(7.0 g) and 10% palladium on charcoal (1 g) in tetrahydrofuran (200 ml) was shaken under 45 psig of hydrogen until the calculated quantity (2 equiv) was consumed. The mixture was then filtered through a celite pad and the solvent was removed by evaporation *in vacuo* to give 4.1 g (66.1%) of crude material. This material was purified no further. Infrared bands were ν 3.08 and 3.20 (NH_2) and 5.78 μ (ester C=O).

3-Carboxymethyl-6-ethoxy-2-iminobenzothiazoline (VIc).—To 2-amino-6-ethoxybenzothiazole (15 g) in a boiling water-ethanol mixture (400–150 ml) was added sodium chloroacetate (20 g) in water (125 ml). This mixture was heated under reflux for 2 hr. The ethanol was then boiled off and the aqueous mixture cooled and filtered. The filter cake was dried and stirred with 250 ml of boiling benzene for 10 min and then filtered to give 10.4 g (53.4%). This material crystallized from water. On heating, the material did not melt but decomposed slowly between 160 and 240°.

Anal. Calcd for $C_{11}H_{12}N_2O_3S$: N, 11.10. Found: N, 10.75.

Registry No.—IVa, 15315-41-0; IVb, 15315-42-1; IVc, 15315-43-2; IVd, 15315-44-3; IVe, 15315-45-4; IVf, 15315-46-5; VIc, 15315-47-6; III, 15315-48-7.

Acknowledgment.—The author wishes to thank Mr. Frank P. Palopoli for his encouragement and assistance.

1-Pyrazoledithiocarboxylates

S. Trofimenko

Contribution No. 1349 from the Central Research Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware

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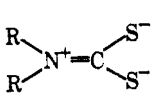
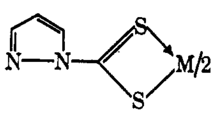
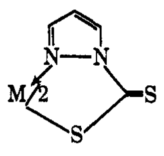
Addition of carbon disulfide to strongly nucleophilic anions yields the anions of dithiocarboxylic acids. Dithiocarbamates, an important class of chelating agents, are produced from secondary amines, base, and carbon disulfide.[1] Much of their stability is attributed to strong ground state contribution of the zwitterionic form, I.


I


II

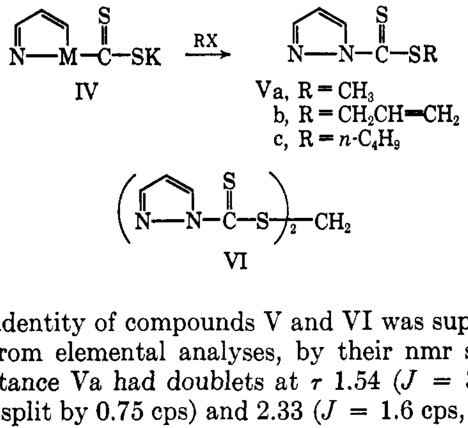

III

It was of interest to prepare 1-pyrazoledithiocarboxylates, since it appeared likely that an analogous structure would be energetically unfavorable[2] and that chelates of structure III rather than II would be formed (with divalent transition metal ions), due to the favorable geometry[3] involved. In a similar case of bis(methylthiohydroxamate)nickel(II), where a question of four *vs.* five-membered ring structure exists, the latter was established by X-ray studies.[4] In fact it should be expected that chelating systems analogous to III will be formed from pyrazolide ion and molecules of general structure A=C=A′ where A,A′ may be for instance, O, S, or NR. Chelates of structure III are also related to those obtained from metal pyrazolides and hexafluoroacetone.[5]

Results and Discussion

Addition of carbon disulfide to a suspension of potassium pyrazolide in benzene or tetrahydrofuran solvent resulted in exothermal formation of a dark yellow solid, soluble in water and alcohols.

This material is moderately stable to storage in a closed container where it develops a pressure of carbon disulfide. The structure IV assigned to it was indicated by the nmr spectrum which was characteristic of 1-substituted pyrazoles. Further support for this structure was obtained by preparing a number of well-characterized derivatives Va–c and VI which were formed in good yields when IV was treated with diverse alkyl halides. Compounds Va–c were bright yellow liquids whereas VI was a bright yellow solid, mp 182–184. They were all indefinitely stable to storage.



The identity of compounds V and VI was supported, apart from elemental analyses, by their nmr spectra. For instance Va had doublets at τ 1.54 (*J* = 3.0 cps, further split by 0.75 cps) and 2.33 (*J* = 1.6 cps, further split by 0.75 cps), a quadruplet made up of two overlapping doublets (*J* = 3.0 and 1.6 cps) at 3.70, and a singlet at 7.47 with relative areas 1:1:1:3. These were assigned to the 5-H, 3-H, 4-H, and methyl hydrogens, respectively, assuming a correlation between coupling constants similar to that found for other 1-substituted pyrazoles.[6]

Similarly, methylenebis(1-pyrazoledithiocarboxylate) (VI) had doublets at τ 1.39 (*J* = 2.9 cps) and 2.20 (*J* = 1.6 cps), a quadruplet made up of two overlapping doublets at 3.52 (*J* = 2.9, 1.6 cps), and a singlet at 4.78 in 1:1:1:1 ratio, assigned to the 5-H, 3-H, 4-H, and methylene protons, respectively.

Sodium 1-pyrazoledithiocarboxylate was prepared analogously from sodium pyrazolide and carbon disulfide. It was less stable to storage than the potassium salt. Solutions of alkali metal 1-pyrazoledithiocarboxylates are less stable than the solid salts, particularly on the acid side. Here the decomposition by acid is even faster than that of alkali dithiocarbamates

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[1] See, for instance, G. D. Thorn and R. A. Ludwig, "The Dithiocarbamates and Related Compounds," Elsevier Publishing Co., Amsterdam, 1962.

[2] The amount of resonance energy gained by the $N^+{=}C{-}S_2^{-2}$ system would not compensate for the loss of the resonance energy of pyrazole, variously estimated from 27 to 41 cal: H. Zimmerman and H. Geisenfelder, *Z. Electrochem.*, **65**, 368 (1961); A. F. Bedford, P. B. Edmondson, and C. T. Mortimer, *J. Chem. Soc.*, 2927 (1962).

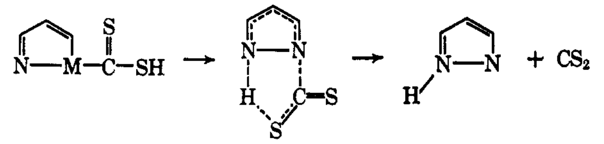
[3] This may be inferred from the formation of a hydrogen-bonded adduct of pyrazole with formaldehyde (R. Hüttel and P. Jochum, *Ber.*, **85**, 820 (1952)) and the facility with which a 1-(2,3-dibromopropyl)pyrazole undergoes cycloquaternization (S. Trofimenko, *J. Am. Chem. Soc.*, **87**, 4393 (1965); T. W. G. Solomons and C. F. Voigt, *ibid.*, **87**, 5256 (1965)).

[4] T. Sato, K. Nagata, Y. Tsukuda, M. Shiro, and H. Koyama, *Chem. Commun.*, 215 (1967).

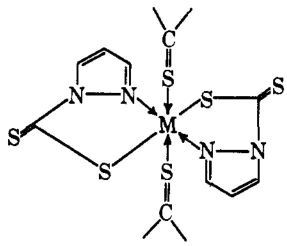
[5] W. Mahler, U. S. Patent 3,265,705 (1966).

[6] L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966), and references cited therein.

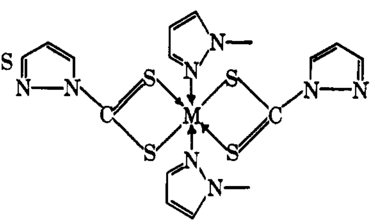
since a direct intramolecular route exists for transferring the proton from sulfur to nitrogen leading to reformation of pyrazole and carbon disulfide. Such a cyclic transition stage is probably operable in most, if not all, reaction of pyrazole involving bond making or bond breaking at the 1 position.[7]



The 1-pyrazoledithiocarboxylate ion reacts instantaneously with Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} ions forming precipitates very insoluble in all solvents, and remarkably stable to acids and bases, their stoichiometry being two ligands per metal ion. Their insolubility and chemical inertness demand a polymeric lattice which can be easily envisaged *via* coordination of the thiocarbonyl sulfur to the transition metal, giving rise to a distorted octahedral array, VII. Although it is possible to construct a similar polymeric lattice, VIII, based on the alternative structure involving four-membered rings, models show the latter to entail considerably greater steric strain.

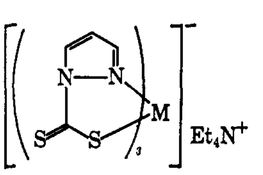


VII



VIII

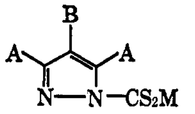
The ferrous ion was different from the others in forming a strikingly deep blue solution containing the uninegative [tris(1-pyrazoledithiocarboxylate)iron(II)] ion which could be readily isolated in the form of its sparingly soluble tetraethylammonium salt IX (M = Fe). The manganous ion behaved similarly but its trischelate could not be satisfactorily recrystallized.



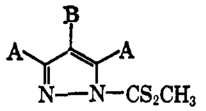
IX

The other ions (Co^{2+}, Cu^{2+}, Ni^{2+}, Zn^{2+}) formed the 3:1 complexes very reluctantly. Nevertheless, it was possible to isolate the tetraethylammonium salts by adding the appropriate metal ion slowly to a large excess of 1-pyrazoledithiocarboxylate and tetraethylammonium ions in the presence of methylene chloride which immediately extracted the ion pair IX. In contrast to the iron compound, however, these other complexes were unstable and tended to disproportionate to the 2:1 chelates.

When salts of C-substituted pyrazoles were treated with carbon disulfide, the reaction proceeded analogously. For instance compounds X (A = CH_3, B = H; A = H, B = Cl, Br; A = CH_3, B = Br) were obtained as yellow-orange solids. They were all soluble in water and alcohols, those with alkyl groups on the pyrazole ring were also soluble in tetrahydrofuran and acetone. Since these salts could not be satisfactorily purified, their identity was established by conversion to the well-defined methyl esters, XI.



X



XI

The ligands with methyl groups in the 3,5 position formed 2:1 chelates which were significantly soluble in organic solvents indicating either their monomeric nature, or low degree of association. This is ascribed to steric effects known to alter drastically both the geometry of tetracoordinate chelates and their degree of association.[8] Ligands containing only one 4 substituent resembled the parent ligand in their behavior. One distinguishing feature, for instance, was that the 4-substituted ligands did form the deep blue complex with ferrous ion while those with 3,5-dimethyl groups did not.

Experimental Section

Potassium 1-Pyrazoledithiocarboxylate.—A slurry of 0.5 mole of potassium pyrazolide[9] in 1 l. of benzene was stirred and refluxed with 0.55 mole of carbon disulfide for 12 hr. The slurry was filtered and the solid was washed with ether and air-dried yielding 91 g (100%) of dark yellow solid melting with decomposition at 202–203°.

Anal. Calcd for $C_4H_3KN_2S_2$: C, 26.4; H, 1.65; S, 35.2. Found: C, 26.8; H, 1.79; S, 33.7.

The nmr spectrum (D_2O) had doublets at τ 1.11 (J = 3.0 cps) and 2.23 (J = 1.4 cps) and a quadruplet, consisting of two overlapping doublets (J = 3.0 and 1.4 cps), at 3.54 in 1:1:1 ratio.

This compound is very soluble in water and methanol.

Bis(1-pyrazoledithiocarboxylate)copper(II).—This compound was obtained in 93% yield as a red solid by mixing aqueous solutions of potassium 1-pyrazoledithiocarboxylate and cupric chloride. It was purified by digestion in 50% aqueous ethanol and drying *in vacuo*. The material remains unchanged beyond 300°.

Anal. Calcd for $C_8H_6CuN_4S_4$: C, 27.3; H, 1.71; S, 36.5. Found: C, 27.6; H, 2.15; S, 36.6.

The infrared spectrum of this material is characterized by bands at 3150 (w), 1420 (m), 1370 (s), 1315 (s), 1250 (s), 1200 (m), 1160 (s), 1079 (s), 1048 (s), 997 (m), 910 (w), 854 (s), and 777 (s).

The infrared spectrum of the orange Ni(II) chelate was similar.

Tetraethylammonium Tris(1-pyrazoledithiocarboxylate)iron(II).—To a stirred solution of 9.0 g (0.05 mole) potassium 1-pyrazoledithiocarboxylate in 100 ml of water, mixed with 25 ml of 1 *M* tetraethylammonium chloride and 100 ml of methylene chloride, was added 25 ml of a freshly prepared 0.5 *M* solution of ferrous sulfate. The blue solid that formed was extracted with methylene chloride. The organic layer was separated, dried, and concentrated whereupon blue crystals formed. They were filtered to give 7.3 g (95% yield). The analytical sample was recrystallized twice from acetonitrile: mp 172–173° dec; λ_{max} 627 mμ (ϵ 10,300), 360 mμ (ϵ 23,900), 281 mμ (ϵ 29,900).

Anal. Calcd for $C_{20}H_{29}FeN_7S_6$: C, 39.0; H, 4.72; Fe, 9.08; N, 16.0; S, 31.2. Found: C, 39.1; H, 4.68; Fe, 9.27; N, 16.1; S, 31.0.

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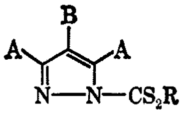
[7] Some of the recently reported reactions of 1-carbamoyl and 1-thiocarbamoylpyrazoles [D. Twomey, *J. Org. Chem.*, **31**, 2494 (1966)] are a good example of this, although the nature of the cyclic transition state involved has not been considered by the author.

[8] F. A. Cotton and R. C. Elder, *Inorg. Chem.*, **4**, 1145 (1965); G. J. Bullen, R. Mason, and P. Pauling, *Nature*, **189**, 291 (1961), and references cited therein.

[9] W. Hückel and H. Bretschneider, *Ber.*, **70**, 2024 (1939).

TABLE I

COMPOUNDS OF STRUCTURE



Method	A	B	R	Yield, %	Bp, °C (mm)	C, %		H, %		N, %		S, %		Nmr[c]
						Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	
A	H	H	CH_3	86	99 (3)	38.0	37.9	3.80	3.91			40.5	41.1	d (3.0) 1.54; d (1.6) 2.33; q (3.0 and 1.6) 3.70; s 7.47 (1:1:1:3)
A	H	H	Allyl	73	97 (1)[d]	45.6	46.2	4.35	4.55			34.8	34.8	d (3.0) 1.44; d (1.4) 2.25; q (3.0 and 1.4) 3.63, allyl H's 3.7–6.1 (1 1:1:5)
A	H	H	*n*-Butyl	16	131–150 (2)	48.0	48.3	6.00	6.26			32.0	33.5	
A	H	H	—CH_2—	86	182–184[a,b]	36.0	35.9	2.67	2.52			42.7	43.3	d (2.9) 1.39; d (2.4) 2.20; q (2.9 and 1.4); s 4.78 (1:1:1:1)
B	H	Cl	CH_3	54	113 (1.8) 45–50[b]	31.1	30.9	2.60	2.76	14.5	14.5	33.3	33.5	s 1.45; s 2.3; s 7.36 (1:1:3)
B	H	Br	CH_3	69	124 (1.7) 68–69[b]	25.3	25.3	2.11	2.17	11.6	11.6			s 1.48; s 2.26; s 7.33 (1:3:3)
B	CH_3	Br	CH_3	43	98–99[b]	31.7	32.1	3.40	3.53	10.6	10.6			s 7.29; s 7.40; s 7.70 (1:1:1)
A	CH_3	H	CH_3	94	125 (1.5) 31–32[b]	45.2	45.0	5.37	5.41	15.1	15.7	34.4	34.9	s 4.00; s 7.35; s 7.48; s 7.80 (1:3:3:3)

[a] Recrystallized from toluene. [b] Melting point. [c] The nmr spectra were taken in deuteriochloroform with tetramethylsilane as internal reference. Listed are multiplicity (coupling constant), chemical shift in τ, plus relative areas. [d] Values from the ultraviolet spectrum are 425 mμ (ε 60.5), 296 mμ (ε 22,100); sh 325 mμ (ε 9500).

Potassium 3,5-Dimethyl-1-pyrazoledithiocarboxylate.—Potassium metal (18.5 g, 0.475 g-atom) was added to 48 g (0.5 mole) of 3,5-dimethylpyrazole in 1 l. of tetrahydrofuran (under N_2) and the mixture was stirred under reflux until hydrogen ceased to be evolved. Excess carbon disulfide (>0.5 mole) was added. A yellow solid formed exothermally. The mixture was refluxed briefly and stirred overnight. The solid was filtered, washed with tetrahydrofuran, and air dried to give 98.6 g (98.6%) of dark yellow solid soluble in water and methanol. It decomposed above 200°.

Anal. Calcd for $C_6H_7KN_2S_2$: C, 34.3; H, 3.33; S, 30.5. Found: C, 35.9; H, 4.33; S, 26.0.

Transition Metal Bis(3,5-dimethyl-1-pyrazoledithiocarboxylates).—The compounds were prepared by mixing aqueous solutions of potassium 3,5-dimethylpyrazol-1-yldithiocarboxylate with the appropriate transition metal ions. The colors of the chelates are Mn(II), yellowish; Fe(II), black; Co(II), reddish; Ni(II), red-brown; Cu(II), black; Zn(II), yellow. The products derived from Co, Ni, Cu, and Zn could be extracted into methylene chloride.

Nickel Bis(3,5-dimethyl-1-pyrazoledithiocarboxylate).—Potassium 3,5-dimethylpyrazol-1-yldithiocarboxylate (14 g, 0.05 mole) was dissolved in 400 ml of water. The solution was stirred and 50 ml of 0.5 *M* nickel acetate solution was added. A red-brown solid precipitated. It was filtered and pressed dry. The crude product was dissolved in methylene chloride and purified by chromatography on alumina (packed and eluted with methylene chloride). The pure compound was obtained in a 4.0-g (40%) yield as shiny red-brown crystals. They slowly turn grey on heating above 300°.

Anal. Calcd for $C_{12}H_{14}N_4NiS_4$: C, 35.9; H, 3.50; Ni, 14.6. Found: C, 35.8; H, 3.72; Ni, 14.4.

On prolonged standing this material decomposes in undetermined fashion. The infrared spectrum exhibits strong bands at about 1560, 1320, 1250, 1130, 1080, 1040, 980, and 880 cm^{-1}.

Alkylation of 1-Pyrazoledithiocarboxylates.—The alkylations of 1-pyrazoledithiocarboxylates were carried out by refluxing together equivalent quantities of the sodium or potassium 1-pyrazoledithiocarboxylate (or a substituted analog) and the alkyl halide. They are exemplified by the following typical procedures. The properties of the compounds are listed in Table I.

A. Methyl 1-Pyrazoledithiocarboxylate.—A mixture of 0.2 mole of potassium 1-pyrazoledithiocarboxylate and 0.2 mole of methyl iodide was refluxed for 8 hr in 250 ml of tetrahydrofuran. The reaction mixture was filtered, the filtrate was stripped, and the residue was distilled *in vacuo* to give 27 g (86%) of bright-yellow liquid, bp 93° (3 mm).

B. Methyl 4-Chloro-1-pyrazoledithiocarboxylate.—To 0.5 mole of sodium hydride (mineral oil suspension) in 200 ml of tetrahydrofuran was added dropwise a solution of 0.5 mole of 4-chloropyrazole in 200 ml of tetrahydrofuran. When the theoretical amount of hydrogen had been evolved, 38 g (0.5 mole) of carbon disulfide was added. The reaction mixture was stirred for 1 hr at room temperature, 0.55 mole of methyl iodide was added, and the mixture was refluxed for 1 hr. It was then filtered, and the filtrate was evaporated to leave a yellow oil. It was distilled *in vacuo* affording 52 g (54%) of methyl 4-chloro-1-pyrazoledithiocarboxylate as a yellow oil, bp 113° (1.8 mm). It solidified on standing, mp 49–50°.

Registry No.—III (M = Cu), 15376-60-0; IV, 15315-15-8; Va, 15315-17-0; Vb, 15315-08-9; Vc, 15315-09-0; VI, 15315-10-3; IX (M = Fe), 15336-50-2; X (A = CH_3, B = H, M = K), 15315-16-9; XI (A = H, B = Cl), 15315-11-4; XI (A = H, B = Br), 15315-12-5; XI (A = CH_3, B = Br), 15315-13-6; XI (A = CH_3, B = H), 15315-14-7; $C_{12}H_{14}N_4NiS_4$, 15336-51-3.

Reactions of Hydrazine and Methylhydrazine with Uracil-5-carboxaldehyde. An Unusual Pyrimidine into Pyrazole Conversion[1]

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Received September 20, 1967

Several substituted hydrazone derivatives, notably the methyl- and formylhydrazones of orotaldehyde and thymine-6-carboxaldehyde,[2] have recently been shown to possess tumor inhibitory activity against the Walker 256 (intramuscular) test system. In connection with our continued efforts in the investigation of hydrazone derivatives, the reactions of uracil-5-carboxaldehyde with hydrazines have been studied.

Phenylhydrazine and hydroxylamine were reported to give normal condensation products with uracil-5-carboxaldehyde[3] (I). When methylhydrazine was used in the condensation reaction, however, the resulting white product ($\lambda_{max}^{pH\ 1}$ 237 mμ; $\lambda_{max}^{pH\ 11}$ 239 mμ) failed to give a characteristic ultraviolet absorption spectrum for a pyrimidine hydrazone derivative (usually a maximum peak is seen at 310–320 mμ in alkali).

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[1] This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, of the National Institutes of Health, Public Health Service, Contract PH-43-65-94.

[2] K. Y. Zee-Cheng and C. C. Cheng, *J. Heterocyclic Chem.*, **4**, 163 (1967).

[3] R. H. Wiley and Y. Yamamoto, *J. Org. Chem.*, **25**, 1906 (1960).