyl-2-methyl-3-bromomethyl-4-bromo-3-pyrazolin-5-one[5] (V) in 200 ml of ethanol was added and stood overnight at room temperature. Solvent was distilled off, water was added to the residue and extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated. The residue was crystallized from ethanol to give colorless prisms of mp 149—150°. Yield 14.5 g. IR ν_{max}^{KBr} cm^{-1}: 3280, 3400 (NH_2), 1660 (C=O).

XVII was similarly prepared from 1-phenyl-2,4-dimethyl-3-bromomethyl-3-pyrazolin-5-one[9] (XIV) and 2-aminothiophenol (VI).

1-Phenyl-2-methyl-3-(2-formamidophenyl)thiomethyl-4-bromo-3-pyrazolin-5-one (VIII) (Table II)——To 20 ml of 99% formic acid, 5 g of VII was dissolved and the solution was stood overnight at room temperature. The solution was poured into water to obtain crystalline powder, which was collected by filtration, dried, and recrystallized from ethanol as colorless prisms of mp 157—158°. Yield 4.5 g. IR ν_{max}^{KBr} cm^{-1}: 3180 (NH), 1690, 1630 (C=O).

XX, XXI, and XXIII were prepared by the same procedure as for VIII.

1-Phenyl-2-methyl-3-(2-benzothiazolyl)-3-pyrazolin-5-one (X) (Table III)——A mixture of 1.95 g (0.005 mole) of VII, 0.8 g of anhydrous potassium carbonate, 0.1 g of copper powder and 20 ml of dry dimethylformamide was refluxed in nitrogen on an oil-bath for 5 hr with mechanical stirring. The mixture was poured into water and extracted with benzene. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled to obtain brown tar, which was chromatographed in chloroform on silica gel. The chloroform eluate was evaporated to 0.1 g of tann prisms of mp 155—165°. Recrystallization from ethanol provided analytical sample as tann prisms of mp 165—167°. IR ν_{max}^{KBr} cm^{-1}: 1650 (C=O). Mass Spectrum[11] *m/e*: 307 (M^+). This compound was also similarly prepared from VIII or IX.

XXIV, XXV, and XXVI were prepared by the same procedure as for X.

1-Methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*][1,5]benzothiazepin-3-one (XI)——To 20 ml of dry refluxed xylene containing 1 ml of dry pyridine was added 2 g of VII. Reflux and stirring were continued for 14 hr. The reaction mixture was filtered hot. From the cooled filtrate 50 mg of tann prisms were obtained. Recrystallization from ethanol gave colorless scales of mp 234—236°. The mother liquor was evaporated to resinous oil, which was chromatographed in chloroform on silica gel. From the chloroform eluate another 10 mg of XI and 60 mg of X were obtained. *Anal.* Calcd. for $C_{17}H_{15}ON_3S$: C, 66.00; H, 4.89; N, 13.58. Found: C, 66.30; H, 5.07; N, 13.35. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1650 (C=O). Mass Spectrum *m/e*: 309 (M^+). NMR ($CDCl_3$) ppm: 6.40 (1H, broad singlet, –NH–), 2.84 (3H, singlet, N–CH_3), 3.78 (2H, singlet, –CH_2–S–), 7.00—7.60 (9H, multiplet, aromatic protons). UV λ_{max}^{EtOH} mμ (log ε): 254 (4.28), 315 (3.85).

1-Methyl-2-phenyl-4-formyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*][1,5]benzothiazepin-3-one (XII)——To 5 ml of 99% formic acid 50 mg of X was added and the mixture was refluxed for 3 hr. After cooling the mixture was diluted with water. Water and formic acid were removed by distillation, and the residue was crystallized from ethanol to give colorless prisms, mp 242—245°. Yield 40 mg. IR ν_{max}^{KBr} cm^{-1}: 1690, 1650 (C=O). *Anal.* Calcd. for $C_{18}H_{15}O_2N_3S$: C, 64.08; H, 4.48; N, 12.45. Found: C, 63.83; H, 4.75; N, 12.72.

1-Phenyl-2-methyl-3-chloromethyl-3-pyrazolin-5-one (XIII)——To a stirred solution of 1 g of IV in 15 ml of dry chloroform, 0.5 g of phosphorus pentachloride was added in portions. Stirring was continued for 5 hr at room temperature. The reaction mixture was poured into 50 ml of water and aqueous layer was separated. The organic layer was extracted with 10% hydrochloric acid. The aqueous layer and extracts were saturated with potassium carbonate and extracted with benzene. The extract was dried over anhydrous sodium sulfate, and benzene was evaporated to dryness to obtain pale yellow prisms of mp 108—110°. Yield 0.1 g. Positive Beilstein test and negative sulfure test. *Anal.* Calcd. for $C_{11}H_{11}ON_2Cl$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.52; H, 5.01; N, 12.77. IR ν_{max}^{KBr} cm^{-1}: 1650 (C=O). NMR ($CDCl_3$) ppm: 3.30 (3H, singlet, N–CH_3), 4.60 (2H, singlet, –CH_2–Cl), 5.82 (1H, singlet, $-\overset{|}{\underset{H}{N}}-$), 7.62 (5H, singlet, aromatic protons).

This compound was identified with that[1] obtained by the chlorination of 1-phenyl-2-methyl-3-hydroxymethyl-3-pyrazolin-5-one[8] with phosphorus pentachloride.

11) Mass spectra were taken on Hitachi Mass Spectrometer, Model RMU-6E equipped with double forcusing system.

1-Phenyl-2-methyl-3-(2-amino-4-fluoromethylphenyl)thiomethyl-4-bromo-3-pyrazolin-5-one (XVIII) (Table I)——To a solution of 1.15 g of sodium in 35 ml of absolute ethanol, was added 10.9 g of zinc salt of 2-amino-4-trifluoromethylbenzenethiol[12] (XV), which was obtained from bis(2-nitro-4-trifluoromethylphenyl)disulfide by the reduction with zinc dust in glacial acetic acid. To this solution 17.4 g of V in 100 ml of absolute ethanol was dissolved and refluxed in nitrogen for 30 min. The reaction mixture was filtered and the filtrate was poured into water to obtain brown solid. Yield 15.1 g. Crystallization from ethanol provided analytical sample as colorless prisms of mp 154—155°. IR ν_{max}^{KBr} cm^{-1}: 3280, 3420 (NH_2), 1650 (C=O).

XIX was similarly prepared from V and 2-amino-4-methylbenzenethiol zinc salt[13] (XVI).

Acknowledgement The authors gratefully acknowledge the assistance of Mr. Y. Kuroyanagi and Mr. S. Sanada. Thanks are also due to the members of Microanalytical center of this Faculty for elemental analysis.

12) A.I. Kiprianov and L.M. Yagupolskill, *Z. Obshch. Khim.*, **22**, 2209 (1952) [*C.A.*, **47**, 4769 (1953)].
13) M.T. Bogert and R.W. Allen, *Ind. Eng. Chem.*, **18**, 532 [*Chem. Zntr.*, **1926**, II, 2062].