Anal. Calcd. for $C_{19}H_{16}N_2O_2 \cdot C_2H_5OH$: C, 71.98; H, 6.33; N, 8.00. Found: C, 72.15; H, 6.30; N, 8.62.

Recrystallization from toluene yielded the unsolvated compound as colorless plates, m.p. 180°.

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.50; H, 5.40; N, 9.40.

1-Acetyl-4-cyano-2-benzyl-3-oxopyrrolidine (IVbm).—Acetylation and cyclization of 24.5 g. (0.1 mole) of N-cyanoethylphenylalanine ethyl ester yielded, after crystallization from ethanol, 12.8 g. (53%) of IVbm as colorless cubes, m.p. 180–181°.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56 Found: C, 69.41; H, 5.81; N, 11.79.

1-Acyl-2-alkyl-4-cyano-3-methoxy-3-pyrrolines (V).—To a vigorously stirred suspension of a compound of type IV (0.05 mole) in ether (150 ml.) was added slowly an ethereal solution of diazomethane (*ca.* 3 g. from 21.5 g. of "Diazald"[15]). The compounds reacted and dissolved with a rapid evolution of nitrogen. The solutions were kept overnight at room temperature and then evaporated under reduced pressure. The residues were crystallized from a suitable solvent as indicated in Table I.

Infrared spectra measured on Nujol mulls showed characteristic bands at 4.5, 6.1, and 6.2 μ in the 2.5- to 6.5-μ range.

1-Acyl-2-alkyl-3-amino-4-cyano-3-pyrrolines (VI).—Solutions of the compounds of type IV (0.02 mole) and ammonium formate (2.52 g., 0.04 mole) in ethanol (20 ml.) were refluxed for 16 hr. The products (VI) precipitated after the solutions were cooled, and were crystallized from ethanol. The compounds prepared are listed in Table I.

Infrared spectra measured on Nujol mulls showed characteristic bands at 2.9, 3.1, 4.5, 6.0, and 6.2 μ in the 2.5- to 6.5-μ range.

6-Acyl-4-amino-2-methyl-6,7-dihydro-5H-pyrrolo[3,4-*d*]pyrimidines (VII).—Solutions of the compounds of type V (0.01 mole) in dry ethanol (10 ml.) were added to filtered solutions of acetamidine [0.02 mole, from 1.88 g. of acetamidine hydrochloride and 0.46 g. of sodium in dry ethanol (50 ml.)]. The solutions were refluxed for 16 hr., then evaporated under reduced pressure. The residues were washed with water and crystallized from suitable solvents as indicated in Table IV.

6-Acyl-4,4-diamino-6,7-dihydro-5H-pyrrolo[3,4-*d*]pyrimidines (VIII). A. From the Enol Ethers V.—Compounds of type V (0.02 mole) were added to filtered solutions of 0.02 mole of guanidine (from 1.92 g. of guanidine hydrochloride and 0.46 g. of sodium) in 50 ml. of absolute ethanol, and the solutions were refluxed for 4 hr., then evaporated under reduced pressure. The residues were washed with water and crystallized from the solvents indicated in Table II.

B. From the Enamines VI.—Solutions of 0.01 mole of the compounds of type VI and 0.015 mole of guanidine in ethanol (prepared as in procedure A) were refluxed for 16 hr., then evaporated. The residues were washed with water and crystallized.

6-Acyl-4-amino-6,7-dihydro-5H-pyrrolo[3,4-*d*]pyrimidines (IX). A. Formamidine Acetate Procedure.[10a]—Solutions of the compounds of type VI (0.01 mole) and formamidine acetate (10.3 g., 0.1 mole) in dimethylformamide (50 ml.) were refluxed for 1 hr. The dark solutions were concentrated to a volume of 20 ml. under reduced pressure, cooled, and filtered to collect the products in the form of black powders. The compounds were crystallized several times from dimethylformamide or ethanol as indicated in Table III.

B. First Ethyl Orthoformate Procedure.[10b-d]—Solutions of the compounds VI (2 g.) in ethyl orthoformte (8 ml.) and acetic anhydride (8 ml.) were refluxed for 2 hr., then evaporated under reduced pressure. The oily residues were dissolved in dry ethanol (25 ml.) and ethanolic ammonia solutions (excess) were added. After 5 min. the ethanol was evaporated and the residue crystallized.

C. Second Ethyl Orthoformate Procedure.—The following procedure[10a] was adopted for compound IXhm when procedure B proved unsuccessful. A mixture containing compound VIhm (2 g.), ethyl orthoformate (8 ml.), and acetic anhydride (8 ml.) was refluxed for 2 hr. while dry ammonia was bubbled into the solution. Then the mixture was cooled and filtered, and the precipitate was washed well with water to remove formamidine acetate formed. The water-insoluble residue was crystallized from dimethylformamide.

2- and/or 7-Substituted 4-Amino-6,7-dihydro-5H-pyrrolo[3,4-*d*]pyrimidines (X, XI, and XII).—To solutions of the 6-acyl derivatives (VII, VIII, or IX) (0.01 mole) in ethanol (135 ml.) were added solutions of sodium hydroxide (7.5 g.) in water (15 ml.). After a reflux period of 8 hr. the solutions were concentrated under reduced pressure to *ca.* 75 ml., cooled, and diluted with water. The products were collected by filtration and crystallized from water. The compounds of types X, XI, and XII which were prepared are listed in Tables IV, II, and III, respectively.

(15) N-Methyl-N-nitroso-*p*-toluenesulfonamide (Aldrich Chemical Co.) was used as described by T. J. DeBoer and H. J. Backer, *Rec. trav. chim.*, **73**, 229 (1954).

Isomeric Pyrazolo[4,3-*d*]pyrimidinediones

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Diazotization of 1,3,6-trimethyl-5-aminouracil (Ia) followed by cyclization of the diazonium salt with strong alkali gave 4,6-dimethylpyrazolo[4,3-*d*]pyrimidinedione (IV), an isomer of theophylline. Methylation of IV produced 1,4,6-trimethylpyrazolo[4,3-*d*]pyrimidinedione (V), m.p. 211–213°. Since this compound differed greatly from one tentatively assigned the same structure by Robins,[5] the methylation of pyrazolo[4,3-*d*]pyrimidinedione was repeated. Both V and the 2,4,6-trimethylpyrazolo[4,3-*d*]pyrimidinedione (VII), m.p. 261–264°, were obtained. The structure of VII was established by an independent synthesis from 1,3-dimethylpyrazole-5-carboxylic acid (VIII). Corresponding triethylpyrazolo[4,3-*d*]pyrimidinediones were also synthesized. The n.m.r. spectra of the various compounds are consistent with the structures assigned by chemical methods.

Our interest in the possible physiological activity of alkyl derivatives of 1-H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (VI), an isomer of xanthine, led to the investigation of methods for the synthesis of the 4,6-dimethyl derivative IV, an isomer of theophylline.[2] We had previously shown that treatment of 5-amino-6-methyluracil (Ib) with excess nitrous acid produced pyrimido[5,4-*d*][1,2,3]triazine-6,8(5H,7H)-dione 3-oxide (IIb).[3] Both Behrend[4] and Robins[5] have reduced IIb with stannous chloride to the pyrazolopyrimidine VI. However, reduction of the corresponding 5,7-dimethylpyrimido[5,4-*d*][1,2,3]triazine-6,8(5H,7H)-dione 3-oxide (IIa) by a similar method failed to give us the desired dimethylpyrazolopyrimidine IV. Instead, a compound analyzing for three nitrogen atoms

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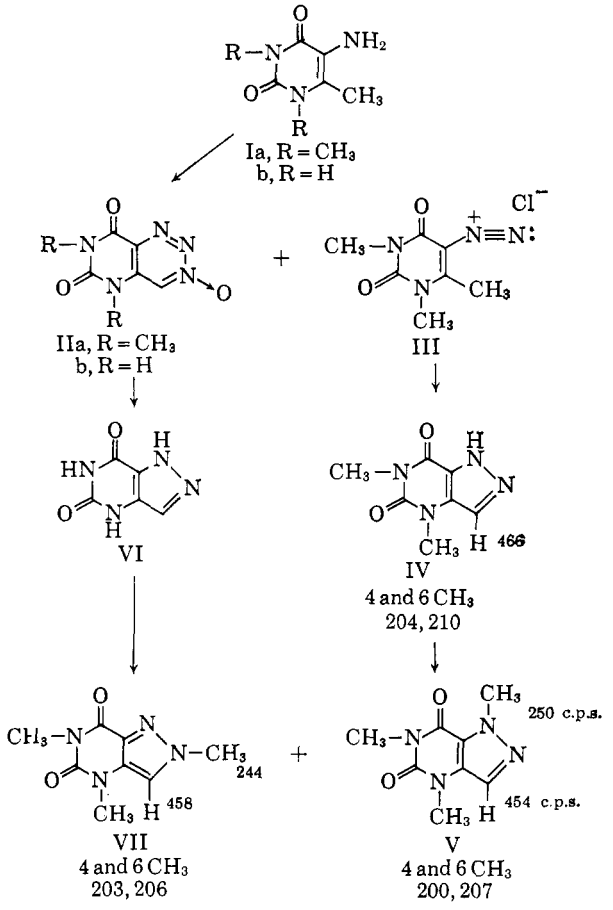
(2) For studies on substituted pyrazolo[3,4-*d*]pyrimidines, see P. Schmidt, K. Eichenberger, and M. Wilhelm, *Helv. Chim. Acta*, **45**, 1620 (1962), and R. K. Robins, *J. Am. Chem. Soc.*, **79**, 6407 (1957), and preceding papers in both series.

(3) V. Papesch and R. M. Dodson, *J. Org. Chem.*, **28**, 1329 (1963).

(4) R. Behrend, *Ann.*, **245**, 213 (1888).

(5) R. K. Robins, F. W. Furcht, A. D. Grauer, and J. W. Jones, *J. Am. Chem. Soc.*, **78**, 2418 (1956).

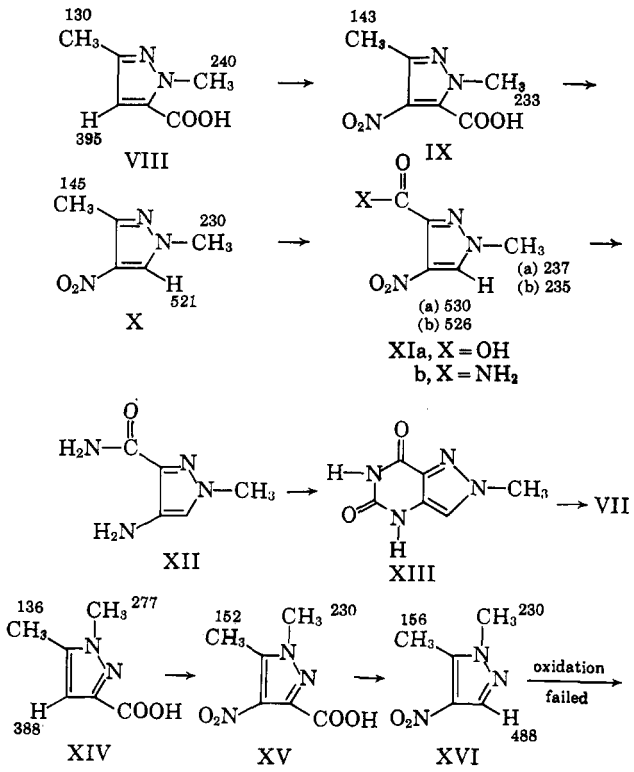
SCHEME I



per molecule was obtained.[6] Rose has prepared a number of pyrazolo[4,3-*d*]pyrimidines by the action of alkali on the diazonium salts of 5-amino-4-methylpyrimidines.[7] This method proved successful in our hands.

1,3,6-Trimethyl-5-aminouracil (Ia) was diazotized using slightly less than one equivalent of sodium nitrite. The 5,7-dimethylpyrimido[5,4-*d*][1,2,3]triazine-6,8(5H,7H)-dione 3-oxide (IIa) which formed in small quantity was removed by filtration, and the soluble diazonium salt III was cyclized to the desired 4,6-dimethyl-1H-pyrazolo[4,3-*d*]pyrimidine-5,7-(4H,6H)-dione (IV) with strong alkali. In order to correlate this material with the trimethylpyrazolopyrimidinedione previously prepared by Robins,[5] the dimethyl compound IV was alkylated with dimethyl sulfate. The trimethylpyrazolopyrimidinedione V, m.p. 211–213°, differed markedly from that previously reported, m.p. 267–269°. Consequently, we repeated the alkylation of VI as reported by Robins[5]; from it we isolated two isomeric trimethylpyrazolopyrimidinediones VII, m.p. 261–263°, and V, m.p. 211–213°.[8] (See Scheme I.)

SCHEME II



The structures of these isomeric trimethylated compounds, V and VII, were established by the independent synthesis of VII. 1,3-Dimethylpyrazole-5-carboxylic acid[9] (VIII) was nitrated with fuming nitric and sulfuric acids, and the resulting 1,3-dimethyl-4-nitropyrazole-5-carboxylic acid (IX) was decarboxylated to 1,3-dimethyl-4-nitropyrazole (X). Oxidation of X with potassium dichromate in sulfuric acid gave 1-methyl-4-nitropyrazole-3-carboxylic acid (XIa), which, in turn, was converted to its amide XIb. The nitroamide, XIb, was reduced to the corresponding 1-methyl-4-aminopyrazole-3-carboxamide (XII). Fusion of XII with urea yielded the 2-methylpyrazolo-[4,3-*d*]pyrimidinedione (XIII). Methylation of XIII gave 2,4,6-trimethyl-2H-pyrazolo[4,3-*d*]pyrimidine-5,7-(4H,6H)-dione (VII), m.p. 261–264°. This structure differs from that tentatively assigned to the compound by Robins, *et al.*[5] (See Scheme II.)

An attempt to synthesize 1,4,6-trimethyl-1H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (V) by way of

(6) It seems probable that this compound, m.p. 261–263°, was a 4,6-dimethylisoxazolopyrimidinedione. However, because of the difficulty of obtaining consistent analyses, no further attempts were made to determine its structure. For the conversion of benz[1,2,3]triazine 3-oxides to benzisoxazoles, see J. Meisenheimer, O. Senn, and P. Zimmermann, *Ber.*, **60**, 1736 (1927).

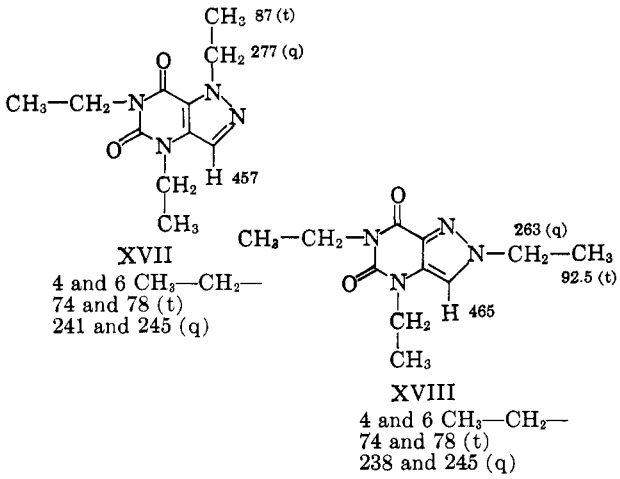
(7) F. L. Rose, *J. Chem. Soc.*, 3448 (1952); 4116 (1954).

(8) We have not investigated the change of isomer ratio with alkylating conditions, and thus have no explanation for the difference between our results and those previously reported.[5] It seems probable, however, that the position of alkylation of the pyrazole ring will vary with conditions, just as K. von Auwers [*J. prakt. Chem.* **143**, 259 (1935)] has found for many other substituted pyrazoles.

(9) K. von Auwers and H. Hollman, *Ber.* **59**, 601, 1282 (1926); K. von Auwers and Th. Breyhan, *J. prakt. Chem.*, **143**, 259 (1935). The structural assignments rest on the failure of 1,3-dialkyl-4-bromopyrazole-5 carboxylic acids to esterify when treated with methanolic hydrogen chloride. 1,5-Dialkyl-4-bromopyrazole-3-carboxylic acids were esterified under the same conditions. While the physical properties given by von Auwers [*J. prakt. Chem.*, **143**, 276 (1935)] correspond to the isomeric dimethylpyrazolecarboxylic acid esters formed under the conditions described, the names of the isomers are interchanged. That this is so can be seen by reference to pages 275 and 264 of that same article and to the two previous references given above. Unfortunately, the data given by T. L. Jacobs ("Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., p. 92) on the methylation of ethyl 3(5)-methylpyrazole-5(3)-carboxylate with methyl iodide was taken from that erroneous page. Thus, in the sentence immediately below the formulas at the top of p. 92 beginning, "thus, methyl iodide yields. . . .," the Roman numerals VI and VII should be reversed.

the 1-methyl-4-aminopyrazole-5-carboxylic acid failed. 1,5-Dimethylpyrazole-3-carboxylic acid (XIV) was easily nitrated to XV, and this, in turn, was readily decarboxylated to 1,5-dimethyl-4-nitropyrazole (XVI). Attempts to oxidize this pyrazole to the desired 5-carboxylic acid by the method used successfully on 1,3-dimethyl-4-nitropyrazole (X) failed. It should be noted that, just as von Auwers[9] failed to esterify 1,4-disubstituted pyrazole-5-carboxylic acids with methanolic hydrogen chloride, we failed to oxidize a 1,4-disubstituted 5-methylpyrazole XVI to the corresponding pyrazole-5-carboxylic acid (Scheme II).

Ethylation of 1H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (VI) with ethyl iodide and potassium carbonate in acetone gave the 1,4,6-triethylpyrazolo[4,3-*d*]-pyrimidinedione (XVII), m.p. 107–108°, and the 2,4,6-triethylpyrazolo[4,3-*d*]pyrimidinedione (XVIII), m.p.



XVII
4 and 6 CH_3—CH_2—
74 and 78 (t)
241 and 245 (q)

XVIII
4 and 6 CH_3—CH_2—
74 and 78 (t)
238 and 245 (q)

148–151°. The structures of these compounds were assigned by comparison of their infrared spectra with those of the trimethyl derivatives V and VII, by the order in which the compounds were eluted from a silica gel column, and finally by the relatively minor differences found in the ultraviolet spectra of the 1- and 2-alkylated derivatives.

In addition to the triethyl compounds XVII and XVIII, a small quantity of a diethylpyrazolo[4,3-*d*]-pyrimidinedione (XIX), m.p. 222–225°, was isolated. From a comparison of the ultraviolet and infrared spectra of this compound with those of the triethyl derivatives, it is believed to be 1,4- (or 6-) diethyl-1H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (XIX).

The n.m.r. spectra[10] of the respective pyrazolopyrimidinediones, IV, V, VII, XVII, and XVIII, are consistent with the structures assigned. The n.m.r. spectrum of caffeine (1,3,7-trimethylxanthine) has absorption bands at 202, 213, and 241 c.p.s. (CH_3 groups, CD_3COOD). These same bands lie at 205, 215, and 241 c.p.s. in deuterated chloroform.[11] The spectrum of theophylline (1,3-dimethylxanthine) has absorption bands at 203 and 214 c.p.s. (CD_3COOD). This comparison clearly establishes that the band at low field (241 c.p.s.) can be assigned to the 7-methyl group (the group attached to the nitrogen of the five-membered ring) and that the change of solvent has little effect on the chemical shifts of the methyl groups. Similar conclusions can be reached from an examination of the spectra of IV and V (see formulas above). From this it is apparent that the methyl group absorbing at lowest field (250 c.p.s.) must be that on the nitrogen of the pyrazole ring. Compound V was also soluble enough in deuterated chloroform for its spectrum to be determined in that solvent (204, 209, and 253 c.p.s., CH_3 groups). Again, it is apparent that the change of solvent has only small effects on the spectra.

Because of the inductive and magnetic anisotropic effect of the carbonyl group at C-7, the n.m.r. spectra of the isomeric trimethylpyrazolopyrimidinediones, V and VII, should differ in the chemical shifts of the methyl groups at N-1 or N-2. That compound with the N–CH_3 absorption at lower field should be methylated at N-1. As can be seen from the formulas V and VII, such an assignment agrees with that made above from the chemical evidence.[12] Similar assignments of structure can be made for the triethyl derivatives XVII and XVIII, on the basis of n.m.r. spectra. Again, these assignments are consistent with those made above.

The diethylpyrazolo[4,3-*d*]pyrimidinedione (XIX) showed chemical shifts at 79 and 240, 87 and 274 (ethyl groups), and 458 c.p.s. (H at C-3). This pattern would correspond to a 1,4- (or 6-) diethylpyrazolopyrimidinedione, a structural assignment also corresponding to that made above from infrared spectral comparisons. With the evidence available, we have not been able to assign unequivocally the chemical shifts of the alkyl groups at 4 and 6 in these compounds.[12a]

The n.m.r. spectra of the pyrazoles are also consistent with their assigned structures; *e.g.*, the 1,3-dimethylpyrazole-5-carboxylic acid (VIII) has the chemical shift for the N–CH_3 group (adjacent to the carboxylic acid) at lower field than that for the N–CH_3 group of 1,5-dimethylpyrazole-3-carboxylic acid (XIV). Also, the effect of an electronegative group (–NO_2 or –COOH) on the chemical shift of an adjacent group (–H or –CH_3) on the pyrazole ring correlates well with the position of the double bond in the valence bond formula of the pyrazole—the greater the double-bond character of the bond between the groups, the greater the deshielding of the adjacent group by the electronegative group.

(10) Because of the insolubility of the pyrazolopyrimidinediones, the n.m.r. spectra of these compounds, unless stated otherwise, were determined in CD_3COOD. The n.m.r. spectra of the pyrazoles were determined in $(CD_3)_2SO$. To save space and to make this manuscript more readable, the positions of the absorption bands in the n.m.r. spectra (the center of the triplets and quartets) are given in cycles per second downfield from tetramethylsilane directly on the formulas of the respective compound. All determinations were run at 60 Mc.p.s. on a Varian A-60 instrument.

(11) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "Varian Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., Spectrum No. 204.

(12) In order to be sure that deuteration of V and VII by CD_3COOD was not markedly influencing the position of the methyl shifts, the n.m.r. spectra of these two compounds were also determined in $(CD_3)_2SO$: V, 1-CH_3 245, 3-H 460; VII, 2-CH_3 239, and 3-H 477 c.p.s.

(12a) NOTE ADDED IN PROOF.—Since submission of this manuscript, a publication definitively assigning the chemical shifts of the 1-, 3-, and 7-methyl groups of caffeine has appeared [T. G. Alexander and M. Maienthal, *J. Pharm. Sci.*, **53**, 962 (1964)]. If it is assumed that the chemical shifts of the groups at the 6- and 4-positions in these pyrazolopyrimidinediones paralled those at the 1- and 3-positions in caffeine, then the group absorbing at highest field (lowest cycles per second) should be at the 6-position. Compound XIX, then, could be assigned the structure, 1,6-diethyl-1H-pyrazolo[4,3-*d*]dione. From the method of synthesis, this would also be the more probable structure.

Experimental[13]

4,6-Dimethyl-1H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (IV).—To a solution of 4.0 g. (0.024 mole) of 1,3,6-trimethyl-5-aminouracil (Ia) in a mixture of 23.6 g. of ice and 5.3 ml. of concentrated hydrochloric acid was added a solution of 1.42 g. (0.021 mole) of sodium nitrite in 4.7 ml. of water. The resulting suspension was stirred for 15 min. at a temperature below 10°. The 5,7-dimethylpyrimido[5,4-*d*][1,2,3]triazine-6,8(5H,7H)-dione 3-oxide (IIa) (200 mg., infrared spectrum identical with that previously described[3]) formed in the reaction was removed by filtration. The filtrate was then added slowly and with stirring to 20% aqueous sodium hydroxide at a temperature below 10°. After the addition was complete (10 min.), the basic solution was filtered, then neutralized with hydrochloric acid. The precipitated material (1.2 g.) was separated by filtration and dried. Crystallization of this material from 400 ml. of methanol yielded 0.80 g. of 4,6-dimethyl-1H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (IV), m.p. 307–308°. The analytical sample [m.p. 307–308°; λ_{max} 285 mμ (ε 4950); n.m.r. (CD_3COOD) 204 and 210 (CH_3 groups), 466 c.p.s. (3-H)] was purified by chromatography on silica gel (elution with 4% ethyl acetate in benzene) and crystallization from water.

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.31; H, 4.73; N, 30.93.

1,4,6-Trimethyl-1H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (V).—Dimethyl sulfate (0.8 ml.) was added to a stirred suspension of 0.80 g. of 4,6-dimethyl-1H-pyrazolo[4,3-*d*]pyrimidine-5,7-(4H,6H)-dione (IV) in 3.2 ml. of 10% aqueous sodium hydroxide. On continued stirring, the solid completely dissolved; then precipitation occurred. The precipitate was separated by filtration. Repeated crystallization of the product from water gave 0.125 g. of the trimethylpyrazolopyrimidinedione V, m.p. 211–213°.

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.77; H, 5.18; N, 28.47.

1,4,6-Trimethyl-1H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (V) and 2,4,6-Trimethyl-2H-pyrazolo[4,3-*d*]pyrimidine-5,7-(4H,6H)-dione (VII).—1H-Pyrazolo[4,3-*d*]pyrimidine-5,7(4H,-6H)-dione (VI) (4.0 g.), prepared by the method of Behrend,[4] was dissolved in 32 ml. of 10% aqueous sodium hydroxide. At a temperature not exceeding 22°, 10.8 g. of dimethyl sulfate was added dropwise with stirring. The alkaline solution became neutral after 0.5 hr. of stirring, and the precipitate which formed was separated by filtration. The filtrate was extracted five times with 10-ml. portions of chloroform, and the precipitate was added to the combined extracts. The chloroform solution was separated from any water present, dried over sodium sulfate, and evaporated to dryness. The residue, dissolved in benzene, was chromatographed on 350 g. of silica gel, using first benzene and then increasing per cents of ethyl acetate in benzene for elution. The benzene eluates gave 1.82 g. (melting points ranging from 205–208° to 211–212°) of 1,4,6-trimethyl-1H-pyrazolo[4,3-*d*]-pyrimidine-5,7(4H,6H)-dione (V). Crystallization from water gave 1.10 g.: m.p. 211–213°; λ_{max} 291 mμ (ε 5670); n.m.r. (CD_3COOD) 200, 207, and 250 (CH_3 groups), 454 c.p.s. (3-H); n.m.r. ($CDCl_3$) 204, 209, and 253 (CH_3 groups), 443 c.p.s. (3-H). This compound was identical (mixture melting point and infrared spectra) with that prepared above.

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.25; H, 4.91; N, 28.52.

Elution of the column with 10% ethyl acetate in benzene yielded, after crystallization from water, 0.75 g. of 2,4,6-trimethyl-2H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (VII): m.p. 261–263°; λ_{max} 288 mμ (ε 5,450); n.m.r. (CD_3COOD) 203, 206, and 244 (CH_3 groups), 458 c.p.s. (3-H); lit.[5] m.p. 267–269°.

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.58; H, 5.42; N, 28.45.

1,3-Dimethyl-4-nitropyrazole-5-carboxylic Acid (IX).—1,3-Dimethylpyrazole-5-carboxylic acid [VIII: 26.0 g.; m.p. 210–212°[6]; n.m.r. in $(CD_3)_2SO$ 130 and 240 (CH_3 groups), 395 c.p.s. (4-H); b.p., of ethyl ester, 92–95° (10 mm.)] was added gradually with stirring at a temperature below 20° to a mixture of 23.6 ml. of 25% fuming sulfuric acid and 19.7 ml. of 5% fuming nitric acid. The stirring was continued until all of the pyrazole VIII had dissolved; the solution was heated on a steam bath for 6 hr., then poured onto 80 g. of ice. The resulting precipitate, after crystallization from water, yielded 29.3 g. of 1,3-dimethyl-4-nitropyrazole-5-carboxylic acid: n.m.r. [$(CD_3)_2SO$] 143 and 233 c.p.s. (CH_3 groups). The analytical sample was crystallized an additional time from water. Since the compound decarboxylated on melting, the melting point (from 158 to 163°) varied with the rate of heating.

Anal. Calcd. for $C_6H_7N_3O_4$: C, 38.92; H, 3.81; N, 22.70. Found: C, 39.29; H, 4.20; N, 22.43.

1,3-Dimethyl-4-nitropyrazole (X).—1,3-Dimethyl-4-nitropyrazole-5-carboxylic acid (IX, 43 g.) was heated without solvent at 130–140° until evolution of carbon dioxide had ceased (*ca.* 30 min.). Crystallization of the residue from ethanol–water (20:80) gave 32 g. of 1,3-dimethyl-4-nitropyrazole (X): m.p. 79–80°; n.m.r. [$(CD_3)_2SO$] 145 and 230 (CH_3 groups), 521 c.p.s. (5-H).

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.68; H, 5.03; N, 29.93.

1-Methyl-4-nitropyrazole-3-carboxylic Acid (XIa).—A solution of 1,3-dimethyl-4-nitropyrazole (X, 5.0 g.) in 30 ml. of concentrated sulfuric acid was treated with 11 g. of finely powdered potassium dichromate gradually with stirring over a period of 30 min. The temperature of the reaction was carefully held between 32° and 35° by external cooling. The mixture was stirred for an additional 30 min., then poured over ice. The product was separated by filtration, then crystallized from water. From this reaction 2.3 g. of 1-methyl-4-nitropyrazole-3-carboxylic acid (XIa), m.p. 170–173° dec., was obtained: n.m.r. [$(CD_3)_2SO$] 237 (CH_3 group), 530 c.p.s. (5-H).

Anal. Calcd. for $C_5H_5N_3O_4$: C, 35.09; H, 2.95; N, 24.56. Found: C, 35.43; H, 2.82; N, 24.84.

1-Methyl-4-nitropyrazole-3-carboxamide (XIb).—A solution of 4.2 g. of 1-methyl-4-nitropyrazole-3-carboxylic acid (XIa) in 20 ml. of thionyl chloride was heated under reflux for 1.5 hr. The thionyl chloride was removed by distillation under vacuum. The residue was treated with a mixture of concentrated ammonium hydroxide and ice. After crystallization from water, the 1-methyl-4-nitropyrazole-3-carboxamide (XIb), 2.0 g., had m.p. 165–167°; n.m.r. [$(CD_3)_2SO$] 235 (CH_3 group), 526 c.p.s.(5-H).

Anal. Calcd. for $C_5H_6N_4O_3$: C, 35.30; H, 3.55; N, 32.93. Found: C, 35.40; H, 3.59; N, 32.89.

1-Methyl-4-aminopyrazole-3-carboxamide (XII).—1-Methyl-4-nitropyrazole-3-carboxamide (XIb, 1.7 g.) in 200 ml. of absolute alcohol was hydrogenated in a Parr apparatus using 0.2 g. of 5% palladium on charcoal at room temperature. The reduction was complete in 1 hr. The catalyst was separated by filtration, and the solution was evaporated to *ca.* 10 ml. When the solution was cooled, the product separated. Two crystallizations of this material from absolute alcohol yielded 0.7 g. of 1-methyl-4-aminopyrazole-3-carboxamide, m.p. 171–172°.

Anal. Calcd. for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.55; H, 5.66; N, 40.07.

2,4,6-Trimethyl-2H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (VII) from 1-Methyl-4-aminopyrazole-3-carboxamide (XII).—1-Methyl-4-aminopyrazole-3-carboxamide (XII, 0.9 g.) and 1.0 g. of urea were heated in a covered dish in a metal bath at 220° (bath temperature) for 15 min. A vigorous reaction ensued. The product was ground to a powder, then dissolved in 9.0 ml. of 2 *N* aqueous sodium hydroxide. The solution was filtered, acidified with acetic acid, and cooled. The crude 2-methyl-2H-pyrazolo-[4,3-*d*]pyrimidine-5,7(4H,6H)-dione so obtained was dissolved in 4.8 ml. of 10% aqueous sodium hydroxide and treated with 1.7 ml. of dimethyl sulfate with stirring. The temperature of the reactiod mixture rose to 60°. The solution was cooled and an additional 1.7 ml. of dimethyl sulfate was added, followed by 0.5 ml. of 50% aqueous sodium hydroxide. The solution was stirred for 0.5 hr., then heated to boiling. The solution was neutralized and cooled. Crystallization of the resulting precipitate from 18 ml. of water gave 0.6 g. of 2,4,6-trimethyl-2H-pyrazolo[4,3-*d*]-pyrimidine-5,7(4H,6H)-dione (VII), m.p. 261–264°, λ_{max} 288 mμ (ε 5,200). This compound was identical in all respects (mixture melting point and infrared spectra) with that prepared above.

1,5-Dimethyl-4-nitropyrazole-3-carboxylic Acid (XV).—1,5-Dimethylpyrazole-3-carboxylic acid [XIV: 6.8 g.; m.p. 174–176°[9]; n.m.r. in $(CD_3)_2SO$ 136 and 227 (CH_3 groups), 388 c.p.s.

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(4-H); b.p., of ethyl ester, 146–148° (10 mm.)] was nitrated using the procedure described above. Two crystallizations of the product from water gave 4.7 g. of 1,5-dimethyl-4-nitropyrazole-3-carboxylic acid, m.p. 153–155° dec., n.m.r. [$(CD_3)_2SO$] 152 and 230 c.p.s. (CH_3 groups).

Anal. Calcd. for $C_6H_7N_3O_4$: C, 38.92; H, 3.81; N, 22.70. Found: C, 39.26; H, 3.90; N,22.87.

1,5-Dimethyl-4-nitropyrazole (XVI).—1,5-Dimethyl-4-nitropyrazole-3-carboxylic acid (60 g.) was decarboxylated in two batches by heating at 150° for 2 hr. Crystallization of the product from methanol gave 39 g. of 1,5-dimethyl-4-nitropyrazole (XVI): m.p. 114–116°; n.m.r. [$(CD_3)_2SO$] 156 and 230 (CH_3 groups), 488 c.p.s. (3-H).

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.77; H, 4.95; N, 29.67.

Repeated attempts to oxidize this pyrazole to 1-methyl-4-nitropyrazole-5-carboxylic acid by the method described above failed. Approximately 50% of the starting material was recovered from each oxidation.

1,4,6-Triethyl-1H-pyrazolo[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (XVII) and 2,4,6-Triethyl-2H-pyrazolo[4,3-*d*]pyrimidine-5,7-(4H,6H)-dione (XVIII).—1H-Pyrazolo[4,3-*d*]pyrimidine-5,7(4H,-6H)-dione (VI, 30 g.), prepared by the method of Behrend,[4] 2.5 l. of acetone, 500 ml. of ethyl iodide, and 550 g. of anhydrous potassium carbonate were heated under reflux with stirring for 18 hr. The mixture was filtered and the filtrate was evaporated to dryness. The residue was extracted repeatedly with chloroform, and the combined chloroform extracts were evaporated to dryness, finally under vacuum. The residue was chromatographed on 1300 g. of silica gel. The column was eluted with benzene containing increasing amounts of ethyl acetate. The fractions eluted with 20% ethyl acetate in benzene weighed 7.71 g., and after crystallization from petroleum ether (b.p. 28–38°) gave 5.2 g. of 1,4,6-triethyl-1H-pyrazolo[4,3-*d*]pyrimidine-5,7-(4H,6H)-dione (XVII): m.p. 107–108°; λ_{max} 291 mμ (ε 5750); n.m.r. (CD_3COOD) 74 (t, J = 7 c.p.s.), 245 (q, J = 7), 78 (t, J = 7), 241 (q, J = 7) (4- and 6-CH_3CH_2–), 87 (t, J = 7), 277 (q, J = 7) (1-CH_3CH_2–), 457 c.p.s. (3-H).

Anal. Calcd. for $C_{11}H_{16}N_4O_2$: C, 55.91; H, 6.83; N, 23.72. Found: C, 55.98; H, 6.59; N, 23.47.

Further elution of the column with 25% ethyl acetate in benzene gave 10.5 g. of a mixture of 2,4,6-triethyl-2H-pyrazolo-[4,3-*d*]pyrimidine-5,7(4H,6H)-dione (XVIII) and a diethylpyrazolo[4,3-*d*]pyrimidinedione. The diethyl compound was isolated from one fraction containing 827 mg. of the mixture. This fraction was dissolved in alcohol (4 ml.) and the resulting solution was diluted with an equal quantity of absolute ether. The resulting precipitate was separated by filtration and washed with ether. The filtrate was cooled and a second crop of the diethyl compound was obtained. Crystallization of the 230 mg. of product so obtained from alcohol gave 175 mg. of 1,4- (or 6-) diethylpyrazolo[4,3-*d*]pyrimidinedione: m.p. 222–225°; λ_{max} 290.5 mμ (ε 5800); n.m.r. (CD_3COOD) 79 (t, J = 7 c.p.s.), 240 (poor q, J = 7) (4- or 6-CH_3CH_2–), 87 (t, J = 7), 274 (q, J = 7, 1-CH_3CH_2–), 458 c.p.s. (3-H).

Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 51.91; H, 5.81. Found: C, 51.78; H, 5.68.

The remaining fractions (9.7 g.) were dissolved in 40 ml. of ethanol; an equal quantity of absolute ether was added; and the precipitate was separated by filtration. The filtrate was evaporated and the residue was rechromatographed on 800 g. of silica gel. The material eluted with 45% ethyl acetate in benzene was purified, first by precipitation of the diethyl compound present using alcohol and absolute ether, then by two crystallizations from alcohol. In this way 1.5 g. of 2,4,6-triethyl-2H-pyrazolo-[4,3-*d*]pyrimidine-5,7-(4H,6H)-dione (XVIII), m.p. 148–151°, was obtained: λ_{max} 289 mμ (ε 5150); n.m.r. (CD_3COOD) 74 (*t*, J = 7), 245 (poor q, J = 7), 78 (t, J = 7), 238 (q, J = 7) (4- and 6-CH_3CH_2–), 92.5 (t, J = 7), 263 (q, J = 7) (2-CH_3CH_2–), 465 c.p.s. (3-H).

Anal. Calcd. for $C_{11}H_{16}N_4O_2$: C, 55.91; H, 6.83; N, 23.72. Found: C, 55.94; H, 6.84; N, 23.48.

Reaction of 2-Pyrones with Cyanide Ion[1]

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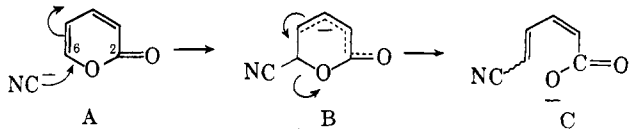
A number of 2-pyrones are shown to react readily with sodium cyanide in various media to give 5-cyano-2,4-pentadienoic acids. The reaction is stereospecific, and in at least one instance the stereochemistry of the product can be controlled by choice of reaction medium. Intramolecular catalysis of the hydrolysis of a cyano group by a neighboring carboxyl is established and used to distinguish between geometrical isomers.

A 2-pyrone offers two likely points of attack to a nucleophile: the carbon of the carbonyl group (position 2) and the carbon terminating the conjugated carbon chain (position 6). Reactions of the first type have been observed to take place with Grignard reagents,[2] alkoxide ions,[3] and complex metal hydrides under certain conditions.[4] Attack at position 6, to which the effect of the ring carbonyl is transmitted by resonance, occurs with diazomethane (in the presence of suitable activation)[5] and with complex metal hydrides under other conditions.[6,7] The best-known reaction of 2-pyrones with a nucleophile, the conversion into 2-pyridones by the action of ammonia, has been formulated by various workers as proceeding by attack at either position 2 or 6, without experimental evidence for either possibility; the point of attack cannot, of course, be established from the ring-closed product.

The present paper reports on the reaction of a number of readily available 2-pyrones **1** with sodium cyanide, which leads to the corresponding 5-cyano-2-*cis*-4-pentadienoic acids (**2** or **3**), and some further reactions of the latter. The mechanism of the reaction undoubtedly includes attack of the cyanide ion on position 6 of the pyrone A to form a resonance-stabilized carbanion intermediate B, which then breaks down with expulsion of the best leaving group to give the very stable carboxylate anion C.



A B C

In accord with this mechanism, the reactivity of 2-pyrones would be expected to be increased by substituents withdrawing electrons from position 6 by resonance, such as a 5-carbalkoxyl group, and de-

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