Synthesis of Substituted 5-Oxo-1-thiocarbamoyl-3-pyrazoline-4-alkanoic Acid Derivatives

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Cyclization of the 4-methyl-3-thiosemicarbazone of diethyl acetylsuccinate (Ia) by the action of ammonium hydroxide followed by acidification afforded ethyl 3-methyl-1-methylthiocarbamoyl-5-oxo-3-pyrazoline-4-acetate (IIa). Pmr spectral analyses using shift reagent, $Eu(fod)_3$, in deuteriochloroform indicated the presence also of approximately 15% of a second tautomer, ethyl 5-hydroxy-3-methyl-1-(methylthiocarbamoyl)pyrazole-4-acetate (IIa′). 3-Methyl-1-methylthiocarbamoyl-5-oxo-pyrazoline-4-acetamide (IIb) was prepared by extending the reaction time of Ia with ammonium hydroxide. Alkaline hydrolysis of IIa provided the corresponding acid 3-methyl-1-methylthiocarbamoyl-5-oxo-3-pyrazoline-4-acetic acid (IIc). Regeneration of IIa was achieved by the reaction of ethyl 3-methyl-5-oxo-3-pyrazoline-4-acetate (IV) with methyl isothiocyanate. The latter reaction provided confirmation of structure for IIa. The preparation of other pyrazolin-5-ones by cyclization of thiosemicarbazones of ethyl formylsuccinate and ethyl acetylglutarate also is presented. All spectra are in accord with the proposed structures.

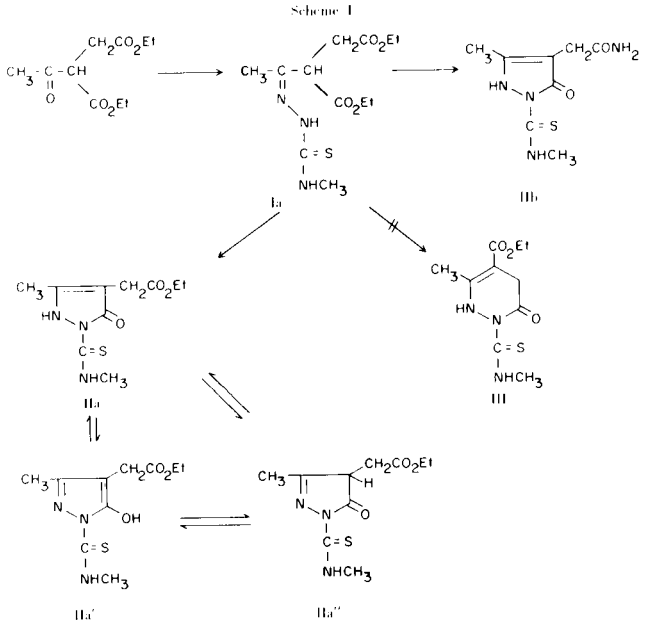
The long-recognized therapeutic value of various classes of thiosemicarbazone derivatives has provided a fertile area for research in the quest for new medicinal agents (1). In the course of a synthetic program involving the preparation of novel anti-infective agents, we have prepared a class of hitherto undescribed substituted 1-thiocarbamoyl-5-oxo-3-pyrazoline-4-alkanoic acid derivatives having antitubercular activity. These were obtained by the cyclization of variously substituted thiosemicarbazone derivatives of ethyl acetylsuccinate, ethyl formylsuccinate and ethyl acetylglutarate. The present communication describes the syntheses and chemistry of these pyrazoline derivatives.

The preparation of ethyl 3-methyl-1-methylthiocarbamoyl-5-oxo-3-pyrazoline-4-acetate (IIa, Scheme I) typifies the method used to prepare the title compounds. The synthesis consists of treating diethyl acetylsuccinate with an equivalent of 4-methyl-3-thiosemicarbazide to give the 4-methyl-3-thiosemicarbazone (Ia). Cyclization was effected by gently warming this intermediate in concentrated ammonium hydroxide for a few minutes followed by acidification. The isomeric dihydropyridazin-6-one (III) was considered as a possible alternative structure for the cyclization product. The results of further work described below, however, eliminated III as a tenable structure for this product and confirmed IIa as the correct structural assignment.

Since pyrazolin-5-ones are capable of existing in several tautomeric forms (2), ir and pmr spectra of this product as well as others in this study were determined under a variety of conditions in order to clarify certain structural ambiguities as well as to obtain information concerning relative proportions of tautomers. The ir spectrum in chloroform showed the presence of an ester C=O band at 5.75 μ and an intense lactam C=O band at 6.02 μ. Similarly, in dimethyl sulfoxide the ester C=O band was present at 5.74 μ and the position of the lactam C=O band was unchanged. The positions and intensities of these bands were essentially unchanged in potassium bromide (5.76, ester C=O and 6.00 μ, lactam C=O). In rescanning the spectrum after the sample in potassium bromide was exposed to an atmosphere of anhydrous ammonia, a sharp reduction in the intensity of the 6.0 μ band was observed while no change occurred in the 5.76 μ band. Exposure of this reground potassium bromide disk to an atmosphere of hydrogen chloride restored the original intensity of the lactam absorption band (3). These changes in ir spectra can be explained from a consideration of the three tautomeric forms of the product, IIa, IIa′, and IIa″. The marked reduction of the lactam carbonyl absorption can be attributed to a tautomeric shift favoring IIa′ resulting in salt formation between the acidic hydroxyl group and the base. The effect is reversed on acidification.

It is apparent from an examination of the pmr spectrum

Scheme I



of the product that tautomer IIa'' cannot be present to any appreciable extent, since no methinyl proton resonance was observed and the 4-methylene absorption appeared as a sharp singlet. The pmr spectrum is consonant with either tautomer IIa or IIa' and therefore cannot be used alone to distinguish between the two. However, the intense ir lactam C=O band, found in the solid phase as well as the solution spectra, strongly suggests that the NH tautomer (IIa) is the predominant form. Although the proton resonance patterns in the "normal" pmr spectrum as run in deuteriochloroform suggests the presence of only a single tautomer (IIa), the addition of shift reagent, $Eu(fod)_3$, to the solution makes it apparent that a second tautomer (IIa') is also present to the extent of about 15%. All of the proton patterns of IIa were shifted downfield by the reagent, with the complex apparently forming on the lactam carbonyl group, while the proton patterns of IIa' remained at their origin. The shift reagent itself apparently has little or no effect on the equilibrium between forms IIa and IIa', since further addition of the reagent did not change the relative proportions of the two tautomers. An additional example of this phenomenon was encountered later with compound IIf, described below.

Treatment of Ia with concentrated ammonium hydroxide solution for several days at room temperature followed by acidification resulted in the formation of 3-methyl-1-methylthiocarbamoyl-5-oxo-3-pyrazoline-4-acetamide (IIb). Hydrolysis of the ester IIa with aqueous sodium hydroxide solution gave the corresponding acetic acid derivative (IIc, Scheme II).

McMillan and King (4) previously studied the reactions of α-acylsuccinic esters with hydrazine. In each reaction two products were isolated. For example, with diethyl acetylsuccinate and hydrazine they reported a moderately high melting pyrazolone derivative which was formulated as ethyl 3-methyl-5-oxo-2-pyrazoline-4-acetate (IV'). A much lower melting isomer, 4-carbethoxy-3-methyl-4,5-dihydro-6-pyridazone, was also observed. We repeated the reaction and obtained a pyrazolone with melting point in good agreement with that of McMillan and King. The pmr and ir spectra of this product, however, indicated that the NH tautomer, *i.e.*, ethyl 3-methyl-5-oxo-3-pyrazoline-4-acetate (IV) rather than the CH tautomer (IV') is the predominant form. This conclusion is based on the fact that no methinyl proton resonance is present in the pmr spectrum and that the 4-methylene group appears as a singlet at 3.30 δ. An intense lactam carbonyl absorption is also present at 6.15 μ in the ir spectrum.

It is well known that 2-pyrazolin-5-ones having no 1-substituent react with acylating agents such as acetic anhydride, alkylchloroformates and isocyanates at the 1-nitrogen (5). Therefore, the reaction of the pyrazolin-5-one IV with an equivalent of methyl isothiocyanate might be expected to afford IIa. When the reaction was carried out in boiling tetrahydrofuran, the product obtained was indeed identical in all respects with that produced previously by the cyclization of the thiosemicarbazone Ia. Thus, the pyrazolone IIa is established unequivocally over the isomeric dihydropyridazin-6-one (III) as the correct product of ring closure.

Cyclization of the 4-methyl-3-thiosemicarbazone of ethyl formylsuccinate (Ic, Table I) proceeded in the same fashion as with Ia. The product thus obtained, ethyl 1-methylthiocarbamoyl-5-oxo-3-pyrazoline-4-acetate (IIf, Table II), had in its ir spectrum an ester C=O absorption at 5.74 μ and an intense lactam C=O band at 6.12 μ. Apart from the expected methyl-methylene proton patterns in the pmr spectrum (deuteriochloroform), the 3-vinylic proton appeared as two separate resonances at 7.70 and 7.43 δ in a ratio of 60:40, the former presumably due to the NH tautomer of IIf and the latter due to the OH form. No evidence for the presence of the CH tautomer was observed. The addition of shift reagent, $Eu(fod)_3$, caused the proton patterns of the NH tautomer to shift downfield while those of the OH tautomer remained at their origin, again in a 60:40 ratio. Increasing the quantity of shift reagent did not affect the relative proportions of tautomers. The tautomeric interconversion rates between the NH and OH forms in examples IIa and IIf appear to be sufficiently slow on the nmr time scale to permit detection of the individual forms (6). To our knowledge, the use of shift reagent for the detection of separate tautomeric forms has not been previously reported. When the spectrum was determined in DMSO-d_6, the vinylic proton was totally accounted for by a single resonance at 7.88 δ. The change to a more polar solvent apparently shifted the equilibrium

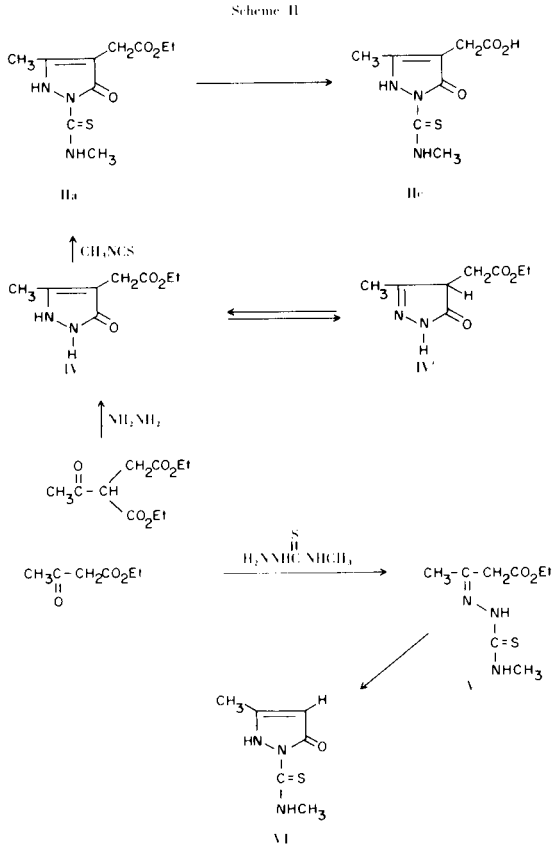
TABLE I

Substituted Thiosemicarbazones

Compound	R_1	R_2	n	M.p., °C	Yield %	Recryst. solvent	Empirical Formula	Calcd., % C	H	N	S	Found, % C	H	N	S
Ia	CH_3	CH_3	1	84-85	99	ethanol	$C_{12}H_{21}N_3O_4S$	47.51	6.98	13.85		47.18	7.14	13.70	
Ib	H	CH_3	1	98-100	91	ethanol-cyclohexane	$C_{11}H_{19}N_3O_4S$	45.66	6.62	14.52		45.64	6.58	14.65	
Ic	CH_3	H	1	102-105	100	ethanol	$C_{11}H_{19}N_3O_4S$	45.66	6.62	14.52	11.08	45.33	6.64	14.65	11.14
Id	H	H	1	110-112	46	ethanol	$C_{10}H_{17}N_3O_4S$	43.62	6.62	15.26	11.64	43.46	6.07	15.39	11.34
Ie (a)	H	CH_3	2		99		$C_{12}H_{21}N_3O_4S$	47.51	6.98	13.85	10.57	47.40	7.17	13.67	10.59

(a) Attempts to obtain a crystalline product were unsuccessful.

Scheme II



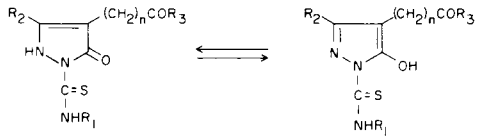
to favor the NH tautomer. Solvent effects have been shown by Katritzky and Maine (2) to greatly influence this type of equilibrium. The authors conclude that the more polar form generally is favored in media of high dielectric constant and hydrogen bonding ability.

The synthesis also was extended to include the cyclization of various thiosemicarbazone derivatives of diethyl acetylglutarate. For example, cyclization of diethyl acetylglutarate thiosemicarbazone under the usual conditions afforded ethyl 3-methyl-5-oxo-1-thiocarbamoyl-3-pyrazoline-4-propionate (IIi) after acidification. When IIi was subjected to reaction with hydrazine hydrate, expulsion of the thiocarbamoyl group resulted, producing ethyl 3-methyl-5-oxo-3-pyrazoline-4-propionate and thiosemicarbazide.

All the substituted pyrazolin-5-one esters obtained in this study (Table II) were prepared by cyclization of the corresponding open-chain thiosemicarbazones summarized in Table I (7). The carboxylic acids were obtained by hydrolysis of the esters. All spectra are in accord with the indicated structures. The presence of alkali appears to be essential for ring closure in these examples, since in the absence of base only uncyclized thiosemicarbazones could be recovered, even after several hours of reflux.

TABLE II

1-Thiocarbamoyl-5-oxo-3-pyrazoline-4-alkanoic Acid Derivatives



Compound	n	R_1	R_2	R_3	M.p., °C	Yield %	Recryst. Solvent	Empirical Formula	Calcd., % C	H	N	S	Found, % C	H	N	S
IIa	1	CH_3	CH_3	OEt	151-153	70	ethanol	$C_{10}H_{15}N_3O_3S$	46.68	5.88	16.33	12.46	46.37	5.91	16.72	12.43
IIb	1	CH_3	CH_3	NH_2	181-183	49	ethanol	$C_8H_{12}N_4O_2S$	42.09	5.30	24.54	14.04	42.01	5.41	24.19	13.79
IIc	1	CH_3	CH_3	OH	180-182	59	water	$C_8H_{11}N_3O_3S$	41.91	4.84	18.33	13.98	42.01	4.99	18.13	14.36
IId	1	H	CH_3	OEt	146-148	36	ethanol	$C_9H_{13}N_3O_3S$	44.43	5.38	17.27	13.18	44.44	5.40	17.64	13.43
IIe	1	H	CH_3	OH	178-179	21	ethanol	$C_7H_9N_3O_3S$	39.06	4.21	19.52		39.35	4.25	19.69	
IIf	1	CH_3	H	OEt	149-151	86	ethanol	$C_9H_{13}N_3O_3S$	44.43	5.38	17.27	13.18	44.06	5.38	17.19	12.77
IIg	1	CH_3	H	OH	192-194	84	water	$C_7H_9N_3O_3S$	39.06	4.21	19.52	14.89	39.06	4.34	19.43	14.54
IIh	1	H	H	OEt	141-142	87	ethanol	$C_8H_{11}N_3O_3S$	41.91	4.84	18.32	13.98	41.75	4.86	18.63	13.82
IIi	2	H	CH_3	OEt	149-150	80	ethanol	$C_{10}H_{15}N_3O_3S$	46.68	5.88	16.33	12.46	46.35	6.00	16.03	12.36
IIj	2	H	CH_3	OH	186-187	45	water	$C_8H_{11}N_3O_3S$	41.91	4.84	18.33		41.58	4.86	18.62	
IIk (a)	2	Et	CH_3	OEt	72-74	77	ethanol	$C_{12}H_{19}N_3O_3S$	50.51	6.71	14.72	11.23	50.24	6.55	14.87	11.72
III	2	Et	CH_3	OH	152-153 (d)	50	water	$C_{10}H_{15}N_3O_3S$	46.68	5.88	16.33		46.57	5.77	16.25	

(a) Prepared *in situ* without direct isolation of open chain thiosemicarbazone intermediate.

For comparative biological studies, it was of interest to prepare a pyrazolin-5-one related to IIa but having the 4-position free of substitution. De and Dutt (8) previously reported that the preparation of 3-methyl-1-methylthiocarbamoyl-2-pyrazolin-5-one (m.p. 83°) was achieved directly by heating ethyl acetoacetate with an equivalent of 4-methyl-3-thiosemicarbazide in refluxing ethanol. When the reaction was repeated in this laboratory, however, only the uncyclized thiosemicarbazone derivative (V) was obtained, which had a melting point of 81-82°, in agreement with the product isolated by De and Dutt. Cyclization of this intermediate with ammonium hydroxide followed by acidification afforded a much higher melting product (m.p. 200-203°), 3-methyl-1-methylthiocarbamoyl-3-pyrazolin-5-one (VI), whose structure was confirmed by elemental, ir, and pmr spectral analysis.

Attempts to form thiosemicarbazone derivatives of diethyl trifluoroacetylsuccinate and diethyl benzoylsuccinate with either thiosemicarbazide or 4-methyl-3-thiosemicarbazide under a variety of conditions were unsuccessful. The reactants were recovered unchanged.

The biological screening results for the pyrazolin-5-ones reported herein will be the subject of a separate communication.

EXPERIMENTAL

Melting points were determined in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Ir spectra were obtained in potassium bromide or in solution, as specified, using a Perkin-Elmer (Model 21) spectrophotometer. Pmr spectra were obtained with a Varian A-60 spectrometer using deuteriochloroform or DMSO-d_6. Chemical shifts were measured in ppm (δ) with respect to tetramethylsilane. The observed spectra are in accord with the assigned structures, with only selected spectral features being presented for representative compounds.

Diethyl Acetylsuccinate (4-Methyl-3-thiosemicarbazone) (Ia).

A mixture of 10.5 g. (0.1 mole) of 4-methyl-3-thiosemicarbazide and 21.6 g. (0.1 mole) of diethyl acetylsuccinate in 250 ml. of ethanol was heated under reflux for 14 hours. The solvent was removed on a rotary evaporator. The residual oil crystallized on scratching and amounted to 30 g. An analytical sample was obtained by recrystallization from ethanol; ir (potassium bromide): μ 3.04, 3.20 (NH), 5.81 (ester C=O); pmr (deuteriochloroform): δ 1.28 (t, 3H, OCH_2CH_3), 1.32 (t, 3H, OCH_2CH_3), 2.88 (d, 2H, $CH_2C(=O)$), 3.82 (t, 1H, $-CHCO_2Et$), 3.21 (d, 3H, $NHCH_3$).

Ethyl 3-Methyl-1-methylthiocarbamoyl-5-oxo-3-pyrazoline-4-acetate (IIa).

To 250 ml. of concentrated ammonium hydroxide was added 20 g. (0.066 mole) of Ia. The reaction mixture was heated gently in a steam bath until an essentially clear solution was obtained (approximately 20 minutes). After filtration by gravity, the solution was cooled in an ice-bath and acidified to *p*H 3 with concentrated hydrochloric acid. The resulting product amounted to 11.8 g. The analytical sample was obtained by recrystallization from ethanol; m.p. 151-153°; ir (potassium bromide): μ 3.15 (NH), 5.76 (ester C=O), 6.00 (lactam C=O); ir (chloroform): μ 5.75 (ester C=O), 6.03 (lactam C=O); ir (DMSO-d_6): μ 5.74 (ester C=O), 6.02 (lactam C=O); ir (potassium bromide + ammonia): μ 3.45 (very broad salt bands), 5.75 (ester C=O), 6.00 (lactam C=O, greatly diminished intensity); ir (potassium bromide + ammonia + hydrogen chloride): μ 5.75 (ester C=O), 6.00 (lactam C=O, intensity restored); pmr (deuteriochloroform): ± shift reagent (S.R.), Eu[fod]$_3$, δ:

	CH_2CH_3	CH_3C-	$NHCH_3$	$CH_2C(=O)$	CH_2CH_3
50 mg. sample	1.28 (t)	2.22 (s)	3.23 (d)	3.31 (s)	4.20 (q)
+ 20 mg. S.R.	1.55	2.46	3.41	3.17	4.83
+ 40 mg. S.R.	1.95	2.76	3.66	5.24	5.68
+ 70 mg. S.R.	2.63	3.28	4.03	7.10	7.10

3-Methyl-1-methylthiocarbamoyl-5-oxo-3-pyrazoline-4-acetic Acid (IIc).

Two g. (0.0078 mole) of the ester (IIa) was dissolved in 30 ml. of 10% sodium hydroxide solution and the solution was allowed to stand at room temperature for 17 hours. Acidification at *p*H 3 with concentrated hydrochloric acid gave 1.0 g. of product. The analytical sample (m.p. 180-182°) was obtained from water; ir (potassium bromide): μ 3.37 (broad NH, OH), 5.84 (carboxyl C=O), 6.07 (lactam C=O); pmr (DMSO-d_6): δ 2.18 (s, 3H, CH_3C-), 3.11 (d, 3H, $NHCH_3$).

3-Methyl-1-methylthiocarbamoyl-5-oxo-3-pyrazoline-4-acetamide (IIb).

Three g. (0.01 mole) of Ia was dissolved in 100 ml. of concentrated ammonium hydroxide and the solution was allowed to stand at room temperature for 3 days. The reaction mixture was cooled in ice and acidified with concentrated hydrochloric acid. The resulting precipitate amounted to 1.3 g. The analytical sample (m.p. 181-183°) was obtained by recrystallization from ethanol; ir (potassium bromide): μ 2.93, 3.04 (NH), 5.93 (amide C=O), 6.03 (lactam C=O); pmr (DMSO-d_6): δ 2.19 (s, 3H, CH_3C-), 3.02 (s, 2H, CH_2), 3.17 (d, 3H, CH_3NH).

Ethyl 3-Methyl-5-oxo-3-pyrazoline-4-acetate (IV).

A solution of 10.8 g. (0.05 mole) of diethyl acetylsuccinate and 2.5 g. (0.05 mole) of hydrazine hydrate (99%) in 250 ml. of ethanol was heated under reflux for 3 hours. Cooling in ice resulted in the deposit of crystals of product amounting to 4.1 g. (m.p. 165-168°). The analytical sample (m.p. 170-171°) was obtained by recrystallization from ethanol; ir (potassium bromide): μ 3.87 (very broad NH), 5.72 (ester C=O), 6.15 (lactam C=O); pmr (deuteriochloroform): δ 2.13 (s, 3H, 3-Me), 3.30 (s, 2H, 4-CH_2), 1.22 (t, 3H, OCH_2CH_3), 4.12 (q, 2H, OCH_2CH_3).

Anal. Calcd. for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.49; H, 6.59; N, 15.21.

Compound IIa *via* the Reaction of IV with Methylisothiocyanate.

To 1.84 g. (0.01 mole) of IV in 125 ml. of dry tetrahydrofuran was added 0.73 g. (0.01 mole) of methylisothiocyanate. The reaction mixture was heated under reflux for 12 hours. An equal volume of petroleum ether was added to the reaction mixture after it was allowed to cool to room temperature. The crystalline product which precipitated amounted to 1.1 g., m.p. 148-151°. There was no depression of m.p. upon admixture with IIa prepared by cyclization of Ia. Their ir spectra were identical.

Diethyl Formylsuccinate (4-Methyl-3-thiosemicarbazone) (Ic).

A solution of 12.1 g. (0.06 mole) of diethyl formylsuccinate and 6.3 g. (0.06 mole) of 4-methyl-3-thiosemicarbazide in 200 ml. of ethanol was heated under reflux overnight. Removal of the solvent gave 17.3 g. of product. The analytical sample (m.p. 102-105°) was obtained by recrystallization from ethanol; ir (potassium bromide): μ 3.00, 3.18 (NH), 5.74 (ester C=O); pmr (deuteriochloroform): δ 2.90 (d, 2H, CH_2), 3.20 (d, 3H, N-CH_3), 3.81 (m, 1H, CH-CO_2), 7.57 (d, 1H, -CH=N).

Ethyl 1-Methylthiocarbamoyl-5-oxo-3-pyrazoline-4-acetate (IIf).

To a solution of 50 ml. of ethanol, 50 ml. of water and 50 ml. of concentrated ammonium hydroxide was added 5 g. (0.017 mole) of Ic. The reaction mixture was heated on a steam bath for 30 minutes, cooled in ice, and acidified with concentrated hydrochloric acid. The product which was deposited amounted to 3.6 g. (m.p. 145-151°). The analytical sample (m.p. 149-151°) was obtained by recrystallization from ethanol; ir (potassium bromide): μ 3.40 (broad NH), 5.74 (ester C=O), 6.12 (lactam C=O); pmr (deuteriochloroform) and shift reagent (S.R.), Eu[fod]$_3$, δ:

pmr (DMSO-d_6): δ 1.20 (t, 3, CH_2CH_3), 3.17 (d, 3, $NHCH_3$), 3.30 (s, 2, CH_2C(=O)), 4.12 (q, 2, CH_2CH_3), 7.88 (s, 1, HC=N), 11.22 (broad, 1, $NHCH_3$).

	CH_2CH_3	$NHCH_3$
50 mg. sample	1.28 (t)	3.25 (d)
+ 20 mg. S.R.	1.37	3.29
+ 40 mg. S.R.	1.44	3.34
+ 70 mg. S.R.	1.72	3.48

CH_2C(=O)	CH_2CH_3	H-C=N		
3.39 (s)	4.21 (q)	7.70 (s)	+	7.43 (s)
3.62	4.39	7.73		7.43
3.83	4.58	7.86		7.43
4.64	5.23	8.12		7.47

Ethyl Acetoacetate (4-Methyl-3-thiosemicarbazone) (V).

A solution of 10.5 g. (0.1 mole) of 4-methyl-3-thiosemicarbazide and 13.0 g. (0.1 mole) of ethyl acetoacetate in 200 ml. of ethanol was heated under reflux for 6 hours. Cooling the reaction mixture in ice resulted in the deposit of a crystalline product amounting to 17.0 g. (m.p. 82-84°). An analytical sample (m.p. 81-82°) was obtained by recrystallization from ethyl acetate-petroleum ether; ir (potassium bromide): μ 3.01, 3.07 (NH), 5.76 (ester C=O).

Anal. Calcd. for $C_8H_{15}N_3O_2S$: C, 44.22; H, 6.96; N, 19.34; S, 14.75. Found: C, 44.22; H, 6.93; N, 19.61; S, 14.98.

3-Methyl-1-methylthiocarbamoyl-3-pyrazoline-5-one (VI).

A solution of 12.3 g. (0.056 mole) of V in 400 ml. of concentrated ammonium hydroxide was allowed to stand at room temperature overnight. Acidification with glacial acetic acid gave a precipitate which amounted to 9.5 g. (m.p. 197-203°). The analytical sample (m.p. 200-203°) was obtained by recrystallization from ethanol; ir (potassium bromide): μ 3.20 (NH), 6.06 (lactam C=O); pmr (DMSO-d_6): δ 2.22 (s, 3H, 3-CH_3), 3.12 (d, 3H, NCH_3), 5.22 (s, 1H, 4-H).

Anal. Calcd. for $C_6H_9N_3OS$: C, 42.09; H, 5.30; N, 24.54; S, 18.72. Found: C, 42.12; H, 5.40; N, 24.21; S, 18.88.

Reaction of Ethyl 3-Methyl-5-oxo-1-thiocarbamoyl-3-pyrazoline-4-propionate (IIi) with Hydrazine Hydrate.

A mixture of 1.4 g. (0.0055 mole) of IIi and 1.0 g. (0.02 mole) of hydrazine hydrate in 50 ml. of ethanol was heated under reflux for 4 hours, during which time a precipitate was deposited. This material (0.4 g.) was removed by filtration and proved to be thiosemicarbazide by m.p. and ir spectral comparison. The filtrate was evaporated to dryness and the residue (0.9 g.) was recrystallized from benzene, giving 0.6 g. of ethyl 3-methyl-5-oxo-3-pyrazoline-4-propionate, m.p. 178-180° dec.; ir (potassium bromide): μ 3.83 (very broad, NH), 5.78 (ester C=O), 6.20 (lactam C=O); pmr (DMSO-d_6): δ 1.15 (t, 3H, CH_2CH_3), 4.03 (q, 2H, CH_2CH_3), 2.48 (s, broad 4H, -CH_2CH_2-), 2.08 (s, 3H, CH_3C=).

Anal. Calcd. for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.19; H, 7.22; N, 14.45.

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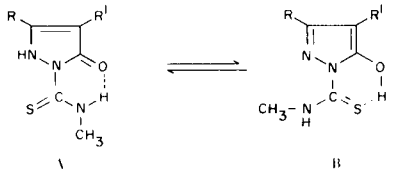
(3) The technique of examining the effects of hydrogen chloride and ammonia gas on compounds in potassium bromide by ir determinations has been described previously by one of us: B. R. Hofmann and G. H. Ellis, *Anal. Chem.*, **39**, 406 (1967).

(4) F. H. McMillan and J. A. King, *J. Am. Chem. Soc.*, 77, 3376 (1955).

(5) R. H. Wiley and P. Wiley, "Pyrazolones, Pyrazolidones and Derivatives," Interscience Publishers, New York, N. Y., 1964, pp. 102-103.

(6) One reviewer has suggested that hydrogen bonding of the types A and B may account for greater stability of tautomers and thus a slow interconversion rate. Other hydrogen bonded structures are also possible. The influence of hydrogen bonding on this rate as well as other factors influencing the equilibrium such as solvent, temperature, and substituent effects have not been studied.



A B

(7) See also A. A. Santilli and D. H. Kim, U. S. Patent, 3,704,242 (1972), in which these products are depicted in their hydroxypyrazole tautomeric form.

(8) S. C. De and N. C. Dutt, *J. Indian Chem. Soc.*, 5, 459 (1928).