Derivatives of the New Ring System Pyrazolo[4,3-*d*]-*v*-triazine and the Synthesis of 5,7-Disubstituted 3-Methylpyrazolo[4,3-*d*]pyrimidines and 5,7-Disubstituted 3-Methylpyrazolo[4,3-*d*]pyrimidine 6-Oxides which are Structurally Related to the Nucleoside Antibiotics Formycin and Formycin B (1)

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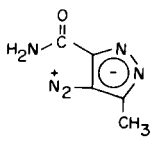
The synthesis of 7-methylpyrazolo[4,3-*d*]-*v*-triazin-4-one (**6**), a derivative of the new ring system, pyrazolo[4,3-*d*]-*v*-triazine, has been accomplished by a diazotization reaction. Ring closure of the appropriate pyrazole derivative and oxidation of the preformed bicyclic heterocycle with *m*-chloroperoxybenzoic acid has furnished 7-substituted 3-methylpyrazolo[4,3-*d*]pyrimidine 6-oxides. Ring closures to yield various 5,7-disubstituted 3-methylpyrazolo[4,3-*d*]pyrimidines are also discussed.

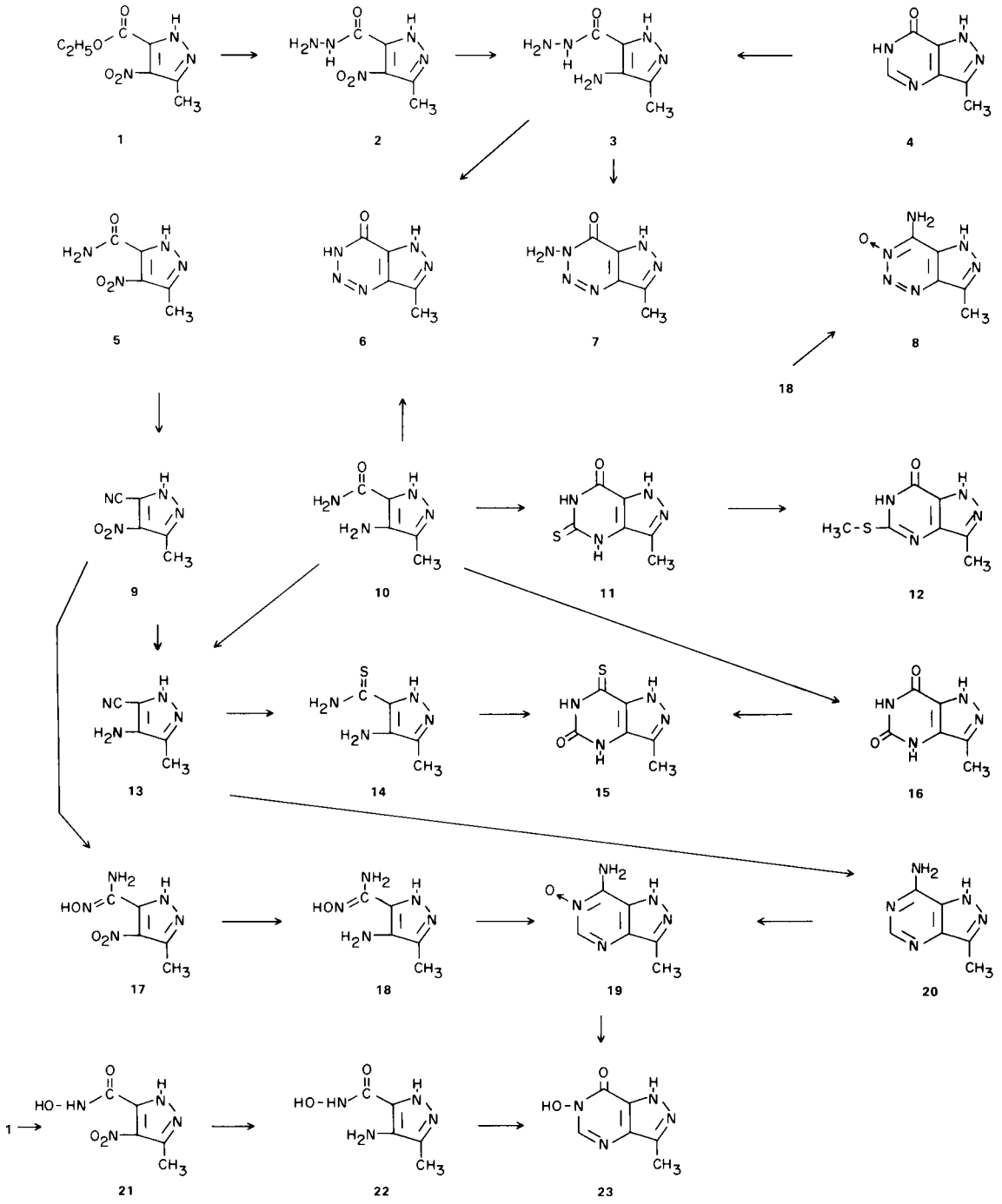
The isolation and characterization of the nucleoside antibiotics formycin and formycin B as 3-β-D-ribofuranosylpyrazolo[4,3-*d*]pyrimidines (4-7) generated a renewed interest in 3-substituted pyrazolo[4,3-*d*]pyrimidines. This interest has been further stimulated by the isolation of a metabolite of formycin and formycin B which was characterized as 3-β-D-ribofuranosylpyrazolo[4,3-*d*]pyrimidin-5,7-dione (oxoformycin) (8,9). This prompted the present study of reaction conditions for ring annulation of several pyrazoles for the preparation of various 3-methylpyrazolo-[4,3-*d*]pyrimidines and functional group transformations of pyrazoles and 3-methylpyrazolo[4,3-*d*]pyrimidines. This has resulted in the preparation of a number of new pyrazoles, pyrazolo[4,3-*d*]pyrimidines and pyrazolo[4,3-*d*]-*v*-triazines as well as the development of new procedures for the preparation of several known heterocycles using ring closure reaction conditions much milder than those previously reported. Derivatives of the pyrazolo-3,4-*d*]-*v*-triazine ring system have been reported, (10, 11a). However, the isomeric pyrazolo[4,3-*d*]-*v*-triazine ring system was unknown (11b) and prompted our investigation for the synthesis of derivatives of this new ring system.

Treatment of ethyl 3-methyl-4-nitropyrazole-5-carboxylate (**1**) with aqueous hydrazine furnished a good yield of 3-methyl-4-nitropyrazole-5-carboxhydrazide (**2**) which was converted to **3** on treatment with palladium on charcoal and hydrogen. This compound was found to be identical with the pyrazole (4-amino-3-methylpyrazole-5-carboxhydrazide) formed by heating 3-methylpyrazolo-4,3-*d*]pyrimidin-7-one (**4**) with 85% hydrazine hydrate at reflux temperature (12a). The ring opening of **4** to afford the pyrazole derivative **3** was ascertained by the loss of uv absorption (*p*H 1) (12b). That reduction of the carboxhydrazide group to the carboxamide group had not occurred on treatment with hydrazine was established by a comparison of **3** with an authentic sample (13a) of 4-amino-3-methylpyrazole-5-carboxamide (**10**). Treatment of **3** with one equivalent of sodium nitrite resulted in the formation of a compound which was assigned the structure 3-amino-7-methylpyrazolo[4,3-*d*]-*v*-triazin-4-one (**7**) on the basis of pmr spectral data. There was observed a peak at δ 6.7 which was assigned to the exocyclic amino group at position three and would not have been observed if a seven membered ring had been formed in the diazotization reaction. When **3** was treated with an excess of sodium nitrite, there was observed a smooth conversion of **3** to 7-methylpyrazolo[4,3-*d*]-*v*-triazin-4-one (**6**). This reaction presumably proceeds *via* **7** with the excess sodium nitrite then removing the exocyclic amino group. This has furnished the first derivatives of the pyrazolo[4,3-*d*]-*v*-triazine ring system. Treatment of **10** with sodium nitrite has also furnished an excellent yield (83.5%) of **6**. It is of interest that the pyrazole intermediate 4-diazo-3-methylpyrazole-5-carboxamide was not



isolated although there was some strong evidence that the reaction conditions could be modified slightly to accomodate the isolation of this intermediate. This intermediate

REACTION SCHEME



could be used to prepare some very interesting heterocycles (14,15). Treatment of 3-methyl-4-nitropyrazole-5-carboxamide (**5**) with phosphorus oxychloride at reflux temperature effected a facile dehydration to afford a 90% yield of 5-cyano-3-methyl-4-nitropyrazole (**9**). This assignment of structure was established by an ir spectrum which revealed a strong band at 2270 cm^{-1} (C≡N). Crystalline hydroxylamine furnished 3-methyl-4-nitropyrazole-5-amidoxime (**17**) (disappearance of the band at 2270 cm^{-1}) which was then converted to 4-amino-3-methylpyrazole-5-amidoxime (**18**) by treatment with 5% palladium on charcoal under a hydrogen atmosphere.

TABLE I

Ultraviolet Absorption Spectral Data for Certain Substituted Pyrazoles, Pyrazolo[4,3-*d*]pyrimidines and Pyrazolo[4,3-*d*]-*v*-triazines (a)

	*p*H 1		MeOH		*p*H 11	
	λ max	ε max	λ max	ε max	λ max	ε max
1	275	6,360	268	6,360	314	9,350
					230*	9,050
2	276	6,560	272.5	6,960	315	9,710
					230*	7.950
3			280	4,800	278	5,110
					235	6,050
4	281	6,450	277	6,450	300*	5,620
					288.5	8,700
					281	8,460
					226	9,600
5	277	6,900	272	6,460	315	9,860
					227.5	3,910
6	272.5	7,250			285	6,950
7	243	11,390	280	6,310	312	4,650
					229	17,200
8	302	3,660	355	2,490	355	3,660
	235*	16,920	299	3,660	295	3,320
	220	19,900	244	24,200	244	38,500
9	275	7,750			310	10,630
10			283	4,060	284	4,060
					230	4,270
11	278	15,500	282	17,490	278	12,750
	260	17,100	260*	13,650	251	20,000
	230*	9,290	232*	7,740	230*	12,750
12	290*	5,880	292*	5,490	297	5,880
	265	8,420	262.5	8,820	238	19,600
	223	17,450	224	20,200		
13					283	3,980
					230	5,000
14	292	8,900			288	10,900
	242.5	8,260			268*	8,425
15	356*	12,750	375	14,750	360	9,650
	343	14,300	304*	7,840	315	13,450
	314	10,900	293.5	8,460	287*	9,100
	262.5	9,300	261	7,650	262.5	10,560
	228*	8,460	233*	14,200	228	20,200
16	291	4,310	288	4,150	307	4,150
17	274	6,660	274	7,040	315	10,550
18			268	6,200	268	5,430
			233	8,360	235.5	8,230
19	297	6,600	305	5,940	315	4,620
	230	12,880	244*	14,200	237	38,600
	212	23,400	230	28,000		
20	302	8,500	306	7,450	307	6,700
	234	10,800	295	10,000	298*	6,250
			287*	8,940	236	17,000
			230	7,900		
21	277	6,890	271	6,900	318	9,850
					230*	10,220
22			280.5	4,210	273.5	7,310
			231	4,840	245*	5,940
23	279.5	6,475	279.5	6,800	292	6,400
			242*	6,800	227	21,410
			224*	14,100		

(*) Shoulder.

(a) Spectra were obtained with a Beckman DK-2 Ultraviolet spectrophotometer.

Sodium nitrite was used to effect a ring closure of **18** to 4-amino-7-methylpyrazolo[4,3-*d*]-*v*-triazine 3-oxide (**8**). The structure of **8** was established by a uv spectrum characteristic of a heterocyclic *N*-oxide (strong absorption at low wavelength) and the absence of a band in the ir spectrum (2250 cm^{-1} region) which indicated that ring closure had occurred and established the absence of the diazo intermediate.

Isolation of the 5,7-disubstituted pyrazolo[4,3-*d*]pyrimidine 3-ribonucleoside oxoformycin (8,9) prompted our preparation of various 5,7-disubstituted 3-methylpyrazolo-[4,3-*d*]pyrimidines structurally related to oxoformycin. Reduction of the nitro group of **9** was accomplished with hydrogen and palladium on carbon to furnish 4-amino-5-cyano-3-methylpyrazole (**13**), which was also prepared by dehydration of the carboxamido group of **10** with phosphorus oxychloride. A conversion of the cyano group to a carboxthioamide group was effected with triethylamine, pyridine and hydrogen sulfide gas to afford 4-amino-3-methylpyrazole-5-carboxthioamide (**14**). The structure of **14** was corroborated by the disappearance of the band in the ir spectrum at 2240 cm^{-1}. Ring annulation of **14** by a urea fusion furnished 3-methylpyrazolo[4,3-*d*]pyrimidin-5-one-7-thione (**15**) where the mercapto group was unequivocally assigned to position seven. The treatment of 3-methylpyrazolo[4,3-*d*]pyrimidin-5,7-dione (**16**), which was prepared by ring closure of **10** with methylisocyanate, with phosphorus pentasulfide and pyridine afforded a monomercapto derivative which was found to be identical to that prepared by ring closure of **14**. This thiation must therefore be analogous to the reported thiation of xanthine (16). The isomeric compound 3-methylpyrazolo[4,3-*d*]pyrimidin-7-one-5-thione (**11**) has been previously reported; however, a new and facile preparation of **11** under milder conditions by ring closure of **10** with methyl isothiocyanate was accomplished in the present investigation for com-

parison with the product obtained by the direct thiation of **16**. Methylation of 3-methylpyrazolo[4,3-*d*]pyrimidin-7-one-5-thione (**11**) furnished a mono methyl derivative and the structure was assigned as 3-methyl-5-methylthiopyrazolo[4,3-*d*]pyrimidin-7-one (**12**) on the basis of pmr spectral data (δ 2.6 for the methyl group on the sulfur atom) (17).

Ring closure of 4-amino-3-methylpyrazole-5-amidoxime (**18**) with methylorthoformate furnished 7-amino-3-methylpyrazolo[4,3-*d*]pyrimidin 6-oxide (**19**). This structure was established by uv spectral data (Table I) which was different from that observed for the other possibility (7-hydroxylamino-3-methylpyrazolo[4,3-*d*]pyrimidine) and in addition there was observed a large absorption band at lower wavelength which is characteristic of heterocyclic *N*-oxides (18a). An identical compound was also obtained by the direct oxidation of 7-amino-3-methylpyrazolo[4,3-*d*]pyrimidine (**20**) which had been prepared from **13** (18b). Additional corroboration for this structure was obtained by the deamination of **19** to afford 6-(*N*-hydroxy)-3-methylpyrazolo[4,3-*d*]pyrimidin-7-one (**23**) which was also prepared unequivocally by ring closure of 4-amino-3-methylpyrazole-5-carbohydroxamic acid (**22**) which had been prepared initially from **1** *via* 3-methyl-4-nitropyrazole-5-carbohydroxamic acid (**21**).

These 5,7-disubstituted 3-methylpyrazolo[4,3-*d*]pyrimidines are of considerable interest in view of the paucity of reported 3-methylpyrazolo[4,3-*d*]pyrimidine derivatives (13a, b) and the recent isolation and structural characterization of formycin, formycin B and oxoformycin. The mild reaction conditions reported herein for most of the ring closures could also be used in the synthesis of nucleosides.

EXPERIMENTAL (19)

3-Methyl-4-nitropyrazole-5-carboxhydrazide (**2**).

Ethyl 3-methyl-4-nitropyrazole-5-carboxylate (13a) (**1**, 20.0 g., 101 mmoles) was added to water (50 ml.) and 85% hydrazine hydrate (50 ml.) and this solution was heated on a steam bath for 2 hours. The solvent was removed *in vacuo*, ethanol (50 ml.) added and again removed *in vacuo*. This process was repeated and the resulting solid was dissolved in a minimum amount of boiling water, filtered and allowed to stand at 0° for 16 hours. The solid was collected by filtration and dried *in vacuo* at 110° to yield 13.3 g. (71.5%) of 3-methyl-4-nitropyrazole-5-carboxhydrazide (**2**). An analytical sample was prepared by two additional recrystallizations from water, m.p. 189-191° dec.

Anal. Calcd. for $C_5H_7N_5O_3$: C, 32.44; H, 3.81; N, 37.83. Found: C, 32.42; H, 3.73; N, 38.21.

4-Amino-3-methylpyrazole-5-carboxhydrazide (**3**).

Method A.

3-Methyl pyrazolo[4,3-*d*]pyrimidin-7-one (13a) (**4**, 2.0 g., 13.3 mmoles) was heated at reflux temperature in 85% hydrazine hydrate (50 ml.) for 2.5 hours. The solvent was removed *in vacuo*, isopropyl alcohol (50 ml.) added and then evaporated *in vacuo* on a steam bath. This process was repeated until a solid was obtained which was recrystallized from isopropyl alcohol to yield 1.2 g. (58%) of product. An analytical sample was prepared by two additional recrystallizations from isopropyl alcohol, m.p. 187.5-190°.

Anal. Calcd. for $C_5H_9N_5O$: C, 38.71; H, 5.85; N, 45.14. Found: C, 38.91; H, 5.99; N, 45.25.

Method B.

3-Methyl-4-nitropyrazole-5-carboxhydrazide (**2**, 1.0 g., 5.4 mmoles) was dissolved in boiling water (50 ml.) and then 50 ml. of ethanol was added. The solution was cooled to room temperature and 5% palladium on charcoal (0.2 g.) was added. The reaction mixture was then treated the same as that described for the preparation of **22**. After evaporation of the combined filtrates to dryness, ethanol (50 ml.) was added and then removed *in vacuo*. The resulting solid was recrystallized from isopropyl alcohol to yield 0.58 g. (69.0%) and shown to be the same as that prepared by Method A.

7-Methylpyrazolo[4,3-*d*]-*v*-triazin-4-one (**6**).

Method A.

4-Amino-3-methylpyrazole-5-carboxamide (**10**, 1.0 g., 7.15 mmoles) was dissolved in a mixture of water (15 ml.) and acetic acid (3 ml.). Sodium nitrite (1.5 g., 21.7 mmoles) was dissolved in water (3 ml.) and then added in the same manner as that described for the preparation and isolation of compound **7**. The solid that had formed was collected by filtration and dried at room temperature to yield 0.9 g., (83.5%) of **6**. An analytical sample was prepared by recrystallization from water three times, m.p. 215° dec.

Anal. Calcd. for $C_5H_5N_5O$: C, 39.67; H, 3.34; N, 46.36. Found: C, 39.25; H, 3.26; N, 46.40.

Method B.

4-Amino-3-methylpyrazole-5-carboxhydrazide (**3**, 1.5 g., 9.69 mmoles) was dissolved in water (25 ml.) and acetic acid (5 ml.). Sodium nitrite (3.4 g., 50 mmoles) was dissolved in water (10 ml.) and added in the same manner as for compound **7** with the isolation and purification being the same as that described in Method A. This furnished 0.97 g. (66.3%) of **6** which was identical in all respects with the compound from Method A.

3-Amino-7-methylpyrazolo[4,3-*d*]-*v*-triazin-4-one (**7**).

4-Amino-3-methylpyrazole-5-carboxhydrazide (**3**, 5.0 g., 32.3 mmoles) was dissolved in water (45 ml.) containing 10 ml. of acetic acid with rapid stirring. This solution was cooled to 5° and then sodium nitrite (2.3 g., 33.3 mmoles) dissolved in water (10 ml.) was added dropwise over a period of 15 minutes to the rapidly stirred solution while maintaining the temperature at 5-10°. After the addition was complete, the solution was stirred an additional 15 minutes and the temperature then allowed to rise to 15°. The solution was maintained at this temperature for 30 minutes at which time a solid began to separate from solution. The reaction mixture was allowed to stand at 5° for 16 hours, the solid removed by filtration, washed with ether and dried at room temperature to yield 3.4 g. (63.4%) of **7**. An analytical sample was prepared by three recrystallizations from ethyl acetate, m.p. 174-177° dec.

Anal. Calcd. for $C_5H_6N_6O$: C, 36.14; H, 3.64; N, 50.60. Found: C, 36.22; H, 3.71; N, 50.68.

4-Amino-7-methylpyrazolo[4,3-*d*]-*v*triazine 3-oxide (**8**).

4-Amino-3-methylpyrazole-5-carboxamidoxime (**18**, 1.0 g., 6.45 mmoles) and sodium nitrite (2.4 g., 34.8 mmoles) were slurried in water (16 ml.) and the mixture then cooled to 0°. Acetic acid (3.2 ml.) in water (2 ml.) was added dropwise over a period of 10 minutes. The mixture was stirred an additional 15 minutes at 0° and then 1 hour at room temperature. The solid was removed by filtration and dried at 110° *in vacuo* to yield 0.18 g. (16.3%). An analytical sample was obtained by 3 recrystallizations from water, m.p. 252° explodes.

Anal. Calcd. for $C_5H_6N_6O$: C, 36.14; H, 3.64; N, 50.60. Found: C, 36.40; H, 3.83; N, 50.81.

5-Cyano-3-methyl-4-nitropyrazole (**9**).

3-Methyl-4-nitropyrazole-5-carboxamide (**5**, 18.3 g., 108 mmoles) and phosphorus oxychloride (500 ml.) were heated at reflux temperature for 1 hour, the excess phosphorus oxychloride (400 ml.) was removed *in vacuo* and the resulting residue poured onto ice (400 ml.) with vigorous stirring. This mixture was stirred for 5 minutes, the solid was then removed by filtration and washed with an additional 100 ml. of ice water. The combined filtrate and washing was extracted with ether (4 x 500 ml.) and the combined ether extracts were washed with water (400 ml.) until the washings were neutral. After drying for three hours over anhydrous sodium sulfate, the ether solution was evaporated to dryness *in vacuo*. The residual solid and the solid filtered from the ice solution were combined and then dissolved in boiling toluene, filtered and allowed to stand at 0° for 16 hours. The crystals which had separated were collected by filtration to yield 13.7 g. (90.2%) of 5-cyano-3-methyl-4-nitropyrazole (**9**). An analytical sample was prepared by two additional recrystallizations from toluene, m.p. 180-181°.

Anal. Calcd. for $C_5H_4N_4O_2$: C, 39.47; H, 2.65; N, 36.80. Found: C, 39.58; H, 2.62; N, 37.09.

3-Methylpyrazolo[4,3-*d*]pyrimidin-7-one-5-thione (**11**).

4-Amino-3-methylpyrazole-5-carboxamide (**10**, 0.5 g., 3.57 mmoles) and methylisothiocyanate (2 g., 27.4 mmoles) were dissolved in pyridine (50 ml.) and the solution heated at reflux temperature for 16 hours. The solution was taken to dryness and then ethanol (50 ml.) was added and removed *in vacuo*. This process was repeated twice more and then boiling benzene (70 ml.) was added and the solid removed by filtration. The solid was dissolved in water by the dropwise addition of a 2*N* sodium hydroxide solution, the resulting solution filtered and then neutralized with glacial acetic acid. After standing at 5° for 16 hours, the solid was removed by filtration, washed with acetone and dried *in vacuo* at 110° to yield 0.32 g. (49.3%) of **11**. The compound was shown to be the same as that prepared by the literature method (13a).

3-Methyl-5-methylthiopyrazolo[4,3-*d*]pyrimidin-7-one (**12**).

3-Methylpyrazolo[4,3-*d*]pyrimidin-7-one-5-thione (**11**, 0.75 g., 4.12 mmoles) was dissolved in water (20 ml.) by the dropwise addition of concentrated ammonium hydroxide. Methyl iodide (0.6 g., 4.23 mmoles) was added and the solution stirred rapidly for one hour (a white solid separated from solution). The solvent was removed *in vacuo* at room temperature, water (10 ml.) added and the solid collected by filtration and dried *in vacuo* at 110° to yield 0.75 g. (92.7%) of **12**. An analytical sample was prepared by two recrystallizations from water, m.p. 248-250°.

Anal. Calcd. for $C_7H_8N_4OS$: C, 42.86; H, 4.11; N, 28.65. Found: C, 42.82; H, 4.36; N, 28.61.

4-Amino-5-cyano-3-methylpyrazole (**13**).

Method A.

4-Amino-3-methylpyrazole-5-carboxamide (**10**, 1.5 g., 10.8 mmoles) in phosphorus oxychloride (50 ml.) was heated at reflux temperature for 1.5 hours, at which time all the solid had dissolved. The phosphorus oxychloride was removed *in vacuo* to yield an oil. The oil was poured onto ice (200 ml.) with vigorous stirring and the resulting mixture carefully neutralized with a sodium hydroxide solution (~ 2*N*), keeping an excess of ice present. This solution was extracted with ethyl acetate (4 x 200 ml.), the combined extracts washed with water (200 ml.), dried for 3 hours over sodium sulfate and the solvent removed *in vacuo* to yield 1.2 g. (27.6%) of 4-amino-5-cyano-3-methylpyrazole (**13**). Two recrystallizations from toluene produced an analytical sample, m.p. 158-160°.

Anal. Calcd. for $C_5H_6N_4$: C, 49.15; H, 4.94; N, 45.81. Found: C, 49.23; H, 4.85; N, 45.66.

Method B.

5-Cyano-3-methyl-4-nitropyrazole (**9**, 3.0 g., 19.7 mmoles) was dissolved in ethanol (100 ml.), flushed well with nitrogen and 10% palladium on charcoal (0.5 g.) added. The mixture was placed under 45 psi of hydrogen, with shaking, for 1.5 hours. The mixture was filtered through celite and the catalyst washed with boiling ethanol (100 ml.). The combined filtrates were evaporated to dryness *in vacuo* and the yellow solid was dissolved in boiling toluene, filtered and allowed to stand at 5° for 12 hours. The solid was collected by filtration to yield 1.55 g. (64.4%) of 4-amino-5-cyano-3-methylpyrazole (**13**) identical with a sample prepared by Method A.

4-Amino-3-methylpyrazole-5-carboxthioamide (**14**).

4-Amino-5-cyano-3-methylpyrazole (**13**, 1.22 g., 10 mmoles) was added to a solution of triethylamine (1.5 ml.) in pyridine (125 ml.). After the solid had dissolved, hydrogen sulfide gas was bubbled into the rapidly stirred solution for five hours. The solution was stirred an additional 16 hours and then evaporated to dryness *in vacuo*. Anhydrous ethanol (50 ml.) was added to the solid and the mixture evaporated to dryness *in vacuo*, with this process being repeated three additional times. Benzene (200 ml.) was added, the solid collected by filtration and washed with an additional 75 ml. of benzene. The solid was recrystallized from boiling water to yield 4-amino-3-methylpyrazole-5-carboxthioamide (0.93 g., 59.6%), m.p. 203.5-205° dec.

Anal. Calcd. for $C_5H_8N_4S$: C, 38.46; H, 5.13; N, 35.90. Found: C, 38.12; H, 5.25; N, 35.44.

3-Methylpyrazolo[4,3-*d*]pyrimidin-5-one-7-thione (**15**).

Method A.

3-Methylpyrazolo[4,3-*d*]pyrimidin-5,7-dione (**16**, 1.5 g., 9.0 mmoles) and phosphorus pentasulfide (8 g., 36.0 mmoles) in pyridine (90 ml.) were heated at reflux temperature for 4.5 hours. The solution was evaporated to dryness *in vacuo*, ice-water (50 ml.) was added and the mixture allowed to stand for 30 minutes then heated on a steam bath for one hour. The mixture was allowed to stand at 5° for 3 hours and the yellow solid collected by filtration. The solid was dissolved in boiling water (50 ml.) by addition of concentrated ammonium hydroxide, decolorized with charcoal, filtered and the solution acidified with glacial acetic acid to *p*H 5. The solution was allowed to stand at 5° for 16 hours and the yellow solid was removed by filtration and dried under vacuum at 110° to yield 0.9 g. (54.9%) of **15**.

An analytical sample was prepared by two additional reprecipitations, m.p. 350° dec.

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.56; H, 3.30; N, 30.77. Found: C, 39.20; H, 3.75; N, 30.61.

Method B.

4-Amino-3-methylpyrazole-5-carboxthioamide (**14**, 0.5 g., 3.2 mmoles) and urea (0.5 g., 8.3 mmoles) were thoroughly mixed and heated at approximately 200° for 30 minutes. The solid was dissolved in boiling water by the addition of concentrated ammonium hydroxide; the solution was then decolorized and acidified with glacial acetic acid to *p*H 5. The yellow solid which separated was identical with a sample prepared by Method A.

3-Methylpyrazolo[4,3-*d*]pyrimidin-5,7-dione (**16**).

4-Amino-3-methylpyrazole-5-carboxamide (**10**, 20 g., 143 mmoles) and methyl isocyanate (25 g., 439 mmoles) were dissolved in pyridine (400 ml.) and heated at reflux temperature for 12 hours. The solution was evaporated to dryness *in vacuo*. Ethanol (50 ml.) was added and removed *in vacuo* with this process being repeated twice more and then benzene (100 ml.) was added. The solid was collected by filtration, recrystallized from boiling water and dried at 110° under vacuum to yield 12.6 g. (53.3%) of **16**. Chromatography in three solvent systems and ultraviolet spectra showed the compound to be the same as that previously reported (13a).

3-Methyl-4-nitropyrazole-5-amidoxime (**17**).

5-Cyano-3-methyl-4-nitropyrazole (**9**, 3.0 g., 19.8 mmoles) and crystalline hydroxylamine (20) (2.0 g., 60.1 mmoles) were dissolved in ethanol (150 ml.) and the solution heated at reflux temperature for 3.5 hours. The solution was then evaporated to dryness *in vacuo*, the yellow solid was recrystallized from water and then dried *in vacuo* at 110° to yield 2.7 g. (73.8%) of **17**. An analytical sample was prepared by two additional recrystallizations from water, m.p. 190-192°.

Anal. Calcd. for $C_5H_7N_5O_3$: C, 32.44; H, 3.81; N, 37.83. Found: C, 32.50; H, 3.85; N, 37.90.

4-Amino-3-methylpyrazole-5-amidoxime (**18**).

3-Methyl-4-nitropyrazole-5-amidoxime (**17**, 8.8 g., 47.6 mmoles) was dissolved in a hot ethanol-water (100:200 ml.) mixture. The solution was allowed to cool to room temperature and 5% palladium on charcaol (0.9 g.) was then added. The reaction mixture was placed under a hydrogen (30 psi) atmosphere in a Paar hydrogenation apparatus for 1.5 hours and then filtered through a celite bed. The catalyst was washed with boiling water (200 ml.) and the combined filtrates evaporated to dryness *in vacuo*. The resulting solid was dissolved in boiling ethanol (200 ml.) by the slow addition of water and then filtered. The solution was allowed to stand at 5° for 16 hours and the solid collected by filtration to yield 3.8 g. (51.6%) of **18**. An analytical sample was prepared by two additional recrystallizations from ethanol, m.p. 188.5-189.5° dec.

Anal. Calcd. for $C_5H_9N_5O$: C, 38.71; H, 5.85; N, 45.14. Found: C, 38.86; H, 5.92; N, 45.24.

7-Amino-3-methylpyrazolo[4,3-*d*]pyrimidine 6-oxide (**19**).

Method A.

To a mixture of 7-amino-3-methylpyrazolo[4,3-*d*]pyrimidine (**20**, 0.94 g., 6.31 mmoles) and *m*-chloroperoxybenzoic acid (1.9 g., 11.1 mmoles) was added glacial acetic acid (10 ml.). The mixture was heated, with stirring, at 65° for 1 hour and then poured with rapid stirring into 200 ml. of water. The mixture was stirred another 10 minutes, the solid collected by filtration and washed with water (50 ml.). The solid was discarded and the combined filtrates were evaporated to dryness *in vacuo*. Ethanol (50 ml.) was added to the residue and then removed *in vacuo*. This evaporation process was repeated twice more, then 50 ml. of ethanol was added, the solid collected by filtration and washed with ethyl acetate (50 ml.). The solid was recrystallized from water and dried *in vacuo* at 110° to yield 0.43 g. (41.3%) of **19**. An analytical sample was prepared by two additional recrystallizations from water and vacuum dried at 110°, m.p. 310-312° dec.

Anal. Calcd. for $C_6H_7N_5O$: C, 43.64; H, 4.24; N, 42.42. Found: C, 43.61; H, 4.48; N, 42.40.

Method B.

4-Amino-3-methylpyrazole-5-amidoxime (**18**, 0.87 g., 5.71 mmoles) and methylorthoformate (75 ml.) were heated at reflux temperature for 5.5 hours. The mixture was cooled to ice-water temperature and the solid collected by filtration. The solid was dried *in vacuo* at 110° to yield 0.5 g. (54.1%) of 19. The solid was recrystallized from water and found to be identical with the product obtained by Method A.

7-Amino-3-methylpyrazolo[4,3-*d*]pyrimidine (**20**).

4-Amino-5-cyano-3-methylpyrazole (**13**, 0.30 g., 2.46 mmoles) and formamidine acetate (0.30 g., 2.89 mmoles) were dissolved in absolute ethanol (20 ml.) and the solution heated at reflux temperature for two hours. The solvent was removed *in vacuo*, ethanol (20 ml.) added and the solution again evaporated to dryness *in vacuo*. The resulting solid was dissolved in a minimum amount of boiling water, filtered and the resulting solution neutralized to *p*H 7 by the slow addition of 1*N* sodium hydroxide. The solution was allowed to stand at 5° for three hours and the crystals collected by filtration and dried *in vacuo* at 110° to yield 0.142 g., 38.8%, m.p. 346-348° dec. The compound was shown to be the same as that previously reported (13a).

3-Methyl-4-nitropyrazole-5-carbohydroxamic Acid (**21**).

Ethyl 3-methyl-4-nitropyrazole-5-carboxylate (**1**, 15 g., 75.4. mmoles) and hydroxylamine (20) (15 g., 455 mmoles) were added to absolute ethanol (300 ml.) and heated at reflux temperature with stirring for 1 hour. After cooling to 0°, the solid was collected by filtration, washed with 50 ml. of cold ethanol and dried *in vacuo* at 110° to yield 12.3 g. (87.8%) of 3-methyl-4-nitropyrazole-5-carbohydroxamic acid (**21**). An analytical sample was prepared by three recrystallizations from water, m.p. 210.5-211.5° dec.

Anal. Calcd. for $C_5H_6N_4O_4 \cdot \frac{1}{2} H_2O$: C, 30.80; H, 3.58. N, 28.70. Found: C, 30.92; H, 3.87; N, 28.90.

4-Amino-3-methylpyrazole-5-carbohydroxamic Acid (**22**).

3-Methyl-4-nitropyrazole-5-carbohydroxamic acid (**21**, 1.0 g., 5.37 mmoles) was dissolved in boiling water (50 ml.), ethanol (50 ml.) was added and the solution cooled to room temperature. Palladium on charcoal (0.2 g. of 5%) was then added and the mixture placed under hydrogen (25 psi) on a Paar hydrogenation apparatus and shaken for one hour. The resulting mixture was filtered through celite, the catalyst washed with boiling water (50 ml.) and the combined filtrates evaporated to dryness *in vacuo*. The resulting red solid was dissolved in boiling water, decolorized and allowed to cool. The solid was removed by filtration and dried *in vacuo* at 110° to yield 0.34 g. (40.6%) of **22**. An analytical sample was prepared by two additional recrystallizations from water, m.p. 215-216°.

Anal. Calcd. for $C_5H_8N_4O_2$: C, 38.46; H, 5.16; N, 35.88. Found: C, 38.46; H, 5.17; N, 35.91.

6-(*N*-Hydroxy)-3-methylpyrazolo[4,3-*d*]pyrimidin-7-one (**23**).

Method A.

4-Amino-3-methylpyrazole-5-carbohydroxamic acid (**22**, 0.27 g., 1.73 mmoles) and methylorthoformate (50 ml.) were heated at reflux temperature for two hours. The mixture was cooled to ice-water temperature, the solid collected by filtration and dried *in vacuo* at 110° to yield 0.25 g. (87%) of **23**. An analytical sample was prepared by three recrystallizations from water, m.p. 310° dec.

Anal. Calcd. for $C_6H_6N_4O_2$: C, 43.37; H, 3.61; N, 33.73. Found: C, 43.37; H, 3.64; N, 34.02.

Method B.

7-Amino-3-methylpyrazolo[4,3-*d*]pyrimidine 6-oxide (**19**, 0.30 g., 1.8 mmoles) and sodium nitrite (0.2 g., 1.21 mmoles) were added to dimethylformamide (5 ml.) and then with stirring, 50% aqueous acetic acid (1.2 ml.) was added dropwise over a period of 10 minutes. The resulting mixture was stirred at room temperature for one hour, then at 55° for two hours. After cooling to room temperature, ethyl ether (20 ml.) was added, the mixture stirred rapidly for 3 minutes, then the liquid carefully decanted. This process was repeated until a yellow viscous liquid was obtained. This yellow liquid was dissolved in water and Dowex 50 resin (5 ml.) (previously washed with 20 ml. of water) was added and the mixture stirred for 30 minutes. The resin was removed by filtration, washed, with boiling water (50 ml.) and the combined filtrates taken to dryness. The resulting solid was shown to be identical to that obtained by Method A by TLC (21).

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