N-Methylpyrazolo-N-hydroxypyrimidinediones[1]

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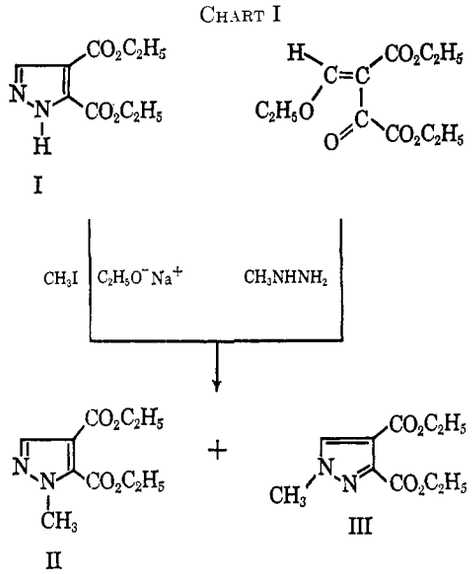
The synthesis and proof of structure of ethyl 1-methyl-3,4- and -4,5-pyrazoledicarboxylates (III and II) are described. These products were converted to N-methylpyrazolo-N-hydroxypyrimidinediones (XIa and XIIa in the case of III and VIa for II). The structures of these pyrazolopyrimidinediones were determined by reduction and methylation to a known trimethylpyrazolopyrimidinedione.

The conversion of 4,5-imidazoledicarboxylic esters to 1-hydroxyxanthines[2] illustrates the synthesis of a condensed N-hydroxyuracil system and this communication describes a cognate series of reactions commencing from vicinal pyrazoledicarboxylic esters.

Methylation of ethyl 3,4- (or 4,5-) pyrazoledicarboxylate (I) yielded a mixture of II and III (in the ratio of 3:4) which were separated readily. An alternate approach consisted of treating ethyl ethoxymethyleneoxalacetate with methylhydrazine which also furnished a mixture of II and III (see Chart I). The

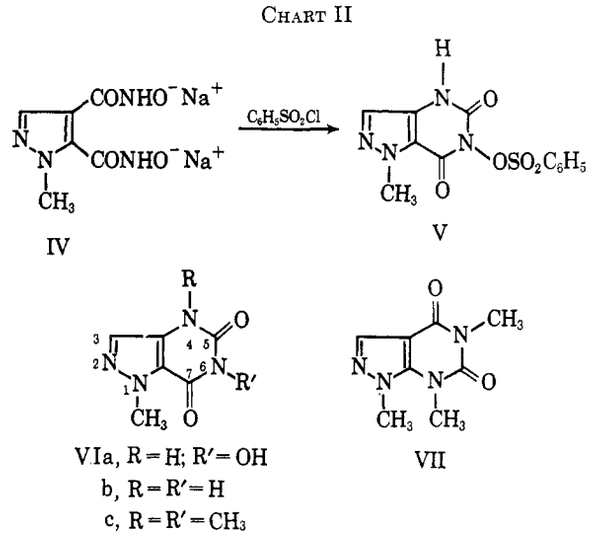
CHART I



formation of these esters by this method appeared to be influenced by the temperature of the reaction; at 5–10°, the ratio of II to III was 4:5, while at 20°, III seemed to be produced exclusively.[3] Immediate assignment of structures to II and III proved difficult since no data had been reported in the literature for either of these esters, and only one of the corresponding acids (*viz.*, 1-methyl-4,5-pyrazoledicarboxylic acid) had been described previously but its physical constants did not agree entirely with either of the two acids which we had isolated.[4] Assignment of structures to II and III (and the corresponding acids) was not feasible on the basis of the chemical shifts of the pyrazole protons since no definitive nmr data was available on the chemical shifts of the ring proton in isomeric 3,4- and 4,5-disubstituted pyrazoles. A recent study[5] established that in a number of isomeric 3,4- and 4,5-disubstituted pyrazoles, the ring proton (H-5) in the former appeared more shielded than that (H-3) in the latter. This phenomenon was found to be the reverse for esters II and III and their corresponding acids. The structures of II and III were established independently by proving the structure of the pyrazolopyrimidinediones derived from them.

The action of hydroxylamine in the presence of sodium ethoxide on II yielded the sodium hydroxamate IV, which on treatment with benzenesulfonyl chloride in tetrahydrofuran[2] produced the sulfonyl ester V (see Chart II). Basic hydrolysis of V furnished the

CHART II



N-hydroxy compound VIa. Its structure was proved by reduction with zinc and hydrochloric acid[6,7] to VIb, followed by methylation to give the known VIc,[8] which was different from the other three isomers, VII,[9] XIc,[9] and XIIc.[8] Not only did this conversion of V to VIc establish the structure of V and that of VIa, but indeed also that of the ester II.

(1) The authors gratefully acknowledge support of this investigation by Public Health Service Research Grant No. CA-04661 from the National Cancer Institute.

(2) L. Bauer, C. N. V. Nambury, and D. Dhawan, *J. Heterocyclic Chem.*, **1**, 275 (1964); L. Bauer and D. Dhawan, *ibid.*, **2**, 220 (1965).

(3) The reaction was carried out by the method described by R. G. Jones and C. W. Whitehead [*J. Org. Chem.*, **20**, 1342 (1955)] for the reaction of ethyl ethoxymethyleneoxalacetate with phenylhydrazine, which yielded only ethyl 1-phenyl-4,5-pyrazoledicarboxylate, the analog of II.

(4) R. Hüttel and M. E. Schön, *Ann.*, **625**, 55 (1959). We are indebted to Dr. Hüttel for a copy of the ultraviolet spectrum of 1-methyl-4,5-pyrazoledicarboxylic acid which was identical with our specimen, although the melting point of his acid differed from the one we observed.

(5) J. D. Albright and L. Goldman, *J. Org. Chem.*, **31**, 273 (1966).

(6) This method has been used successfully in the reduction of N-hydroxyuracil and related compounds [see W. Klötzer and M. Herberz, *Monatsh.*, **96**, 1721 (1965), and papers quoted therein].

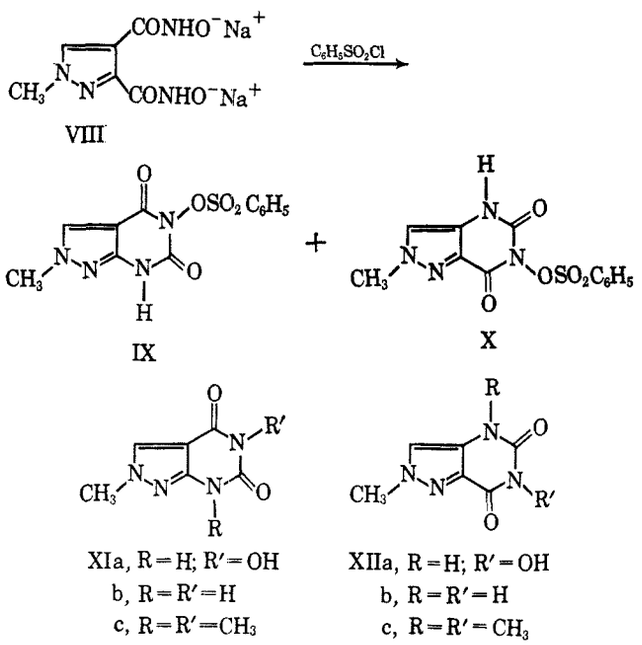
(7) A. Dornow and K. Fischer [*Chem. Ber.*, **99**, 72 (1966)] reported the reduction of a number of 3-hydroxy-4-quinazolones to the corresponding 4-quinazolones by means of zinc and dilute acetic acid, but this method failed to reduce XIa and XIIa.

(8) V. Papesch and R. M. Dodson, *J. Org. Chem.*, **30**, 199 (1965).

(9) P. Schmidt, K. Eichenberger, M. Wilhelm, and J. Druey, *Helv. Chim. Acta*, **42**, 349 (1959).

A similar series of reactions was investigated starting from III. This ester readily furnished the corresponding hydroxamate salt VIII, but the reaction of the latter with benzenesulfonyl chloride in tetrahydrofuran gave a mixture of IX and X (see Chart III). This was

CHART III



evident when basic hydrolysis of this product afforded a mixture of XIa and XIIa, whose nmr spectrum consisted of four singlets indicative of the presence of two NCH_3 and two pyrazole ring protons. It was possible to separate XIa and XIIa by means of ion-exchange chromatography.[10] Fractional crystallization of either IX and X or XIa and XIIa proved tedious and was only partially effective. However, XIa and XIIa were separated by several crystallizations from a zinc acetate–acetic acid solution.[11] The structures of the pure isomers were determined, individually, by reduction and subsequent methylation, XIa and XIIa giving rise to XIc and XIIc, respectively.

The reaction of VIII with benzenesulfonyl chloride was investigated in a number of different solvents. All gave mixtures of products except in N,N-dimethylformamide which gave only IX as the major product.

The results of this study indicate that in both series, starting from either IV or VIII, the hydroxamic acid group at the more exposed position, *i.e.*, at C-4 in IV and at C-3 or C-4 in VIII, underwent this modified Lossen rearrangement. This mode of selective rearrangement follows the pattern observed in the reaction of 1-alkyl-4,5-imidazoledicarbohydroxamic acids when the hydroxamic acid at position 4 of the imidazole ring was degraded.[2] This unique behavior exhibited by vicinal imidazole- and pyrazoledicarbohydroxamic acids tends to suggest that (at least) in tetrahydrofuran it is the less hindered hydroxamate anion which attacks benzenesulfonyl chloride preferentially, thus initiating a series of reactions which leads to these condensed N-hydroxyuracils.

(10) We are indebted to Drs. Bernard Weissmann and M. Litwack for their advice on ion-exchange chromatography; see also B. Weissmann, P. A. Bromberg, and A. B. Gutman, *J. Biol. Chem.*, **224**, 407 (1957).

(11) This difference in solubility may be due to partial complex formation since this separation was much more tedious when zinc acetate was omitted. The pK_a of XIa, as determined by the ultraviolet method described by C. E. Meloan and R. W. Kiser, "Problems and Experiments in Instrumental Analysis," Charles E. Merrill Books, Inc., Columbus, Ohio, 1963, p 9, was 5.6 while that of a mixture of XIa and XIIa (1:1) was 5.5.

Experimental Section[12]

Ethyl 1-Methyl-3,4- and -4,5-pyrazoledicarboxylates. A.—A stirred solution of ethyl 3,4- (or 4,5-) pyrazoledicarboxylate[3] (I, 17 g, 0.08 mole) in ethanol (250 ml) containing sodium ethoxide (from 2 g of sodium) was treated dropwise with methyl iodide (12 ml) at 15–20°. The mixture was then heated under reflux for 4 hr. More methyl iodide (3 ml) was added and heating was continued for another 2 hr. Solvents were removed *in vacuo*, and the residue was dissolved in chloroform. The chloroform extract was washed with 5% sodium carbonate solution (three 75-ml portions), dried (sodium sulfate), and distilled.

Ethyl 1-methyl-4,5-pyrazoledicarboxylate (II, 6.5 g, 36%) distilled as a colorless liquid: bp 100–105° at 0.5 mm, $n^{13}D$ 1.4870, λ_{max} 234 mμ (log ε 3.91). Its infrared spectrum (film) showed the ester C=O stretching vibration at 1725 cm^{-1}. The nmr spectrum ($CDCl_3$) showed resonances due to the pyrazole proton (H-3) at δ 7.82, the NCH_3 at 4.00, the ethyl group of the ester as two overlapping quartets centered at 4.30 (CH_2) and as two overlapping triplets at 1.38 (CH_3), respectively. In $(CH_3)_2SO$, these signals occurred at δ 7.90, 4.01, 4.35, and 1.33, respectively.

Anal. Calcd for $C_{10}H_{14}N_2O_4$: N, 12.38. Found: N, 12.26.

Ethyl 1-methyl-3,4-pyrazoledicarboxylate (III, 8.5 g, 47%), was obtained as a yellow oil bp: 135–145° at 0.5 mm, $n^{12.5}D$ 1.4920, λ_{max} 224 mμ (log ε 3.98), $\gamma_{C=O}$ (film) 1725 cm^{-1}. Its nmr spectrum showed H-5, NCH_3, and the ethyl resonances at δ 8.00, 3.95, 4.32 (CH_2), and 1.33 (CH_3) in $CDCl_3$ and at δ 8.35, 3.97, 4.30, and 1.30 in $(CH_3)_2SO$, respectively.

Anal. Calcd for $C_{10}H_{14}N_2O_4$: N, 12.38; Found: N, 12.45.

It was also possible to separate these isomeric esters on alumina (Alcoa Chemicals, F-20). The ester II was eluted by benzene and III by chloroform.

B.—To a stirred, ice-cold solution of ethyl ethoxymethyleneoxalacetate[3] (24.4 g, 0.1 mole) in ethanol (75 ml) was added an ethanolic solution of methylhydrazine (4.6 g, 0.1 mole in 25 ml), keeping the temperature between 5 and 10°. After stirring for 0.5 hr at 20°, solvents were removed *in vacuo*, and the residue was dissolved in chloroform and washed several times with 5% sodium carbonate solution. Distillation gave II (6.5 g, 36%), bp 103–105° at 0.5 mm, and III (8.0 g, 45%), bp 138–145° at 0.5 mm. When the initial addition of methylhydrazine to ethyl ethoxymethyleneoxalacetate was carried out at 20°, followed by the same work-up, distillation gave a minute quantity of II and 74% of III.

1-Methyl-4,5-pyrazoledicarboxylic Acid.—The ester II (2.3 g, 0.01 mole) was heated with 3% aqueous sodium hydroxide solution (50 ml) at 100° for 1 hr and cooled, and the solution was acidified to pH 2. The product (1.2 g, 70%) was recrystallized from water: mp 182–184° dec, λ_{max} 239 mμ (log ε 4.00), λ_{max} (1,4-dioxane) 250 mμ (log ε 3.92); lit.[4] mp 234–235° dec, λ_{max} (1,4-dioxane) 250 mμ (log ε 3.92). Its nmr spectrum showed two singlets due to pyrazole and NCH_3 protons at δ 7.97 and 4.12 in D_2O at 60°, and at δ 7.95 and 4.08 in $(CH_3)_2SO$, respectively.

Anal. Calcd for $C_6H_6N_2O_4$: N, 16.64. Found: N, 16.22.

1-Methyl-3,4-pyrazoledicarboxylic Acid.—Hydrolysis of III (2.3 g) as described above for II yielded on adjusting the pH to 6, the **sodium salt** (1.2 g) which crystallized from water: mp 355° dec. Its nmr spectrum (D_2O) showed the pyrazole and NCH_3 protons at δ 8.15 and 4.00, respectively.

Anal. Calcd for $C_6H_4N_2Na_2O_4$: N, 13.10. Found: N, 13.42.

When a solution of this salt was acidified to pH 2, the **acid** precipitated, which crystallized from water: mp 239–241°

(12) All melting and boiling points are uncorrected. Analyses were performed by Dr. Kurt Eder, Geneva, and Micro-Tech Laboratories, Inc., Skokie, Ill. Nmr spectra were recorded at 60 Mc by means of the Varian A-60 spectrometer, all signals being recorded in parts per million (δ) downfield from tetramethylsilane (TMS) as internal standard. Ultraviolet spectra were obtained in 95% ethanol (unless stated otherwise) by means of the Beckman DK-1 spectrophotometer. Infrared spectra were determined in Nujol mulls (unless otherwise specified) on the Perkin-Elmer 337 spectrophotometer.

dec, λ_{max} 229 mμ (log ε 3.95), λ_{max} (1,4-dioxane) 237 mμ (log ε 3.98). Its nmr spectrum showed the pyrazole and NCH_3 protons at δ 8.22 and 4.00 (in D_2O at 60°) and at δ 8.45 and 4.01 in $(CH_3)_2SO$, respectively.

Anal. Calcd for $C_6H_6N_2O_4$: N, 16.64. Found: N, 16.35.

1-Methyl-6-benzenesulfonyloxy-1H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (V).—To a stirred suspension of powdered, dried hydroxylammonium chloride (3.06 g, 0.044 mole) in ethanol was added a solution of sodium ethoxide (1.01 g of sodium in 100 ml of ethanol) below 20°; when neutral to litmus (about 0.5 hr), the precipitate of sodium chloride was filtered off. Ethyl 1-methyl-4,5-pyrazoledicarboxylate (II, 4.58 g, 0.02 mole) was added to the ethanolic solution of hydroxylamine prepared above, followed by a solution of sodium ethoxide (1.0 g of sodium in 100 ml of ethanol). The mixture was allowed to stand for 18 hr, and then sodium 1-methyl-4,5-pyrazoledicarbohydroxamate (IV, 4.5 g) was filtered off, washed with ethanol and ether, dried *in vacuo*, and used immediately.

To a stirred suspension of the dry powdered salt (4.75 g from several batches) in tetrahydrofuran (50 ml) was added a solution of benzenesulfonyl chloride in tetrahydrofuran (5.5 ml, 0.044 mole in 25 ml), dropwise, the temperature of the mixture being kept below 20°. After 1 hr, sodium acetate trihydrate (4.0 g) was added, and stirring was continued for 0.5 hr. Solids were filtered off, washed with tetrahydrofuran, and worked up separately as shown below. The filtrate was concentrated to about 25 ml *in vacuo* and diluted with water (200 ml) and petroleum ether, bp 30–60° (125 ml). After 20 hr, the solid which had separated was filtered and washed with cold ethanol and ether. The solid which had been filtered off was triturated also with water and petroleum ether to yield some additional product. The combined yield (1.8 g, mp 228–232°, 28% based on the starting ester) was crystallized from cold dimethyl sulfoxide and ethanol: mp 234–236° dec; λ_{max} 269 mμ (sh) (log ε 3.74), 276 (3.80), 289 (3.81); $\gamma_{C=O}$ 1765 and 1715 cm^{-1}. Its nmr spectrum in $(CH_3)_2SO$ showed singlets due to the pyrazole (δ 7.47) and NCH_3 (δ 4.07) and a multiplet due to the phenyl protons between δ 7.7 and 8.2.

Anal. Calcd for $C_{12}H_{10}N_4O_5S$: C, 44.73; H, 3.13; N, 17.39. Found: C, 44.86; H, 3.26; N, 17.38.

When this rearrangement was carried out in N,N-dimethylformamide and the reaction worked up as described under IX (below), V was isolated in 25% yield.

1-Methyl-6-hydroxy-1H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (VIa).—A solution of V (1.0 g) in aqueous 5% sodium hydroxide solution (20 ml) was heated on a steam bath for 5 min and filtered hot. The filtrate was cooled, acidified to pH 3 with hydrochloric acid, and kept at 5° for 8 hr. The product (0.5 g, 89%) crystallized from water: mp 309–312° dec, λ_{max} 243 mμ (log ε 3.90) and 284 (log ε 3.79), $\gamma_{C=O}$ 1730 (s) and two bands at 1675 (s) and 1660 (s) cm^{-1}. The nmr spectrum in $(CH_3)_2SO$ showed the resonances for the pyrazole and NCH_3 protons at δ 7.39 and 4.09, respectively.

Anal. Calcd for $C_6H_6N_4O_3$: C, 39.57; H, 3.32; N, 30.76. Found: C, 39.60; H, 3.36; N, 30.61.

1-Methyl-1H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (VIb).—A mixture of VIa (0.5 g) in 2 *N* hydrochloric acid (100 ml) was heated at 100° while zinc dust (5.0 g) was added in four portions (at 15-min intervals), and the mixture was heated 2 hr longer, with occasional shaking. It was filtered hot and the residue was washed with hot 2 *N* hydrochloric acid (25 ml). The filtrate was cooled at 5° for 20 hr to furnish the product (0.2 g, 44%): mp 380–382° dec, λ_{max} 287 mμ (log ε 3.75), $\gamma_{C=O}$ 1725 and 1690 cm^{-1}. Its nmr spectrum showed the pyrazole and NCH_3 protons at δ 7.37 and 4.08 in $(CH_3)_2SO$ and at δ 7.95 and 4.40 in CF_3CO_2H, respectively.

Anal. Calcd for $C_6H_6N_4O_2$: C, 43.38; H, 3.64; N, 33.72. Found: C, 43.71; H, 3.58; N, 34.01.

Reduction of the sulfonate V (0.5 g) directly with zinc and hydrochloric acid as above also furnished VIb (0.06 g, 24%), mp 381–382° dec.

1,4,6-Trimethyl-1H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (VIc).—A solution of VIb (0.25 g) in 10% sodium hydroxide solution (10 ml) was treated with methyl sulfate (1.5 ml). The mixture was shaken and the precipitate was filtered off after 1 hr. Crystallization from water afforded needles: mp 209–211°; λ_{max} 290 mμ (log ε 3.79); $\gamma_{C=O}$ 1713, 1705 sh, and a band at 1672 cm^{-1}; nmr signals in $CDCl_3$ at δ 7.38 (pyrazole proton), 4.22, 3.47, 3.40 (NCH_3 groups), and in $(CH_3)_2SO$ at δ 7.70 (pyrazole proton), 4.09, 3.35, 3.22 (NCH_3 groups); lit.[8,13] mp 211–213°, λ_{max}^{MeOH} 291 mμ (log ε 3.75), and identical nmr resonances in $CDCl_3$.

2-Methyl-5-benzenesulfonyloxy-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5H,7H)-dione (IX).—Ethyl 1-methyl-3,4-pyrazoledicarboxylate was converted to VIII as described above for IV under the preparation of V. A stirred suspension of VIII in N,N-dimethylformamide (4.75 g in 25 ml) was treated dropwise with benzenesulfonyl chloride (5.5 ml) in N,N-dimethylformamide (10 ml) below 20°. Sodium acetate trihydrate (4.0 g) was added after 1 hr and stirring continued for 0.5 hr. The reaction mixture was poured into ice–water (200 ml) and after 15 hr, the product was filtered off and washed with methanol (25 ml) and ether (25 ml): mp 252–253° dec. After one crystallization, it weighed 2.4 g (38% based on III): mp 254–256° dec, λ_{max} 262 mμ (broad) (log ε 3.95), $\gamma_{C=O}$ 1750 and 1725 cm^{-1}. Its nmr spectrum in $(CH_3)_2SO$ showed singlets due to the pyrazole proton (δ 8.48) and NCH_3 (δ 3.90) and a multiplet due to the phenyl protons between δ 7.7 and 8.2.

Anal. Calcd for $C_{12}H_{10}N_4O_5S$: C, 44.73; H, 3.13; N, 17.39. Found: C, 44.85; H, 3.31; N, 17.30.

2-Methyl-5-hydroxy-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5H,7H)-dione (XIa).—A solution of IX (0.5 g) in 4% sodium hydroxide solution (10 ml) was heated on the steam bath for 5 min and then filtered hot. The filtrate was cooled to 0° and acidified to pH 3. After 8–10 hr, the product was filtered and crystallized from water (0.25 g, 89%): mp 370–372° dec (sealed tube); λ_{max} 254 mμ (log ε 3.87); $\gamma_{C=O}$ 1740 (s), 1685 (vs), and a band at 1635 (m) cm^{-1}; nmr signals in $(CH_3)_2SO$ at δ 8.40 (pyrazole proton) and 3.90 (NCH_3).

Anal. Calcd for $C_6H_6N_4O_3$: C, 39.57; H, 3.32; N, 30.76. Found: C, 39.05; H, 3.51; N, 30.80.

2-Methyl-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5H,7H)-dione (XIb).—Reduction of XIa (0.5 g) as described for the preparation of VIb gave XIb (0.15 g, 33%) which crystallized from water: mp >400°; λ_{max} 260 mμ (log ε 3.79); $\nu_{C=O}$ 1745 and 1695 cm^{-1}; nmr signals at δ 8.30 (pyrazole proton) and 3.85 (NCH_3) in $(CH_3)_2SO$, and at δ 8.35 and 4.15 in CF_3CO_2H.

Anal. Calcd for $C_6H_6N_4O_2$: C, 43.38; H, 3.64; N, 33.72. Found: C, 43.09; H, 3.90; N, 33.35.

2,5,7-Trimethyl-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5H,7H)-dione (XIc).—Methylation of XIb (0.1 g) by the method described under the preparation of VIc, yielded the product (0.08 g, 69%) which crystallized in needles from ethanol: mp 196–198°; λ_{max} 240 mμ (log ε 3.73) and 264 mμ (log ε 3.85); $\nu_{C=O}$ 1700 (s) and 1650 (m) cm^{-1}; nmr resonances in $CDCl_3$ at δ 7.97 (pyrazole proton), 3.97, 3.51, 3.38 (NCH_3 groups), or in $(CH_3)_2SO$ at δ 8.38, 3.91, 3.37, and 3.22, respectively; lit.[9] mp 199–200°, λ_{max} (in 95% ethanol) 240 mμ (log ε 3.73) and 266 mμ (log ε 3.86).

2-Methyl-6-hydroxy-2H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (XIIa).—The preparation of VIII from III was followed as described under V. When VIII was treated with benzenesulfonyl chloride in tetrahydrofuran as described under V, a product (1.9 g, 30% based on III), mp 244–250° dec, was shown to be a mixture since its nmr spectrum in $(CH_3)_2SO$ possessed signals due to two NCH_3 groups (δ 3.90, 4.08) indicative of IX and X in the ratio of 1:1. Crystallization of the mixture from $(CH_3)_2SO$ afforded IX (0.7 g, 11%), mp 256–258° dec. However, this method was ineffective to separate the mixture satisfactorily.

Hydrolysis of this mixture of IX and X (0.5 g) by the method described for the preparation of XIa yielded a mixture of XIa and XIIa (0.25 g), mp 325–327° dec, in the ratio of 1:1 (by nmr analysis). Separation of these isomers was effected by the following procedures.

Three to five crystallizations of the mixture of XIa and XIIa (0.1 g) from small aliquots of a solution of zinc acetate dihydrate (0.25 g) in aqueous acetic acid (1:1, 100 ml) yielded (0.03 g) of XIIa: mp 328–330° dec; λ_{max} 242 mμ (log ε 3.76) and 282 mμ (log ε 3.68); $\nu_{C=O}$ 1740 (s), 1705 (s), and two other bands at 1670 (s) and 1620 (w) cm^{-1}. Its nmr spectrum in $(CH_3)_2SO$ showed resonances at δ 7.73 (pyrazole proton) and 4.00 (NCH_3).

Anal. Calcd for $C_6H_6N_4O_3$: C, 39.57; H, 3.32; N, 30.76. Found: C, 39.78; H, 3.47; N, 30.97

When the mother liquors from the crystallizations were concentrated *in vacuo* to about 10 ml and cooled, a mixture of XIa

(13) We are indebted to Dr. V. Papesch of G. D. Searle and Co., Skokie, Ill., for a copy of the infrared spectrum of their sample which was identical with our sample.

and XIIa (about 3:1) separated. Two additional crystallizations from the same solution yielded XIa (0.03 g), mp 370° dec, identical with the sample described above.

Separation by ion-exchange chromatography on Dowex 1-X8 in the acetate form was carried out as follows.[10] Dowex 1-X8 chloride (200–400 mesh) was washed several times with water to remove fines. The well-settled resin was cycled successively with 10-column volumes each of 1 *M* sodium carbonate solution, water, 2 *M* acetic acid, and finally with water, ensuring that the effluent did not show appreciable absorption in the ultraviolet. The resin was filtered and stored moist at 5°. A slurry of this resin (20 ml) was transferred with water into a column (50 × 1 cm) and washed with 50 ml of 0.02 *M* ammonium acetate buffer solution, pH 9.6. A solution of XIa and XIIa (10 mg) was dissolved in this ammonium acetate buffer solution and placed on the column. Elution was then carried out with ammonium acetate buffer solutions of decreasing pH. The ultraviolet spectrum of each 10-ml eluate was checked for its contents. Effluents from elution with ammonium acetate buffer solutions (50 ml) of pH 7.5, 6.5, and 6.0 did not contain either required isomer, but with a buffer solution of pH 5.8, an effluent (60 ml) with characteristic maxima at 244 and 284 mμ was obtained. Evaporation of these fractions to about 2 ml yielded XIIa (3 mg), mp 328–330° dec.

Continued elution of the column with the same ammonium acetate buffer (pH 5.8) solution (60 ml) gave mixtures of XIa and XIIb (λ_{max} 248–254 mμ) followed by fractions showing λ_{max} 255 mμ, characteristic of XIa. This isomer was taken off the column more efficiently by an ammonium acetate buffer solution pH 4.5 (50 ml) and then pH 3.5 (50 ml) and finally by 0.1 *N* acetate acid. All fractions with λ_{max} 255 mμ were combined and concentrated to about 5 ml to give pure XIa (5 mg), mp 370° dec.

2,4,6-Trimethyl-2H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (XIIc).—Reduction of XIIa (0.2 g) as described for VIb was followed except for one modification. It was essential to increase the pH and thus the acidic filtrate was treated with sodium acetate trihydrate until the pH reached 4. On cooling at 5° for 15 hr, XIIb (0.1 g, 55%) separated: mp 400–410° dec; λ_{max} 283 mμ (log ε 3.74); $\nu_{C=O}$ 1740 and 1705 cm^{-1}; nmr signals in $(CH_3)_2SO$, δ 7.66 (pyrazole proton) and 3.98 (NCH_3).

This product (0.08 g) was methylated by the method described for VIc, to produce XIIc (0.06 g): mp 259–261°; λ_{max} 288 mμ (log ε 3.73); $\nu_{C=O}$ 1720, other bands at 1665, 1625, and 1540 cm^{-1}; lit.[8,13] mp 261–263°, λ_{max}^{MeOH} 288 mμ (log ε 3.74). Its nmr spectrum in $(CH_3)_2SO$ exhibited resonance at δ 7.99 (pyrazole proton), 4.01, 3.33, and 3.25 (NCH_3 groups) and correspondingly in $CDCl_3$ at δ 7.32, 4.07, 3.47, 3.43.

The Thermal Cleavage of 1-Carbamoyl- and 1-Thiocarbamoylpyrazole Derivatives

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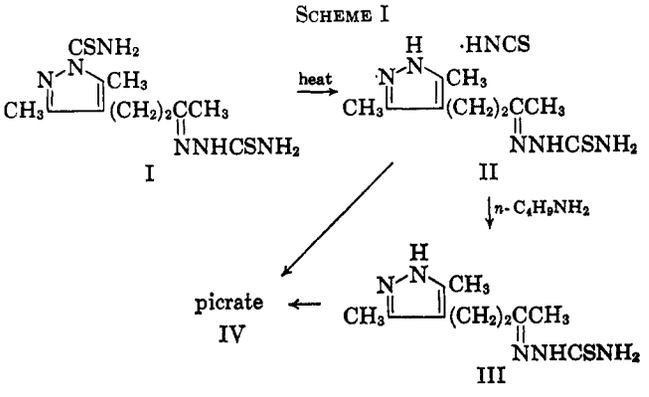
1-Thiocarbamoylpyrazoles undergo thermal decomposition with formation of thiocyanate salts while 1-N-methylthiocarbamoylpyrazoles decompose to yield methyl isothiocyanate and N^1-unsubstituted pyrazoles. Under more vigorous conditions 1-carbamoylpyrazoles also yield N^1-unsubstituted pyrazoles and cyanic acid which trimerizes to cyanuric acid.

In the course of a program of synthesis aimed at relating chemical structure and antitumor activity in a series of pyrazole derivatives it became necessary to examine the thermal cleavage of 1-carbamoyl- and 1-thiocarbamoylpyrazole derivatives. It is well known that 1-acylpyrazoles are readily cleaved with formation of N^1-unsubstituted derivatives together with products which arise from the substituents on the nitrogen atom. Scott and his co-workers[2] have described the aminolysis of 1-carbamoyl- and 1-thiocarbamoyl-3,5-dimethylpyrazole with formation of, among other products, substituted ureides and 3,5-dimethylpyrazole. Ried and Schleimer[3] have found that the cyanoacetyl residue is removed from 1-cyanoacetyl-3,5-dimethylpyrazole by treatment with amines in refluxing benzene while Ried and Konigstein[4] have reported a method of preparing aldehydes by the hydrogenolysis of 1-acylpyrazoles with lithium aluminum hydride. However the thermal cleavage of carbamoyl- and thiocarbamoylpyrazole derivatives has not been recorded.

The work described herein arose as a result of an examination of the pyrazole thiosemicarbazone (I) obtained by treatment of 3-acetyl-2,6-heptanedione with thiosemicarbazide. This compound on drying at 100° for a short period underwent a facile transformation yielding a product which, on the basis of elemental analysis and infrared examination, was shown to be the thiocyanate salt II (Scheme I). This salt on treatment with hydrazine hydrate in ethanolic solution yielded, among other products, thiosemicarbazide while treatment with *n*-butylamine yielded the base III. Further evidence in favor of structure II was obtained by conversion to a picrate which was identical with the picrate obtained from III.

SCHEME I



The thermal splitting of 1-thiocarbamoylpyrazoles with formation of the corresponding thiocyanate salts has now been found to be a more general reaction. The presence of the salt was established by infrared examination and elemental analysis while in a number of cases the thiocyanic acid has been displaced by picric

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