[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Studies in Purine Chemistry. IX. A New Pyrimidine Synthesis from *o*-Aminonitriles[1]

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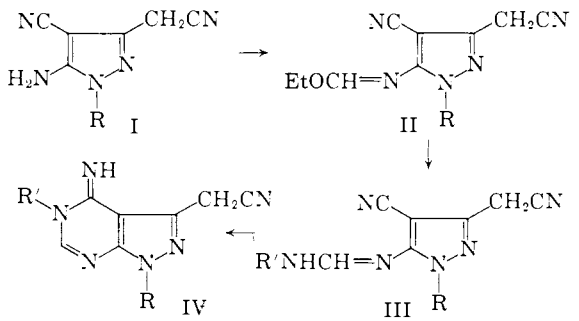
A convenient method is described for the synthesis of pyrazolo[3,4-d]pyrimidines and purines from 1-methyl-4-cyano-5-aminopyrazole (V) and 1-methyl-4-amino-5-cyanoimidazole, respectively. For example, reaction of V with ethyl orthoformate and acetic anhydride gives a 5-ethoxymethyleneamino derivative VI which upon treatment with methylamine yields 1-methyl-4-cyano-5-methylaminomethyleneaminopyrazole (VII); VII undergoes a base-catalyzed intramolecular ring closure to 1,5-dimethyl-4(5*H*)-iminopyrazolo[3,4-d]pyrimidine (VIII), which in turn rearranges readily in the presence of base to 1-methyl-4-methylaminopyrazolo[3,4-d]pyrimidine. A similar sequence of reactions starting with 1-methyl-4-amino-5-cyanoimidazole yields correspondingly substituted 7-methylpurines. The use of other amines (*e.g.*, hydrazine, *n*-butylamine, D-glucamine, D-ribamine) has led to the synthesis of a variety of new pyrazolo[3,4-d]pyrimidine and purine derivatives. The mechanism of the base-catalyzed rearrangement is discussed.

A recent paper from this Laboratory[3] described the synthesis of a number of pyrazolo[3,4-d]pyrimidines (IV) by the reaction of 3-cyanomethyl-4-cyano-5-aminopyrazoles (I) with ethyl orthoformate and acetic anhydride to give intermediate ethoxymethyleneamino derivatives (II) which upon subsequent treatment with amines were converted to IV by intramolecular cyclization of the initially formed formamidines (III). This procedure for the synthesis of a fused pyrimidine ring *via* an



o-aminonitrile appeared to be potentially generally applicable to the preparation of other condensed 4-aminopyrimidine systems, and the present paper is concerned with the application of this reaction sequence to the synthesis of purines and some additional pyrazolo[3,4-d]pyrimidines.

The use of C-ethoxymethylene derivatives as intermediates in pyrimidine synthesis has been widely exploited, particularly in syntheses involving the reaction of a 3-carbon intermediate with amidines. The condensation of amidines with ethyl ethoxymethylenemalonate,[4] ethyl ethoxymethylenecyanoacetate[4,5] and ethoxymethylenemalononitrile[4] are representative. The extensive recent work by Shaw and co-workers on the synthesis of pyrimidine nucleosides from cyanoethoxyacrylamide derivatives and related intermediates[6] is illustrative of closely related ring closures. However, N-ethoxymethylene derivatives appear not to have been utilized for pyrimidine syntheses, although such intermediates have been employed by Shaw[6] (*e.g.*, ethoxymethyleneaminocyanoacetamide) for the unequivocal synthesis of 1-substituted-5-aminoimidazole-4-carboxamides.[6a]

Condensation of 1-methyl-4-cyano-5-aminopyrazole (V)[7] with an equimolar mixture of ethyl orthoformate and acetic anhydride yielded crystalline 1-methyl-4-cyano-5-ethoxymethyleneaminopyrazole (VI). Treatment of VI in benzene solution with alcoholic methylamine resulted in the immediate separation of 1-methyl-4-cyano-5-methylaminomethyleneaminopyrazole (VII). The structure of VII was evident from its microanalysis, the presence of a nitrile band in the infrared spectrum and the absence of significant ultraviolet absorption. However, refluxing VII in dry pyridine rapidly converted it into an isomeric compound. The disappearance of the nitrile band and the appearance of strong ultraviolet absorption substantiated the conclusion that intramolecular cyclization to 1,5-dimethyl-4(5*H*)-iminopyrazolo[3,4-*d*]pyrimidine (VIII) had taken place. Compound VIII could be prepared directly and very rapidly from VI by reaction with ethanolic methylamine at room temperature. Under these conditions, VII started to separate from solution immediately following addition of the methylamine, but it quickly dissolved with the formation of VIII. The latter compound could be isolated in high yield provided that the reaction mixture, carefully protected from moisture, was evaporated to dryness within one hour. However, when the reaction mixture was allowed to stand exposed to the atmosphere at room temperature for twenty-four hours, the only product which could be isolated was a second isomer of VII. This product was identified as 1-methyl-4-methylaminopyrazolo[3,4-*d*]pyrimidine (IX) by comparison with an authentic sample,[7] and must have resulted from a base-catalyzed rearrangement of 1,5-dimethyl-4(5*H*)-iminopyrazolo[3,4-*d*]pyrimidine (VIII). This conclusion follows from the observations that VIII rapidly rearranged to IX in

(1) This investigation was supported in part by a grant (C-2551) to Princeton University from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) For the previous paper in this series, see E. Richter, J. E. Loeffler and E. C. Taylor, THIS JOURNAL, **82**, 3144 (1960).

(3) E. C. Taylor and K. S. Hartke, *ibid.*, **81**, 2456 (1959).

(4) C. W. Whitehead and J. J. Traverso, *ibid.*, **78**, 5294 (1956).

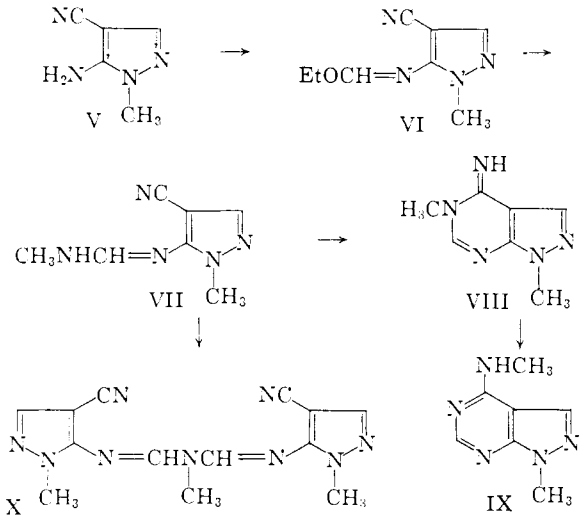
(5) T. L. V. Ulbricht and C. C. Price, *J. Org. Chem.*, **21**, 567 (1956).

(6) G. Shaw, R. N. Warrener, D. N. Butler and R. K. Ralph, *J. Chem. Soc.*, 1648 (1959), and preceding papers in this series.

(6a) NOTE ADDED IN PROOF.—A more recent paper by Shaw (G. Shaw and D. N. Butler, *J. Chem. Soc.*, 4040 (1959)) describes the reaction of 1-methyl-4-cyano-5-aminoimidazole with ethyl orthoformate to give 1-methyl-4-cyano-5-ethoxymethyleneaminoimidazole, which upon treatment with ammonia gives 9-methyladenine. This reaction sequence parallels that described in the present paper for the synthesis of fused 4-aminopyrimidine heterocycles from *o*-aminonitriles.

(7) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **21**, 1240 (1956).

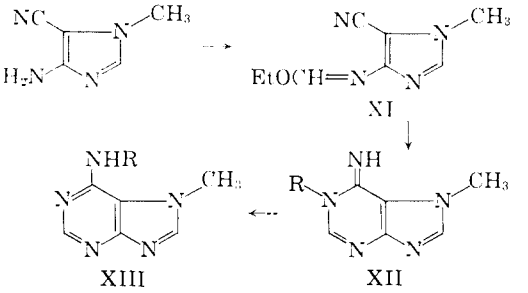
water or in 0.1 *N* sodium hydroxide but could be recovered unchanged after refluxing for several hours with dilute hydrochloric acid. The initial ring closure of VII to VIII is also base catalyzed, for the conversion was readily carried out in dry pyridine or in ethanol containing excess methylamine, although VII was completely stable in refluxing dry ethanol or even to vacuum sublimation. When an alcoholic solution of methylamine was added dropwise to VI, so that the reaction mixture never became basic, the initially formed methylaminomethyleneamino intermediate VII reacted with unchanged VI to give X as the only isolable product.



Treatment of VI with alcoholic ammonia led directly to 1-methyl-4-aminopyrazolo[3,4-*d*]pyrimidine, and treatment with *n*-butylamine, D-glucamine and D-ribamine yielded the correspondingly 5-substituted 1-methyl-4(5*H*)-iminopyrazolo[3,4-*d*]pyrimidines. However, the only product isolated upon treatment of VI with hydrazine was 1-methyl-4-hydrazinopyrazolo[3,4-*d*]pyrimidine; apparently the initially formed 5-amino-4(5*H*)-imino derivative underwent rearrangement under the reaction conditions in the presence of excess hydrazine.

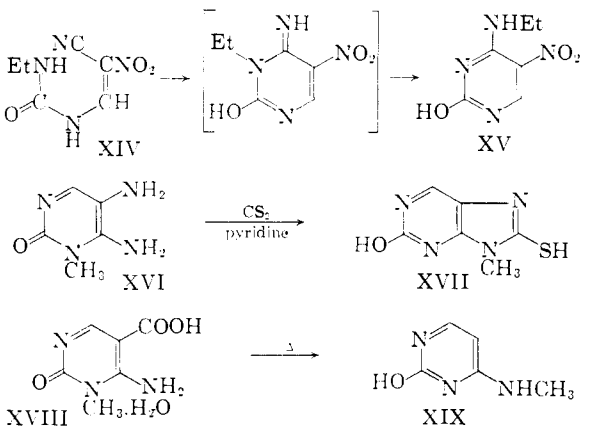
An analogous series of 7-methyladenine derivatives was prepared by reaction of 1-methyl-4-amino-5-cyanoimidazole[8] with ethyl orthoformate and acetic anhydride to give 1-methyl-4-ethoxymethyleneamino-5-cyanoimidazole (XI), followed by treatment with amines. The resulting 1-substituted 6(1*H*)-imino-7-methylpurines (XII) rearranged in the presence of base to 6-substituted amino-7-methylpurines (6-substituted-7-methyladenines) (XIII). Reaction of hydrazine with XI yielded 1-amino-6(1*H*)-imino-7-methylpurine (XII, R = $-NH_2$), but attempted rearrangement to 6-hydrazino-7-methylpurine with base resulted only in decomposition.

The structures of the isomeric pyrazolo(3,4-*d*)-pyrimidines (*e.g.*, VIII and IX) and purines (XII and XIII) were clearly assignable by inspection of their ultraviolet absorption spectra. In both series, the ring-substituted imino derivatives exhibited ultraviolet absorption maxima at a lower wave



length than the isomeric substituted amino derivatives, both in ethanol and in dilute hydrochloric acid. It should be noted, however, that no generalizations about structure *vs.* spectrum can be drawn from these observations, since it has previously been shown that in simple pyrimidines, the reverse relationship holds; *i.e.*, 1-methyl-2-(1*H*)-iminopyrimidine absorbs at higher wave lengths than the aromatic isomer, 2-methylaminopyrimidine.[9] The correctness of our structural assignments can scarcely be questioned, however, since the substituted amino derivatives in both series were compared directly with authentic samples. For example, 1-methyl-4-methylaminopyrazolo(3,4-*d*)pyrimidine (IX) prepared by rearrangement of VIII was identical with the product obtained by treatment of 1-methyl-4-chloropyrazolo(3,4-*d*)pyrimidine with methylamine, and 6-methylamino-7-methylpurine, prepared by rearrangement of XII (R = $-CH_3$), was identical with the corresponding product prepared from 6-chloro-7-methylpurine. Since a very close correspondence of spectra was observed for all compounds within any given series, structural assignments could be given without question to all compounds prepared.

Rearrangements of the type observed here, resulting in an apparent migration of a substituent from a ring nitrogen to a substituent amino group, have been observed previously. For example, 1-methyl-2(1*H*)-iminopyrimidine has been reported to rearrange to 2-methylaminopyrimidine in 71% yield upon treatment with *N* sodium hydroxide for ten minutes.[4] Treatment of 1-cyano-1-nitro-2-(3-ethylureido)-ethylene (XIV) with sodium ethoxide yielded 2-hydroxy-4-ethylamino-5-nitropyrimidine (XV) by rearrangement of the initially

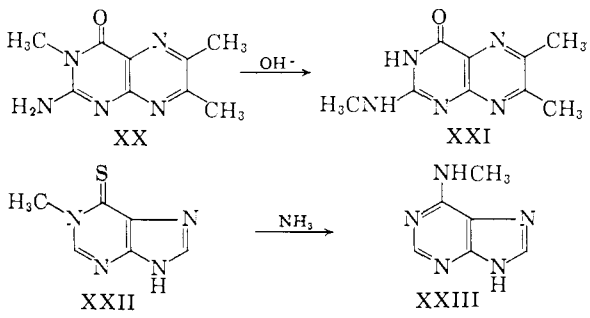


(8) R. N. Prasad and R. K. Robins, THIS JOURNAL, **79**, 6401 (1957).

(9) D. J. Brown, E. Hoerger and S. F. Mason, *J. Chem. Soc.*, 4035 (1955).

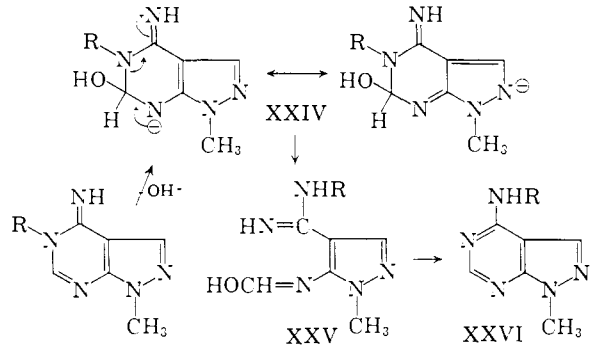
formed 3-ethyl-4(3*H*)-imino isomer. Similarly, the corresponding N-butyl derivative gave 2-hydroxy-4-(*n*-butylamino)-5-nitropyrimidine upon treatment with sodium ethoxide.[10] The facility with which this rearrangement takes place is evident from the conversion of 3-methyl-4,5-diamino-2(3*H*)-pyrimidone (XVI) to 2-hydroxy-8-mercapto-9-methylpurine (XVII) upon heating with carbon disulfide and pyridine.[10] A related change is the conversion of 3-methyl-4-amino-5-carboxy-2(3*H*)-pyrimidone (XVIII) to 2-hydroxy-4-methylaminopyrimidine (XIX) upon thermal decarboxylation [11]; in this latter example, it is significant that the starting material was a monohydrate.

This rearrangement is also known with condensed pyrimidine heterocycles.



For example, 3,6,7-trimethyl-2-amino-4(3*H*)-pteridone (XX) rearranges to 2-methylamino-6,7-dimethyl-4(3*H*)-pteridone (XXI) in dilute alkali,[12] and 1-methyl-6(1*H*)-purinethione (XXII) is converted by alcoholic ammonia at 160° to 6-methylaminopurine[13] (XXIII). Nothing has been published, however, which is concerned with the nature of these facile rearrangements.

We consider that all of these isomerizations involve an initial nucleophilic attack of hydroxide ion or other base at a pyrimidine C=N bond with subsequent cleavage of the pyrimidine ring to give an intermediate amidine (XXV). Ring re-closure can then either regenerate starting material or yield the isomeric, aromatic exocyclic substituted derivative XXVI. Since all of these steps are presumably reversible, complete conversion under the reaction conditions into the more stable isomer should take place. One would therefore anticipate that structural features in the pyrimidine or condensed pyrimidine system which would tend to facilitate the initial nucleophilic attack (*i.e.*, which would tend to stabilize the resulting anionic intermediate) should accelerate the rearrangement. In accord with these expectations, we have observed that the pyrazolo(3,4-*d*)pyrimidines rearrange more rapidly than do the isomeric purines derivatives. This result can be attributed to stabilization of the intermediate anion by resonance structures involving the 2-nitrogen atom of the pyrazole ring (XXIV). Comparable structures cannot be written for the purines, which consequently rearrange more slowly.[14]



In attempt to extend these reactions to the preparation of a series of 9-methylpurines, 1-methyl-4-chloro-5-nitroimidazole (XXVII)[15] was treated with potassium iodide and potassium cyanide in ethanol under conditions which had proved to be effective for the conversion of 1-methyl-4-nitro-5-chloroimidazole to 1-methyl-4-nitro-5-cyanoimidazole (XXVIII). No exchange took place, even when the reactants were heated in ethanol solution at 150° in a sealed tube. Refluxing the reactants in dimethylformamide, however, resulted in a rapid exchange of halogen for the nitrile group, with the unexpected formation of 1-methyl-4-nitro-5-cyanoimidazole (XXVIII). The nature of this transmethylation reaction is not known.[15a]

Experimental[16]

1-Methyl-4-cyano-5-ethoxymethyleneaminopyrazole (VI).—A mixture of 20 g. of 1-methyl-4-cyano-5-aminopyrazole,[7] 80 ml. of ethyl orthoformate and 80 ml. of acetic anhydride was heated under reflux for 2 hours, evaporated to a small volume under reduced pressure and the residual oil chilled overnight at 0°. The resulting solid (20 g., 69%) was recrystallized from petroleum ether to give colorless crystals, m.p. 48–49°.

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.9; H, 5.7. Found: C, 53.8; H, 6.0.

1-Methyl-4-cyano-5-methylaminomethyleneaminopyrazole(VII).—To 1 g. of 1-methyl-4-cyano-5-ethoxymethyleneaminopyrazole in 15 ml. of dry benzene was added all at once 2 ml. of ethanol saturated with methylamine. After standing at room temperature for 20 hours, the mixture was filtered to give 0.5 g. of fine, white needles. Concentration of the filtrate gave an additional 0.2 g.; total yield, 0.7 g. (77%). The product when recrystallized from petroleum ether–ethanol melted at 140–142°.

Anal. Calcd. for $C_7H_9N_5$: C, 51.5; H, 5.6; N, 42.9. Found: C, 51.2; H, 5.7; N, 43.1.

When the above reaction was run in ethanol rather than in benzene solution, the product started to separate immediately after addition of the methylamine. Filtration after 2 minutes gave VII in 43% yield, while concentration of the filtrate (which had stood at room temperature for 24 hours —see below) gave 1-methyl-4-methylaminopyrazolo(3,4-d)-pyrimidine (IX) in 50% yield.

(10) D. J. Brown, *J. Appl. Chem.*, **9**, 203 (1959).

(11) D. J. Brown, *ibid.*, **5**, 358 (1955).

(12) W. V. Curran and R. B. Angier, THIS JOURNAL, **80**, 6095 (1958).

(13) G. B. Elion in "The Chemistry and Biology of Purines," A Ciba Foundation Symposium, ed. by G. E. W. Wolstenholme and C. M. O'Connor, J. and A. Churchill Ltd., London, 1957, p. 44.

(14) A systematic study of the contribution of such factors to this and related conversions has been under study in our laboratory for some time. The results of this investigation will be published independently.

(15) J. Sarasin and E. Wegmann, *Helv. Chim. Acta*, **7**, 713 (1924).

(15a) NOTE ADDED IN PROOF.—By an interesting coincidence, Baddiley and co-workers have described in a recent paper (J. Baddiley, J. G. Buchanan, F. E. Hardy and J. Stewart, *J. Chem. Soc.*, 2893 (1959)) the same unusual transformation of XXVII to XXVIII with potassium cyanide and potassium iodide in dimethylformamide solution.

(16) All melting points are corrected. We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J.

1,5-Dimethyl-4(5*H*)-iminopyrazolo(3,4-d)pyrimidine-(VIII). Method A.—To a magnetically-stirred solution of 1.25 g. of 1-methyl-4-cyano-5-ethoxymethyleneaminopyrazole in 5 ml. of ethanol was added in one portion 5 ml. of ethanol saturated with methylamine. 1-Methyl-4-cyano-5-methylaminomethyleneaminopyrazole started to precipitate immediately from solution, but on continued stirring it rapidly dissolved. After 15 minutes, a second solid precipitated. Filtration yielded 0.25 g. while immediate concentration of the filtrate to dryness *in vacuo* and recrystallization of the residue from benzene gave an additional 0.8 g.: total yield, 1.05 g. (92%), m.p. 145–147°. After drying at 100° (0.1 mm.), the product melted at 164–165°. Standing in moist air resulted in rapid conversion back to the monohydrate, m.p. 145–147°; $\lambda_{max}^{0.1\ N\ HCl}$ 259 mμ, log ε 3.86; λ_{max}^{EtOH} 258, 266.5 mμ, log ε 3.82, 3.83.

Anal. Calcd. for $C_7H_9N_5.H_2O$: C, 46.4; H, 6.1; N, 38.65. Found: C, 46.6; H, 6.3; N, 38.5. Calcd. for $C_7H_9N_5$: C, 51.5; H, 5.6; N, 42.9. Found: C, 51.7; H, 5.8; N, 43.1.

Method B.—A solution of 7.5 g. of 1-methyl-4-cyano-5-methylaminomethyleneaminopyrazole and 200 ml. of dry benzene was heated under reflux for 5 hours, and then allowed to stand overnight at room temperature. During the refluxing the color of the solution became deep purple, which bleached to a light honey color upon cooling. Evaporation of the solution to dryness and recrystallization of the residue from benzene gave 7 g. (93%) of colorless crystals, m.p. 145–147°, identical with the product obtained by method A.

1-Methyl-4-methylaminopyrazolo(3,4-d)pyrimidine(IX).—A solution of 1 g. of 1,5-dimethyl-4(5*H*)-iminopyrazolo(3,4-d)pyrimidine in 20 ml. of water was heated under reflux for 30 minutes and then evaporated to dryness. Recrystallization of the residue from ethanol–petroleum ether gave 1 g. (quantitative) of colorless crystals, m.p. 196–197°. The reported[7] melting point of this compound is 200–201°; $\lambda_{max}^{0.1\ N\ HCl}$ 263 mμ, log ε 4.04; λ_{max}^{EtOH} 282 mμ, log ε 4.01.

Anal. Calcd. for $C_7H_9N_5$: C, 51.5; H, 5.6; N, 42.9. Found: C, 51.3; H, 5.4; N, 42.6.

The hydrochloride salt of IX was prepared by treating an ethanolic solution of Im with dry hydrogen chloride. Recrystallization of the salt from ethanol gave colorless crystals, m.p. 290–292° dec.

Anal. Calcd. for $C_7H_9N_5.HCl$: C, 42.1; H, 5.05; N, 35.1. Found: C, 41.8; H, 5.3; N, 34.9.

The progress of the isomerization of VIII to IX was readily followed by paper chromatography, since the R_f values in aqueous butanol for the two compounds were widely separated (VIII, 0.23; IX, 0.76). It was shown by this means that complete conversion of VIII to IX could be achieved under the following conditions:

Solvent	Temp., °C.	Time
H_2O	25	24 hr.
H_2O	100	30 min.
0.1 *N* NaOH	25	1 hr.
0.1 *N* NaOH	100	7 min.

Compound X.—To a solution of 1 g. of 1-methyl-4-cyano-5-ethoxymethyleneaminopyrazole in 20 ml. of ethanol was added dropwise, over a period of 1 hour, 5 ml. of a solution of methylamine in ethanol, care being taken that the reaction mixture did not become basic. Under these conditions, no precipitate appeared and the solution turned yellow. After standing at room temperature for 1 day, it was evaporated under reduced pressure, and the oily, partly crystalline residue recrystallized from ethanol; yield 0.3 g. (36%), m.p. 260°. Vacuum sublimation followed by a further recrystallization from ethanol raised the melting point to 265–268°.

Anal. Calcd. for $C_{13}H_{13}N_9$: C, 52.8; H, 4.4; N, 42.7. Found: C, 53.1; H, 4.15; N, 42.8.

1-Methyl-4-aminopyrazolo(3,4-d)pyrimidine.—Alcoholic ammonia was added to a solution of 2 g. of 1-methyl-4-cyano-5-ethoxymethyleneaminopyrazole in 20 ml. of ethanol until the mixture was strongly alkaline. After standing at room temperature for 5 minutes, the mixture was filtered to give 1.5 g. (90%). Several recrystallizations from boiling water with the use of charcoal gave colorless needles, m.p. 270–272°. The reported[7] melting point for this compound is 266–268°.

1-Methyl-5-(*n*-butyl)-4(5*H*)-iminopyrazolo(3,4-d)pyrimidine.—A solution of 1.5 g. of 1-methyl-4-cyano-5-ethoxymethyleneaminopyrazole, 1.4 ml. of *n*-butylamine and 25 ml. of dry pyridine was heated under reflux for 3 hours and then evaporated to dryness under reduced pressure. Recrystallization from petroleum ether gave 1.6 g. (93%), m.p. 80–81°. The analytical sample was prepared by vacuum sublimation; $\lambda_{max}^{0.1\ N\ HCl}$ 259 mμ, log ε 3.84; λ_{max}^{EtOH} 259, 267 mμ, log ε 3.82, 3.92.

Anal. Calcd. for $C_{10}H_{15}N_5$: C, 58.5; H, 7.4; N, 34.1. Found: C, 58.8; H, 7.7; N, 33.4.

1-Methyl-5-(D-1-sorbityl)-4(5*H*)-iminopyrazolo(3,4-d)pyrimidine. Method A.—A mixture of 5 g. of 1-methyl-4-cyano-5-ethoxymethyleneaminopyrazole, 8.1 g. of D-glucamine and 400 ml. of dry pyridine was heated under reflux for 3 hours, evaporated to dryness and the residue recrystallized from 1 l. of methanol to give 4.7 g. (55%) of an amorphous solid, m.p. 196–198° dec.; $\lambda_{max}^{0.1\ N\ HCl}$ 259 mμ, log ε 3.83; λ_{max}^{EtOH} 259, 267 mμ, log ε 3.76, 3.78.

Anal. Calcd. for $C_{12}H_{19}N_5O_5$: C, 46.0; H, 6.1; N, 22.35. Found: C, 45.6; H, 6.0; N, 22.4.

Method B.—An intimate mixture of 5 g. of 1-methyl-4-cyano-5-ethoxymethyleneaminopyrazole and 5 g. of D-glucamine was heated on a steam-bath for 5 minutes. To the partly molten solid was added 300 ml. of ethanol and the mixture heated under reflux for 30 minutes. Precipitation from the initially clear solution began after a few minutes of heating. Cooling and filtering gave 5.0 g. (57%) of a solid identical with the product obtained by method A.

Recrystallization of 1-methyl-5-(D-1-sorbityl)-4(5*H*)iminopyrazolo(3,4-d)pyrimidine from aqueous ethanol gave long, colorless needles, m.p. 130–132°. This material appears to be a polymorphic form of the material, m.p. 196–198° dec., obtained upon recrystallization from methanol (or aqueous methanol), since it resolidifies upon melting and then remelts at 196–198° dec. Furthermore, it is isomeric with the higher-melting form, and possesses the same ultraviolet absorption spectrum and R_f values. The infrared spectra of the two forms are almost identical except for some differences in the fingerprint region.

1-Methyl-5-(D-ribityl)-4(5*H*)-iminopyrazolo(3,4-d)pyrimidine.—A mixture of 7 g. of 1-methyl-4-cyano-5-ethoxymethyleneaminopyrazole, 14 g. of D-ribamine (61% solution in water) and 400 ml. of pyridine was treated as described above in method A to give 3.5 g. (31%) of crude product, m.p. 170–182°. This material gave two spots on paper chromatography and was a mixture of the isomeric pyrazolo(3,4-d)-pyrimidines; from a second preparation, allowed to stand for a longer time, only 1-methyl-4-(D-ribamino)-pyrazolo-(3,4-d)pyrimidine was isolated. The presence of water in the reaction mixture also brought about some hydrolysis of the ethoxymethyleneaminopyrazole, since small amounts of 1-methyl-4-cyano-5-aminopyrazole were isolated from the mother liquors.

Repeated recrystallization of the crude product from a mixture of methanol and ethanol gave the pure imino isomer, m.p. 185–189°; $\lambda_{max}^{0.1\ N\ HCl}$ 259 mμ, log ε 3.84; λ_{max}^{EtOH} 259, 267 mμ, log ε 3.78, 3.81.

Anal. Calcd. for $C_{11}H_{17}N_5O_4$: C, 46.6; H, 6.05; N, 24.7. Found: C, 46.7; H, 5.7; N, 25.0.

1-Methyl-4-(*n*-butyl)-aminopyrazolo(3,4-d)pyrimidine was prepared by rearrangement of 1-methyl-5-(*n*-butyl)-4-(5*H*)-iminopyrazolo(3,4-d)pyrimidine by the procedure described above for the conversion of VIII to IX. Recrystallization from dioxane–petroleum ether gave long, coarse needles, m.p. 85°. The reported[7] melting point for this compound is 87–88°; $\lambda_{max}^{0.1\ N\ HCl}$ 263 mμ, log ε 3.99; λ_{max}^{EtOH} 283 mμ, log ε 3.98.

Anal. Calcd. for $C_{10}H_{15}N_5$: C, 58.5; H, 7.4; N, 34.1. Found: C, 58.3; H, 7.2; N, 33.9.

1-Methyl-4-(D-glucamino)-pyrazolo(3,4-d)pyrimidine was prepared by rearrangement of 1-methyl-5-(D-1-sorbityl)-4(5*H*)-iminopyrazolo(3,4-d)pyrimidine by the procedure described above for the conversion of VIII to IX. Recrystallization from methanol gave colorless crystals, m.p. 197–199°; $\lambda_{max}^{0.1\ N\ HCl}$ 266 mμ, log ε 4.11; λ_{max}^{EtOH} 281 mμ, log ε 4.07.

Anal. Calcd. for $C_{12}H_{19}N_5O_5$: C, 46.0; H, 6.1; N, 22.35. Found: C, 46.2; H, 6.0; N, 21.9.

1-Methyl-4-(D-ribamino)-pyrazolo(3,4-d)pyrimidine was prepared from 1-methyl-5-(D-1-ribityl)-4(5*H*)-iminopyrazolo(3,4-d)pyrimidine by the procedure described above. Recrystallization from methanol gave colorless crystals, m.p. 182–185°; $\lambda_{max}^{0.1\ N\ HCl}$ 266 mμ, log ε 4.10; λ_{max}^{EtOH} 281 mμ, log ε 4.09.

Anal. Calcd. for $C_{11}H_{17}N_5O_4$: C, 46.6; H, 6.05; N, 24.7. Found: C, 46.75; H, 5.9; N, 24.75.

1-Methyl-4-hydrazinopyrazolo(3,4-d)pyrimidine.—Treatment of an ethanolic solution of 1-methyl-4-cyano-5-ethoxymethyleneaminopyrazole with 98% hydrazine hydrate and standing resulted in the deposition of crystalline 1-methyl-4-hydrazinopyrazolo(3,4-d)pyrimidine, m.p. 247°, identical with an authentic sample.[7] Attempts to isolate the reaction product after a short reaction time invariably led to an impure material exhibiting a wide melting point range, and from which only the above product could be isolated.

1-Methyl-4-ethoxymethyleneamino-5-cyanoimidazole (XI).—A mixture of 9 g. of 1-methyl-4-amino-5-cyanoimidazole,[8] 45 ml. of ethyl orthoformate and 90 ml. of dimethylformamide was heated under reflux for 2 hours and then evaporated to dryness under reduced pressure. Recrystallization of the yellow, crystalline residue from ethanol, with the use of charcoal, yielded 10.5 g. (80%) of colorless plates, m.p. 125–127°.

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.9; H, 5.7; N, 31.45. Found: C, 54.1; H, 5.85; N, 31.4.

1-Amino-6(1*H*)-imino-7-methylpurine.—To a solution of 1 g. of 1-methyl-4-ethoxymethyleneamino-5-cyanoimidazole in 40 ml. of benzene was added 5 ml. of 98% hydrazine hydrate in 15 ml. of water. After a few minutes, a heavy precipitate of colorless crystals occurred; yield 0.85 g. (92%), m.p. 193–195° dec. Recrystallization from ethanol raised the melting point to 199–200° dec.; $\lambda_{max}^{0.1\ N\ HCl}$ 267 mμ, log ε 3.87; λ_{max}^{EtOH} 270, log ε 4.07.

Anal. Calcd. for $C_6H_8N_6$: C, 43.9; H, 4.9; N, 51.2. Found: C, 44.2; H, 4.9; N, 51.0.

1-Methyl-6(1*H*)-imino-7-methylpurine.—A solution of 0.85 g. of 1-methyl-4-ethoxymethyleneamino-5-cyanoimidazole, 20 ml. of benzene and 10 ml. of ethanolic methylamine was heated under reflux for 40 minutes, diluted with a little petroleum ether and then chilled overnight. The product was collected by filtration and recrystallized from benzene; yield 0.7 g. (90%), m.p. 170–171°; $\lambda_{max}^{0.1\ N\ HCl}$ 270 mμ, log ε 3.86; λ_{max}^{EtOH} 264.5 mμ, log ε 3.93.

Anal. Calcd. for $C_7H_9N_5$: C, 51.5; H, 5.6; N, 42.9. Found: C, 51.8; H, 5.7; N, 42.4.

1-(*n*-Butyl)-6(1*H*)-imino-7-methylpurine.—A solution of 1 g. of 1-methyl-4-ethoxymethyleneamino-5-cyanoimidazole, 1 ml. of *n*-butylamine and 25 ml. of benzene was heated under reflux for 2 hours, and then evaporated to dryness under reduced pressure. The oily residue was dissolved in ethanol, charcoal added, and the filtrate again evaporated to dryness. Recrystallization of the residual yellow solid from benzene–petroleum ether gave 0.4 g. (35%) of light yellow crystals, m.p. 125–126°; $\lambda_{max}^{0.1\ N\ HCl}$ 268 mμ, log ε 3.92; λ_{max}^{EtOH} 265 mμ, log ε 4.00.

Anal. Calcd. for $C_{10}H_{15}N_5$: C, 58.5; H, 7.4; N, 34.1. Found: C, 58.5; H, 7.1; N, 34.4.

1-(D-Sorbityl)-6(1*H*)-imino-7-methylpurine.—A mixture of 9 g. of 1-methyl-4-ethoxymethyleneamino-5-cyanoimidazole, 9 g. of D-glucamine and 1 l. of methanol was heated under reflux for 2 hours to give a clear solution which upon chilling deposited 13.4 g. (85%) of colorless crystals, m.p. 193° dec. Recrystallization from methanol did not raise the melting point: $\lambda_{max}^{0.1\ N\ HCl}$ 271 mμ, log ε 3.85; λ_{max}^{EtOH} 265 mμ, log ε 3.83.

Anal. Calcd. for $C_{12}H_{19}N_5O_5$: C, 46.0; H, 6.1; N, 22.35. Found: C, 45.9; H, 6.0; N, 22.6.

7-Methyladenine.—Alcoholic ammonia was slowly added to 0.5 g. of 1-methyl-4-ethoxymethyleneamino-5-cyanoimidazole in 10 ml. of ethanol until the solution was strongly basic. Stirring at room temperature resulted in the gradual deposition of fine, colorless crystals which were collected by filtration and recrystallized from aqueous ethanol; yield 0.35 g. (84%), m.p. 345°. The reported melting point for this compound is 351°[17] and 344–346° dec.[8]

6-Methylamino-7-methylpurine was prepared in essentially quantitative yield by heating an aqueous solution of 1-methyl-6(1*H*)-imino-7-methylpurine under reflux for 20 hours, evaporating to dryness and recrystallizing the residue from ethanol. The product was obtained in the form of colorless needles, m.p. 311°. The reported[8] melting point for this compound is 300° dec.; $\lambda_{max}^{0.1\ N\ HCl}$ 278 mμ, log ε 4.24; λ_{max}^{EtOH} 272, 278 mμ, log ε 4.11, 4.12.

Anal. Calcd. for $C_7H_9N_5$: C, 51.5; H, 5.6; N, 42.9. Found: C, 51.9; H, 5.7; N, 42.95.

6-(*n*-Butyl)-amino-7-methylpurine.—An aqueous solution of 1-(*n*-butyl)-6(1*H*)-imino-7-methylpurine was heated under reflux for 20 hours and then evaporated to dryness under reduced pressure. The residue was dissolved in ethanol, petroleum ether added, and the resulting very light precipitate of 7-methylhypoxanthine removed by filtration. The filtrate was evaporated to dryness and the residue recrystallized from benzene and then sublimed at 280° (0.1 mm.) to give an almost quantitative yield of 6-(*n*-butyl)-amino-7-methylpurine, m.p. 144–146°; $\lambda_{max}^{0.1\ N\ HCl}$ 279 mμ, log ε 4.18; λ_{max}^{EtOH} 273, 278 mμ, log ε 4.09, 4.10.

Anal. Calcd. for $C_{10}H_{15}N_5$: C, 58.6; H, 7.4; N, 34.1. Found: C, 58.2; H, 7.05; N, 34.6.

6-(D-glucamino)-7-methylpurine was similarly prepared in almost quantitative yield by heating an aqueous solution of 1-(D-1-sorbityl)-6(1*H*)-imino-7-methylpurine under reflux for 20 hours, evaporating to dryness and recrystallizing the residue from methanol; m.p. 215° dec.; $\lambda_{max}^{0.1\ N\ HCl}$ 281 mμ, log ε 4.11; λ_{max}^{EtOH} 272, 278 mμ, log ε 3.97, 3.98.

Anal. Calcd. for $C_{12}H_{19}N_5O_5$: C, 46.0; H, 6.1; N, 22.35. Found: C, 46.0; H, 6.0; N, 22.6.

1-Methyl-4-nitro-5-cyanoimidazole.—A mixture of 93 g. of 1-methyl-4-chloro-5-nitroimidazole,[15] 80 g. of potassium cyanide, 10 g. of potassium iodide and 1 l. of dimethylformamide was heated under reflux with stirring for 2.5 hours and then evaporated to a small volume under reduced pressure. Addition of water resulted in the separation of 46 g. (52%) of a crystalline solid, m.p. 130–138°, which was recrystallized from benzene. The product, m.p. 141–143°, was identical in every respect with an authentic sample of 1-methyl-4-nitro-5-cyanoimidazole.[15]

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