crystalline mass which was recrystallized from acetonitrile and from isopropyl acetate. The physical data are given in Table III.

6-Methoxy-4-(1-methyl-3-pyrrolidinylmethylamino)quinoline. Into a 100-ml., three-neck flask equipped with gas inlet tube, thermometer, stirrer, and condenser were placed 13.7 g. (0.048 mole) of 4-phenoxy-6-methoxyquinoline hydrochloride[13] and 8.8 g. (0.072 mole) of 1-methyl-3-pyrrolidinylmethylamine. The mixture was stirred with heating at 125° (internal temperature) under a nitrogen atmosphere for 24 hr. The product was isolated according to the procedure for 7-chloro-4-(1-methyl-3-pyrrolidinylmethylamino)-3-methylquinoline.

The remaining 4-aminoquinolines of Table III were obtained from 4-phenoxyquinolines as above. 7-Chloro-4-phenoxyquinoline hydrochloride was prepared according to the method reported.[8]

7-Chloro-4-(1-methyl-3-pyrrolidinylmethoxy)quinoline. To a suspension of 2.8 g. of 51.5% sodium hydride emulsion (0.06 mole of sodium hydride) in 60 ml. of dry toluene was added dropwise with stirring a solution of 6.9 g. (0.06 mole) of 1-methyl-3-pyrrolidinemethanol[5] in 40 ml. of dry toluene. After addition was complete the mixture was warmed with stirring for 0.5 hr. and then 9.9 g. (0.05 mole) of 4,7-dichloroquinoline[14] was added. The stirred mixture was refluxed for 6 hr. and then allowed to stand overnight. The cooled mixture was extracted with three 60-ml. portions of dilute hydrochloric acid. The combined acid extracts were washed with ether and then made alkaline with 20% aqueous sodium hydroxide to furnish an oily mixture which was extracted with ether. The ether solution was dried over magnesium sulfate and concentrated to an oil which solidified on cooling. The material was purified as described in Table III.

The remaining ethers of Table III were prepared as above from 4,7-dichloroquinoline[14] or 4-chloro-6-methoxyquinoline[15] and 1-substituted 3-pyrrolidinemethanols.[8]

Acknowledgment. We are indebted to Dr. R. F. Feldkamp for his helpful suggestions in the initiation of this work.

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(13) M. V. Rubstov, M. V. Lizgunova and E. D. Sazonova, *J. Gen. Chem. (USSR)*, 16, 1873 (1946); *Chem. Abstr.*, 41, 6254c (1947).

(14) The 4,7-dichloroquinoline was purchased from the Sterling-Winthrop Chemical Co.

(15) C. C. Price and R. N. Roberts, *J. Am. Chem. Soc.*, 68, 1204 (1946).

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES, BURROUGHS WELLCOME AND CO. (U.S.A.) INC.]

4-Hydroxypyrrolo[2,3-d]pyrimidine: Mannich Reaction

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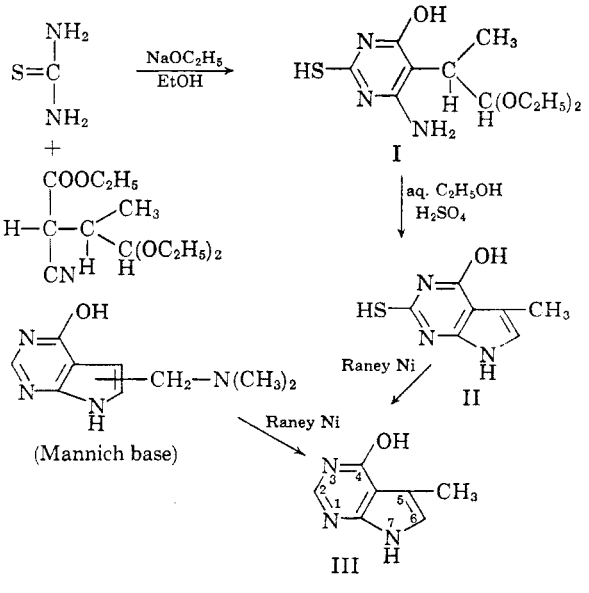
The pyrrolo[2,3-d]pyrimidine system undergoes the Mannich reaction with the same facility as the analogous indoles. A reaction sequence proved that the point of attack is at the β-pyrrole carbon as is true with indoles. The pyrrolopyrimidine Mannich base undergoes typical conversion to the acetamide and acetic acid derivatives.

The pyrrolo[2,3-d]pyrimidine bicycle bears structural analogy to indole and as such might be expected to undergo typical indole reactions such as the Mannich reaction. This investigation includes preparations of a simple Mannich base of 4-hydroxypyrrolo[2,3-d]pyrimidine, derivatives from this base, and proof of position of Mannich attack on this pyrrolopyrimidine system.

It has been well established that the Mannich attack in the indole series is at carbon 3 (the β-pyrrole carbon) if that position is unsubstituted. The reaction scheme shown below demonstrates that the comparable position in the pyrrolo[2,3-d]-pyrimidine system is also substituted under Mannich conditions.

The ethyl-α-cyano-β-methyl-γ,γ-diethoxy butyrate was prepared from ethyl cyanoacetate and α-bromopropionacetal by the method of West and Hitchings.[1] Reaction of this compound with thiourea conventionally gave the pyrimidine (I). Under acid catalysis, I cyclized to the pyrrolo-[2,3-d]pyrimidine (II) assumedly through hydrolysis of the acetal grouping to an aldehyde which then underwent an internal Schiff-base reaction forming the pyrrole ring. This 2-mercaptopyrrolopyrimidine was reductively desulfurized, giving



(1) R. A. West and G. H. Hitchings, Wellcome Foundation Ltd., Brit. Patent 812,366, April 22, 1959; *Chem. Abstr.*, 54, 592 (1960).

TABLE I
PYRROLO[2,3-d]PYRIMIDINES ULTRAVIOLET SPECTRAL DATA AND R_f VALUES

Compound	pH 1.0		pH 11.0		
	λ_{max} (mμ)	$\epsilon(10^3)$	λ_{max} (mμ)	$\epsilon(10^3)$	R_f[a]
4-Hydroxy	263	9.65	265	10.30	0.45
4-Hydroxy Mannich base	264	10.0	265	9.40	0.80
Mannich base methiodide	261	10.9	264	11.0	—
4-Hydroxy-5-acetamide	266	10.0	268	10.5	0.61
4-Hydroxy-5-acetic acid	267	7.85	269	7.50	0.53
4-Hydroxy-5-methyl[b]	275	8.50	273	9.20	0.41
4-Chloro-5-methyl[b]	273	3.08	272	3.30	0.30
			302	2.90	
2-Mercapto-4-hydroxy-5-methyl	247	8.60	297	13.1	0.28
	302	14.40			

[a] Chromatographic solution: mixture of 5 ml. of 2-propanol and 95 ml. of 5% aqueous ammonium sulfate. Spots detected using a Fisher Mineralite ultraviolet lamp (2537A). Ascending technique was used throughout on Whatman No. 1 paper strips. [b] From either source.

4 - hydroxy - 5 - methylpyrrolo [2,3 - d] pyrimidine (III).

High pressure Raney nickel reduction of the dimethylamino Mannich base of 4-hydroxypyrrolo-[2,3-d]pyrimidine yielded the same compound (III) as identified by elemental analyses, spectral data (ultraviolet and infrared) and by paper chromatography. Likewise, the 4-chloro derivatives from both 4-hydroxy-5-methyl compounds are similar by melting point, mixed melting point, spectral and chromatographic data as well as elemental analysis. It was therefore established that the Mannich attack on this pyrrolopyrimidine was on the β-pyrrole carbon (position 5). The Mannich base does not give the Ehrlich color reaction for pyrroles as does 4-hydroxypyrrolopyrimidine itself.

The Mannich base, like gramine,[2] undergoes conversion to the 5-acetamide and 5-acetic acid derivatives in the molar ratio of 1 to 3.7, respectively, when refluxed for seventy-five to eighty hours with excess aqueous sodium cyanide solution. This reaction apparently involves displacement of dimethylamine by cyanide ion. The nitrile thus formed is then hydrolyzed in the strongly alkaline medium to the amide and thence to the acid. By taking periodic aliquots (eleven to twelve-hour samples) of this reaction mixture and paper chromatographing them, it was noted that the base disappears within twelve hours and that the amide and acid were the only compounds evident after forty-eight hours. Between twelve and thirty-five hours the probable nitrile intermediate was indicated by streaking from the origin to R_f = 0.62. It is probable that the streaking was a composite of the nitrile, the amide, and the acid as the latter compounds have R_f values falling in this range. Ultraviolet spectral properties of these compounds are quite characteristic and are listed in Table I along with chromatographic data.

EXPERIMENTAL[3]

2-Mercapto-4-hydroxy-6-amino-5-(α-methyl-β,β-diethoxy)-ethylpyrimidine (I). Sodium metal (0.8 g.; 0.033 mole) was treated with 55 ml. of absolute ethanol. To this were added 2.6 g. of (0.035 mole) thiourea and 7.5 g. (0.03 mole) of ethyl-α-cyano-β-methyl-γ,γ-diethoxybutyrate. The solution was refluxed for 3 hr., then added to 100 ml. of ice-water mixture and acidified with glacial acetic acid to *p*H 6.0. An oil first formed which solidified after chilling overnight, yielding a yellowish solid which after filtering and drying melted at 290–295° dec. The 5.6 g. of crude product thus obtained represented an 82% yield. It showed only one fluorescing spot at R_f = 0.31 when chromatographed in the usual solvent. The material recrystallized well from hot water, from which needles formed, decomposing at 296–299°.

Anal. Calcd. for $C_{11}H_{19}N_3O_3S$: C, 48.4; H, 6.8; N, 15.3. Found: C, 48.7; H, 7.1; N, 15.0.

2-Mercapto-4-hydroxy-5-methylpyrrolo[2,3-d]pyrimidine (II). Into 100 ml. of 90% aqueous ethanol was added 2.9 g. (0.011 mole) of the above pyrimidine (I) and 3 ml. of concd. sulfuric acid. After 2 hr. at reflux, chilling, and filtering, 2.0 g. of crude pyrrolopyrimidine was obtained which gave only one fluorescing spot on the chromatogram at R_f = 0.28. The material crystallized well from 50% aqueous ethanol (Darco) yielding 1.7 g. (86% yield) of the desired product. The material neither melted nor decomposed below 310°.

Anal. Calcd. for $C_7H_7N_3OS$: C, 46.4; H, 3.9. Found: C, 46.5; H, 4.0.

4-Hydroxy-5-methylpyrrolo[2,3-d]pyrimidine (III). Into 80 ml. of water containing 5 ml. of settled Raney nickel and 4 ml. of concd. ammonium hydroxide was added 1.5 g. (0.0083 mole) of the above 2-mercapto compound (II). After refluxing for 3 hr., the catalyst was filtered and extracted with three 50-ml. portions of boiling water. The extracts and mother liquor were combined and taken to dryness *in vacuo*. The pinkish residue was triturated with 25 ml. of cold water, acidified to *p*H 5.0 with glacial acetic acid, and filtered. The product after drying weighed 0.96 g. (80% yield) and decomposed at 290–291°. It was recrystallized from absolute ethanol with no change in melting properties.

Anal. Calcd. for $C_7H_7N_3O$: C, 56.4; H, 4.7; N, 28.2. Found: C, 56.4; H, 4.6; N, 28.6.

4-Chloro-5-methylpyrrolo[2,3-d]pyrimidine. The above hydroxy compound (III, 0.2 g.) was added to 5 ml. of phosphorus oxychloride and refluxed for 50 min., then slowly poured into 150 ml. of ice-water mixture with vigorous stirring. The chloro compound was extracted from suspension using two 50-ml. portions of ether. The ether solution was dried over anhydrous sodium sulfate overnight, the desiccant filtered and the ether taken to dryness by air-jet at room temperature leaving 0.12 g. of yellow amorphous solid melting 226–229° dec. Recrystallization from benzene (Darco) yielded a white product melting at 227–228° dec.

Anal. Calcd. for $C_7H_6N_3Cl$: N, 25.1. Found: N, 25.2.

4-Hydroxy-5-dimethylaminomethylpyrrolo[2,3-d]pyrimidine. Dimethylamine hydrochloride (4.4 g.; 0.054 mole) was added to 4.1 g. (0.054 mole) of anhydrous sodium acetate in 30 ml. of cold water and shaken for several minutes. Four grams (0.05 mole) of 37% aqueous formaldehyde and 6.7 g. (0.048 mole) of 4-hydroxypyrrolopyrimidine were added. The stoppered flask in a brace was heated over low steam for 3 hr. whereupon the pyrimidine slowly disappeared and the solution became amber. At the end of this period a clear tan solution was obtained. A small amount of Darco was added to the hot solution, shaken well and filtered. A chromatogram run on this mother liquor showed only one absorbing spot (R_f = 0.80). The mother liquor was allowed to evaporate

(2) H. R. Snyder and F. J. Pilgrim, *J. Am. Chem. Soc.*, **70**, 3770 (1948).

(3) All melting point data herein reported are uncorrected using a Köfler hot stage apparatus.

slowly over the weekend leaving a tan gummy solid. This material was stirred vigorously with a mixture of 400 ml. of absolute ethanol and 400 ml. of benzene. The inorganic material was filtered and the filtrate taken to dryness *in vacuo* in a 45–50° water bath leaving 6.7 g. of a pinkish solid (80% yield) which gave an analysis corresponding to the monohydrate of the Mannich base. The amorphous form turned yellow at 250° and decomposed with gas evolved between 260° and 300°.

Anal. Calcd. for $C_9H_{12}N_4O + H_2O$: C, 51.3; H, 6.6; N, 26.7. Found: C, 51.3; H, 6.2; N, 27.0.

The anhydrous base was obtained by recrystallization from acetone with no change in melting properties.

Anal. Calcd. for $C_9H_{12}N_4O$: C, 56.3; H, 6.3. Found: C, 56.3; H, 6.1.

A quantitative yield of the methiodide was obtained using a slight excess of methyl iodide with the above Mannich base in methanol. This yellowish product melted at 228–229° dec.

Anal. Calcd. for $C_{10}H_{15}N_4OI$: C, 35.8; H, 4.5; N, 16.8. Found: C, 35.5; H, 4.8; N, 17.0.

4-Hydroxy-5-acetamide and 5-acetic acid pyrrolo[2,3-d]-pyrimidines. Five grams of the Mannich base and 5.7 g. of sodium cyanide were refluxed for 80 hr. in 60 ml. of ethanol and 15 ml. of water during which a volatile amine was liberated. Seventy milliliters of water and a small amount of Darco were added to the warm brown solution and filtered after shaking well. The solution was concentrated to one-third volume and chilled. Filtration yielded 0.9 g. of the amide. The filtrate was acidified with dilute hydrochloric acid to *p*H 1.0–2.0 and chilled overnight, yielding 3.3 g. of the acid after filtering and drying.

The amide was recrystallized from hot water yielding a white amorphous solid which turned yellow at 250–260°, then decomposed from 303–310°.

Anal. Calcd. for $C_9H_9N_4O_2$: C, 50.0; H, 4.2; N, 29.2. Found: C, 50.2; H, 4.2; N, 29.4.

The acid recrystallized from water as a pinkish solid decomposing between 225–235° (gas evolved).

Anal. Calcd. for $C_8H_7N_3O_2$: C, 49.8; H, 3.6; N, 21.7. Found: C, 49.9; H, 3.4; N, 21.5.

Reduction of the Mannich base. Into 200 ml. of absolute ethanol containing 15 g. of Raney nickel was added 6.9 g. of the Mannich base in a high pressure hydrogenator equipped for heating. The temperature was raised slowly to 140–145° over 4 hr. at 1000 p.s.i. initial pressure and held there for 15 hr. longer. The warm solution smelled of a volatile amine and was charcoal treated and filtered. The solvent was driven off over steam and the resulting residue was recrystallized from water, yielding 5.3 g. of white product which had an analysis corresponding to 4-hydroxy-5-methylpyrrolo[2,3-d]pyrimidine. The compound was similar to the preparation III by paper chromatography, infrared and ultraviolet spectra, melting properties and elemental analysis.

Anal. Calcd. for $C_7H_7N_3O$: C, 56.4; H, 4.7. Found: C, 56.2; H, 4.7.

Chloro compound derived from the above preparation. One gram of the above hydroxy compound derived by reduction of the Mannich base was treated with 20 ml. of phosphorus oxychloride by the exact procedure above yielding 0.75 g. of a chloro compound which after recrystallizing from benzene had the same melting point, infrared and ultraviolet spectra, nitrogen analysis, and R_f value as that of the 4-chloro-5-methylpyrrolo[2,3-d]pyrimidine prepared above. No melting point depression resulted with a mixture of both chloro compounds.

Anal. Calcd. for $C_7H_5N_3Cl$: N, 25.1. Found: N, 25.1.

Acknowledgment. Our thanks go to Mr. Charles Marr, Dr. Samuel Blackman, and Mrs. R. Purdy for their microanalytical contributions and to Miss L. Beauchamp for technical assistance.

TUCKAHOE, N. Y.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Studies in Purine Chemistry. X. Some Derivatives of 9-Aminopurines[1,2]

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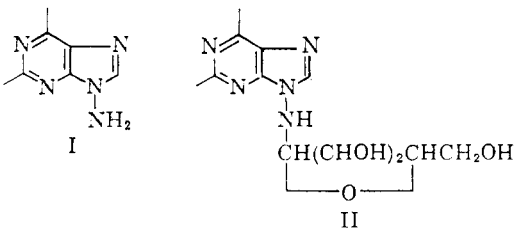
The synthesis of a number of derivatives of 6-methyl- and 6-methylmercapto-9-aminopurine has been carried out. Attempts to obtain 6-methyl-9-aminopurine itself by acid hydrolysis of 6-methyl-9-formylaminopurine or 6-methyl-9-(*p* aminobenzal)aminopurine led to ring expansion with the formation of 5-methyl-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine. Further treatment with acid then resulted in ring contraction of the latter compound to 6-methyl-9-aminopurine, which could not, however, be isolated because of its subsequent rapid hydrolysis to 4-hydrazino-5-amino-6-methylpyrimidine.

As a part of the intensive current effort to find more effective antitumor agents, considerable attention has been given to the field of purine chemistry in a search for potential antagonists of the naturally-occurring purines involved in nucleic acid biosynthesis. We wish to describe in this paper our preliminary efforts to prepare some representative 9-aminopurines (I) as examples of a class of derivative potentially capable of transformation into an interesting type of 'pseudo' nucleoside (II).



I II

2 - Mercapto - 4 - hydroxy - 5 - phenylazo - 6-methylpyrimidine (III), prepared from ethyl phenylazoacetoacetate and thiourea by a modifi-

(1) For the previous paper in this series, see E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960).

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