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Department of Chemistry, Carnegie Institute of Technology

The Synthesis of 6,7-Dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines. II. 4-Hydroxy, 4-Mercapto, 2-Amino-4-hydroxy and 2,4-Dihydroxy Derivatives (1a)

Tuvia Sheradsky (1b) and Philip L. Southwick (1c)

Several new types of compounds in the 6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine series have been prepared. Included are a 6-acyl derivative unsubstituted in the pyrimidine ring, as well as 4-hydroxy, 4-mercapto, 2-amino-4-hydroxy and 2,4-dihydroxy derivatives. These products were derived directly or indirectly from 4-cyano- or 4-carbethoxy-1-acyl-3-amino-3-pyrroline intermediates. 3-Hydroxy, 3-amino, and 3-thioformylamino-1-acyl-3-pyrroline-4-thiocarboxamides have been obtained and the 3-thioformylamino derivatives shown to undergo base-catalyzed cyclization to close a 4-mercaptopyrimidine ring.

Two preceding papers (2,3) have described methods for obtaining compounds in the new pyrrolo[3,4-*d*]-pyrimidine series from appropriately substituted pyrrolidines. The more recent of the previous papers (3) was devoted to the preparation of 6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines having amino substituents in the 4- or the 2- and 4-positions. 2-Methyl-4-amino derivatives were also described. Included was the description of a method of synthesis for 3-hydroxy or 3-amino-1-acyl-4-cyano-3-pyrrolines (XIII or X), and of the use of these compounds as intermediates for the synthesis of 6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine derivatives which carry a 4-amino substituent.

It was desirable to devise methods to obtain additional compounds in the new series with substitution corresponding to that found in other important members of the pyrimidine and purine classes. In the present investigation it has been demonstrated that the same precursors can serve for the convenient preparation of compounds in the 6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine series that contain a 4-mercapto substituent (XIX and XXII; formulas show the thioamide tautomer). It has also been shown that corresponding 4-hydroxy derivatives (IV and V; formulas show the amide tautomer) can be obtained from 1-acyl-3-amino-4-carbethoxy-3-pyrrolines (III). In addition, compounds with two other types of substitution in the pyrimidine ring, the 2-amino-4-hydroxy and 2,4-dihydroxy derivatives (VIII and IX), have been obtained from previously described 2,4-diamino derivatives (VII) (3), and one compound completely unsubstituted in the pyrimidine ring (XXIII) has been obtained from a 4-mercapto derivative (XIX) (4).

Some of the more commonly employed methods for forming a pyrimidine ring with the desired substituents failed completely when applied to our pyrrolidine intermediates. The only pyrimidine ring closures which succeeded were those in which at one stage in the reaction sequence ethyl orthoformate was used to introduce a reactive ethoxymethylene group onto the 3-amino nitrogen of a 4-carbethoxy- or 4-cyano-3-amino-3-pyrroline derivative. Related methods have been employed for the synthesis of a pyrimidine portion of this (3) and other fused heterocyclic systems (5). In the present investigation these methods were extended in scope, and in the case of the synthesis of the 4-mercapto compounds some new observations were made concerning intermediate products involved. The synthesis of derivatives with different kinds of substitution in the pyrimidine ring are discussed below under separate headings. The numbered formulas in the charts denote structure types; in the discussion individual compounds will be identified by appending one or two letters to the appropriate numeral. The first letter will designate the group R (h = hydrogen and m = methyl) and a second letter, when given, the group R' (m = methyl and p = phenyl).

4-Hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines (IV and V) from 1-Acyl-3-amino-4-carbethoxy-3-pyrrolines (III).

The 1-acyl-3-amino-4-carbethoxy-3-pyrrolines (III) had not been employed previously as intermediates for pyrrolo[3,4-*d*]pyrimidine synthesis. Such compounds are readily formed by heating the extensively enolized 1-acyl-4-carbethoxy-3-pyrrolidinones (II) (shown here in enolic form) with ammonium formate in ethanol solution (2,3,6). The pyrrolidinones (II) were obtained by cyclizations of

the Dieckmann type carried out as described previously (7). The 3-amino-3-pyrrolines (III), unlike the 3-pyrrolidinones (II), are relatively stable substances which can be recrystallized readily and kept for extended periods of time without undergoing decomposition.

Initially, a number of attempts were made to obtain 2-amino-4-hydroxy-6,7-dihydro-5*H*-pyrrolo-[3,4-*d*]pyrimidines (VIII) *via* the condensation of guanidine with 1-acyl-4-carbethoxy-3-pyrrolidinones (II), or with 1-acyl-3-amino-4-carbethoxy-3-pyrrolines (III), but the original starting materials were recovered unchanged. Corresponding reactions of guanidine with the related 4-cyano derivatives (X) and with 1-alkyl-3-amino-4-carbethoxy-3-pyrrolin-2-ones had been used successfully in the previous investigations (2,3). The failure of these condensations in the present instance suggests that the occurrence of this type of reaction is strongly favored by the increased electron-withdrawal from the 3-pyrroline olefinic bond produced by a lactam carbonyl or a cyano group. Such an effect would be expected if the initial nucleophilic attack by guanidine were at carbon-3 of the 3-amino-3-pyrroline with eventual elimination of the 3-amino nitrogen as ammonia.

After these efforts to obtain 2-amino-4-hydroxy derivatives (VIII) by use of the guanidine condensations had been abandoned, it was found that the 1-acyl-3-amino-4-carbethoxy-3-pyrroline derivatives (III) were, however, suitable precursors for the synthesis of 6-acyl-4-hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine derivatives (V). By analogy to the method which has been used for converting various *o*-amino nitriles to pyrimidine derivatives (5), the 3-amino-4-carbethoxy-3-pyrrolines were treated with ethyl orthoformate and acetic anhydride to form the *N*-ethoxymethylene derivatives (VI), which yielded the 6-acyl-4-hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines (V) upon treatment with ammonia in ethanol (8). The yields of the three compounds of this type which were prepared ranged from 35 to 63%. Alkaline hydrolysis removed the 6-acyl groups and afforded 4-hydroxy derivatives of structure IV. All of these compounds displayed ultraviolet spectra (see Table I) resembling those of related previously known 4-hydroxy pyrimidines.

2-Amino-4-hydroxy- and 2,4-Dihydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines (VIIIh and IXh).

After the failure of attempts described above to obtain these compounds by direct synthesis, experi-

Chart I

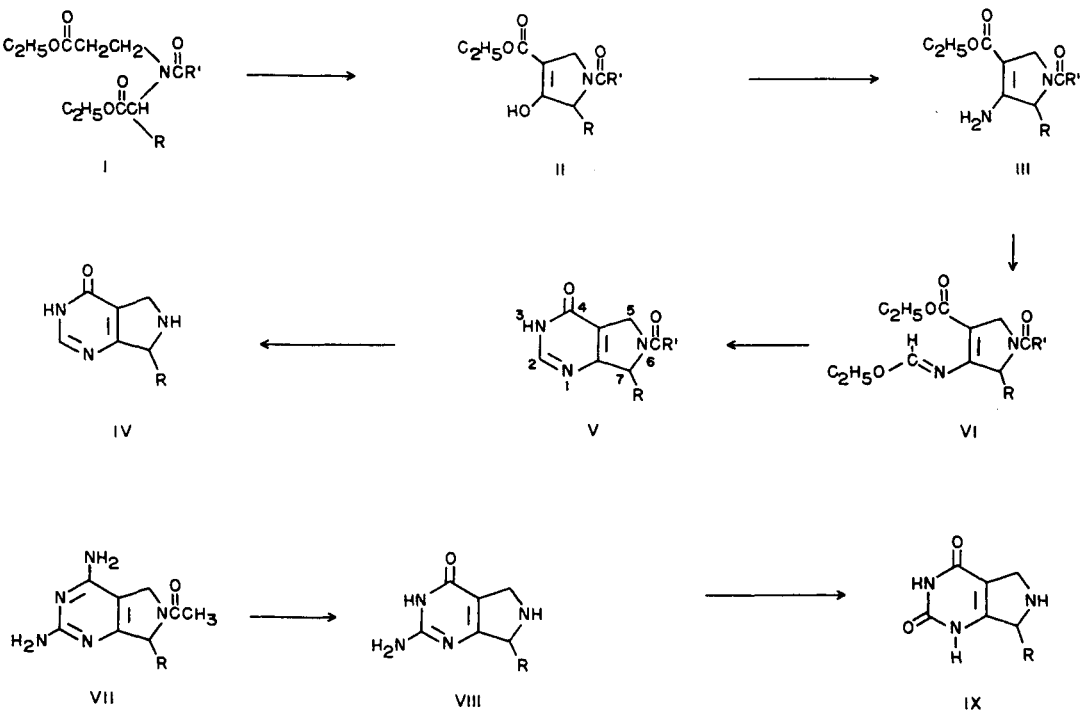
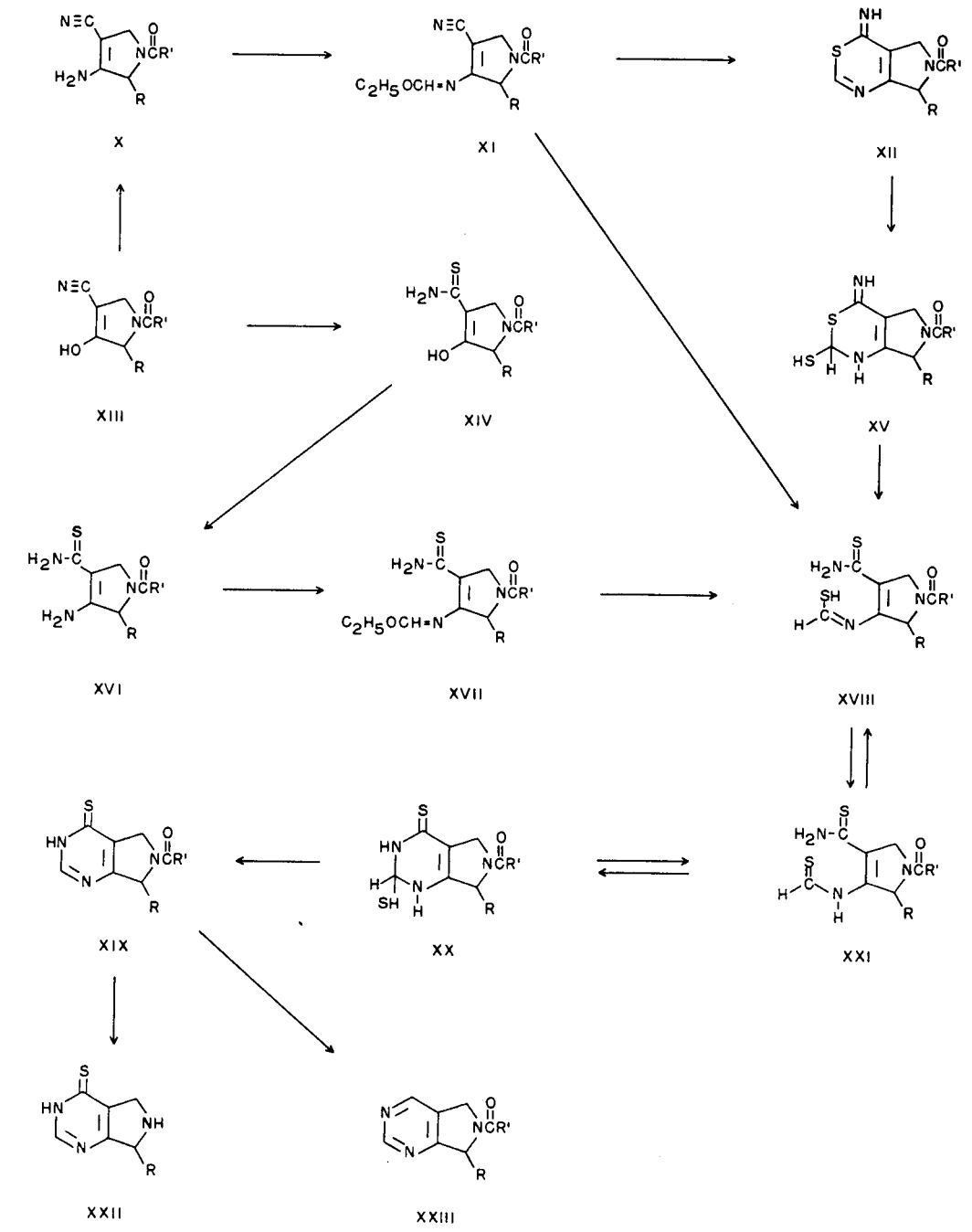
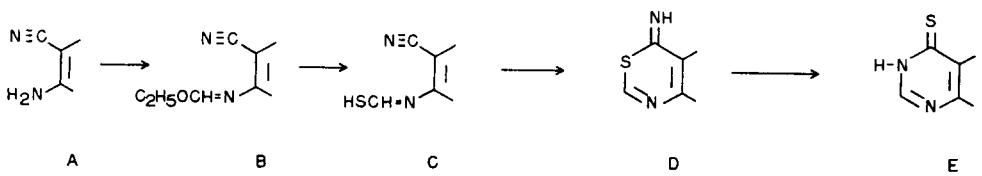


Chart II





ments were conducted to determine whether selective hydrolysis of the corresponding 2,4-diamino derivative (3) (VIIhm) might produce them. The 4-amino group of 2,4-diaminopyrimidines is reported to be hydrolyzed more rapidly by acid treatment than is the 2-amino group (9). By following changes in the ultraviolet spectra of acid hydrolysis mixtures it was possible to obtain a 72% yield of 2-amino-4-hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine (VIIIh) or a 52% yield of 2,4-dihydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine (IXh) after refluxing the 2,4-diamino derivative (VIIhm) with concentrated hydrochloric acid for 2.5 hours in the first instance and 16 hours in the second. Again the ultraviolet spectra (Table I) resembled those of pyrimidines with corresponding substitution in the 2- and 4-positions.

4-Mercapto-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines.

A number of attempts were made to convert various derivatives in this series to the corresponding 4-mercapto derivatives by the direct action of phosphorus pentasulfide, but the resulting tarry reaction mixtures yielded no pure compounds. The possibility of effecting the same type of conversion in two or more steps *via* 4-chloro derivatives was also explored without success; the action of phosphorus oxychloride on the 4-hydroxy derivatives resulted in the formation of intractible amorphous mixtures.

The 4-mercapto compounds were, however, successfully prepared by application of a method for mercapto pyrimidine synthesis recently introduced by Taylor and Vroman (10). As described by these authors, the scheme utilized *o*-amino nitriles (A) as the starting materials, and involved conversion of these substances by the action of ethyl orthoformate to 4-ethoxymethyleneamino derivatives (B), which then yielded 4-mercaptopyrimidines (E) upon treatment with hydrogen sulfide in pyridine solution. It was postulated that intermediate products of the action of hydrogen sulfide on (B) were first a thioformamide derivative (C) and then an iminothiazine derivative (D), which underwent a base-catalyzed rearrangement to (E). We found that when the method was applied to 1-acetyl-3-amino-4-cyano-3-pyrroline (Xhm) a solid product precipitated from the pyridine solution of the ethoxymethyleneamino derivative XIhm soon after hydrogen sulfide was introduced. This substance, which corresponded in composition to the formula $C_8H_{11}N_3OS_2$, was also obtained, although in low yield, by treating 1-acetyl-3-amino-3-pyrroline-4-thiocarboxyamide (XVI) successively with ethyl orthoformate and acetic anhydride, then with hydrogen sulfide in pyridine solution. It seems evident, therefore, that the substance is 1-acetyl-3-thioformylamino-3-pyrroline-4-thiocarboxamide (XXIhm) or one of the possible tautomers of that structure, XXhm or XVIIIhm. It dissolved in aqueous sodium hydroxide, and upon acidification of the resulting solution 6-acetyl-4-mercapto-6,7-dihydropyrrolo[3,4-*d*]pyrimidine (XIXhm) was precipitated.

No similar intermediate was observed when the same process was carried out with the methyl derivative Xmm; conversion to the 4-mercaptopyrimidine derivative XIXmm *via* the intermediate XImm occurred directly in 64% yield. Probably the isolation of the intermediate XXIhm is a consequence of its low solubility in pyridine. It is possible that formation of iminothiazines of structure XII precedes the formation of the thioamide intermediates XXI in each instance; the conversion XII ⟶ XVIII could be envisioned *via* a hydrogen sulfide addition product of structure XV. However, we observed no direct evidence of the presence of the iminothiazines XII, and there is no reason to assume that the action of two moles of hydrogen sulfide on the ethoxymethylene derivative XI could not yield XVIII by a path not involving XII. On the other hand, although the thioamides XXI can be regarded as established intermediates, they may not be the sole source of the mercaptopyrimidine derivatives XIX, since other pathways from XII to XIX can be conceived (11).

1-Acetyl-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine (XXIIIh).

Preparation of this compound was achieved in 76% yield by Raney nickel desulfurization of the corresponding 4-mercapto compound. Attempts at removal of the 1-acetyl group by hydrolysis with acids or bases were not successful, however, and no product could be isolated when desulfurization of the unacetylated 4-mercapto derivative (XXIIh) was attempted. The results suggested that 6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine is highly reactive, and that it was probably formed but then rapidly destroyed in these unsuccessful experiments.

EXPERIMENTAL (12)

1-Acetyl-3-amino-4-carbethoxy-3-pyrroline (IIIhm).

A solution of 1-acetyl-4-carbethoxy-3-pyrrolidone (IIhm) (7,13) (4 g., 0.02 mole) and ammonium formate (2.52 g., 0.04 mole) in absolute ethanol (20 ml.) was refluxed for 16 hours. Upon cooling the product precipitated and was crystallized from ethanol; yield 3.2 g. (82%); m.p. 203-206°; λ max (EtOH), 273 mμ (ε, 18,570).

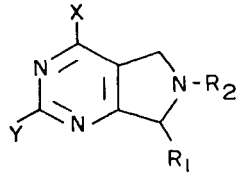
Anal. Calcd. for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.38; H, 7.13; N, 14.28.

1-Acetyl-2-methyl-3-amino-4-carbethoxy-3-pyrroline (IIImm).

1-Acetyl-2-methyl-4-carbethoxy-3-pyrrolidone (7) (0.02 mole) and ammonium formate (2.52 g., 0.04 mole) in absolute ethanol (20 ml.) were refluxed for 16 hours. The solution was concentrated to a small volume, water was added and the mixture extracted with benzene. The benzene was dried and evaporated. The oily residue solidified upon standing and was crystallized from benzene-petroleum ether (b.p. 30-60°); yield 2.13 g. (52%); m.p. 106-107°; λ max (EtOH), 274 mμ (ε, 16,210).

TABLE I

Ultraviolet Spectra of 6,7-Dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines



Compound	X	Y	R_1	R_2	Maxima, mμ (a) 0.1 *N* HCl λ	0.1 *N* HCl ε	Neutral Solvents λ	Neutral Solvents ε	0.1 *N* NaOH λ	0.1 *N* NaOH ε
IVh	OH	H	H	H	270	4,200	268 (b)	4,530	231	8,500
									261	4,350
IVm	OH	H	CH_3	H	268	4,750			233	5,040
									263	3,060
Vhm	OH	H	H	$COCH_3$	267	4,070	269 (b)	5,350	232	10,650
									262	5,870
Vhp	OH	H	H	COC_6H_5	263	7,350	265 (c)	7,065	232	16,500
									257(s)	5,830
Vmm	OH	H	CH_3	$COCH_3$	266	5,900	265 (b)	5,930	231	8,640
									260	5,200
VIII	OH	NH_2	H	H	274	7,440	284 (b)	7,570	279	6,860
IX	OH	OH	H	H	262	8,940	264 (b)	5,950	284	9,290
XIX	SH	H	H	$COCH_3$	286	9,870	294 (c)	9,480	300	17,860
					325	10,470	330(s)	5,550		
XIXmm	SH	H	CH_3	$COCH_3$	286	9,500	293 (c)	12,850	300	15,870
					326	10,200	331	8,360		
XXIIh	SH	H	H	H	288	10,400	290 (b)	12,860	300	17,300
					329	8,690	327	9,800		
XXIIm	SH	H	CH_3	H	288	13,480	294 (c)	10,690	300	14,840
					322	10,880	330	6,390		
XXIIIm	H	H	H	$COCH_3$	256	2,190	258 (c)	2,470	256	2,670

(a) The notation (s) indicates a shoulder or inflection. (b) In water solution. (c) In 95% ethanol solution.

Anal. Calcd. for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.37; H, 7.37; N, 13.60.

1-Benzoyl-3-amino-4-carbethoxy-3-pyrroline (IIIhp).

Ethyl *N*-(β-carbethoxyethyl) glycinate (20.3 g., 0.1 mole) was dissolved in pyridine (100 ml.). To the cooled, stirred solution benzoyl chloride (17 g.) was added dropwise at such a rate that the temperature did not rise above 10°. After stirring at room temperature overnight the solution was poured into water (400 ml.). The oily layer was taken up in ether. The ether solution was washed twice with 5% hydrochloric acid, then with 5% sodium bicarbonate, and finally with water, dried over sodium sulfate and evaporated. The residue was dissolved in absolute ethanol (50 ml.) and a sodium ethoxide solution (0.1 mole, from 2.3 g. of sodium and 100 ml. of ethanol) was added. After a 2-hour reflux period the ethanol was evaporated under reduced pressure and the solid residue was dissolved in water (100 ml.). The aqueous solution was extracted with ether, cooled and acidified with 20% hydrochloric acid. The oil which precipitated was taken up in ether and the ether was evaporated. 1-Benzoyl-3-carbethoxy-3-pyrrolidone was obtained as a red oil, yield 13.8 g. (53%). Ten grams of this oil was refluxed with 4 g. of ammonium formate in 50 ml. of ethanol for 15 hours. When the mixture was cooled the product precipitated and was crystallized from ethanol. The yield was 7.7 g. (77%); m.p. 171-172°; λ max (EtOH), 274 mμ (ε, 15,530).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.11; H, 6.34; N, 11.00.

1-Benzoyl-2-methyl-3-amino-4-carbethoxy-3-pyrroline (IIImp).

1-Benzoyl-2-methyl-3-amino-4-carbethoxy-3-pyrroline was prepared in the same manner as compound IIIhp above starting with 21.7 g. (0.1 mole) of ethyl *N*-(β-carbethoxyethyl)alaninate. 1-Benzoyl-2-methyl-4-carbethoxy-3-pyrrolidone was obtained as a red oil (16.5 g., 65%). Treatment of 10 g. of the oil with 4 g. of ammonium formate as described above yielded the product IIImp; yield 7.5 g. (75%);

170-171°; λ max (EtOH), 275 mμ (ε, 14,550).

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.22; H, 6.14; N, 10.15.

6-Acetyl-4-hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine (Vhm).

A solution of compound IIIhm (2 g.) in ethyl orthoformate (8 ml.) and acetic anhydride (8 ml.) was refluxed for 2 hours, then evaporated under reduced pressure. The oily residue was dissolved in absolute ethanol (28 ml.) and a solution of dry ammonia in absolute ethanol (excess) was added. After 2 hours the solution was concentrated to 10 ml. and cooled. The product was filtered and crystallized from dimethylformamide to yield 0.62 g. (35%) of a white product; m.p. 314-315° dec.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.43; H, 5.02; N, 23.24.

6-Benzoyl-4-hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine (Vhp).

The procedure was the same as that used for the 6-acetyl compound (Vhm) given above. A 2.6 g.-quantity of IIIhp yielded 1.5 g. (63%) of compound Vhp, m.p. 258-259° dec.

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.40; H, 4.64; N, 17.47.

6-Acetyl-4-hydroxy-7-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine (Vmm).

When applied to 2.15 g. of compound IIImm this procedure yielded 1.15 g. (60%) of compound Vmm, m.p. 256-257° dec.

Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.79; N, 21.75. Found: C, 55.82; H, 5.72; N, 21.56.

4-Hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine Hydrochloride (IVh).

Compound IIIhp (1.2 g.) in 6 *N* hydrochloric acid (50 ml.) was refluxed for 2 hours and the solution was cooled. Benzoic acid was filtered out and the filtrate was evaporated under reduced pressure. Recrystallization of the solid residue from ethanol afforded 0.7 g. (82%) of white crystals, m.p. 300-301° dec.

Anal. Calcd. for $C_6H_8ClN_3O$: C, 41.51; H, 4.64; N, 24.20. Found: C, 41.33; H, 4.61; N, 24.14.

4-Hydroxy-7-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine Hydrochloride (IVm).

Prepared as IVh above. Compound IIImm (1.9 g.) was hydrolyzed in the same manner as IIIhp to give 1.6 g. (84%) of compound IVm as the hydrochloride, m.p. 257-259° dec.

Anal. Calcd. for $C_7H_{10}ClN_3O$: C, 44.80; H, 5.37; N, 22.40. Found: C, 45.31; H, 5.41; N, 22.27.

2-Amino-4-hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine Hydrochloride (VIIIh).

6-Acetyl-2,4-diamino-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine (VIIhm) (3) (9.65 g., 0.05 mole) in 6 *N* hydrochloric acid (500 ml.) was refluxed for 2.5 hours and the solution was then evaporated under reduced pressure. The solid residue was recrystallized from 70% ethanol to yield 7.5 g. (72%) of compound VIIIh as a hydrate, m.p. 301-302° dec. The usual procedures for drying analytical samples did not produce an anhydrous form of this substance.

Anal. Calcd. for $C_6H_9ClN_4O \cdot H_2O$: C, 34.87; H, 5.36; N, 27.11. Found: C, 34.89; H, 5.13; N, 26.85.

2,4-Dihydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine Hydrochloride (IXh).

6-Acetyl-2,4-diamino-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine (VIIhm) (9.65 g., 0.05 mole) in 6 *N* hydrochloric acid (500 ml.) was refluxed for 16 hours, then the solution was evaporated under reduced pressure and the residue recrystallized from 70% ethanol to yield 5.8 g. (52%) of compound IXh, m.p. 345-346° dec.

Anal. Calcd. for $C_6H_8ClN_3O_2$: C, 38.00; H, 4.25; N, 22.16. Found: C, 37.66; H, 4.57; N, 22.31.

6-Acetyl-4-mercapto-7-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine (XIXmm).

1-Acetyl-2-methyl-3-amino-4-cyano-3-pyrroline (Xmm) (4 g.) in acetic anhydride (15 ml.) and ethyl orthoformate (15 ml.) were refluxed for 2 hours. The solvents were evaporated under reduced pressure and the oily residue dissolved in pyridine (50 ml.). Hydrogen sulfide was bubbled through the solution. The temperature rose to about 50°, and after about 15 minutes precipitation of the product began. After another five minutes water was added, and the product was filtered out and crystallized twice from ethanol to yield 3.2 g. (64%) of light yellow crystalline powder, m.p. 273-274° dec.

Anal. Calcd. for $C_9H_{11}N_3OS$: C, 51.67; H, 5.30; N, 20.09; S, 15.29. Found: C, 51.22; H, 5.48; N, 19.60; S, 14.96.

1-Acetyl-4-mercapto-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine (XIXhm).

(a) Isolation of 1-Acetyl-3-thioformylamino-3-pyrroline-4-thiocarboxamide (XXIhm).

To a boiling suspension of 1-acetyl-3-amino-4-cyano-3-pyrroline (Xhm) (4 g.) in acetic anhydride (30 ml.) ethyl orthoformate (15 ml.) was added, and heating under reflux was continued until solution occurred (about 10 minutes). The solution was evaporated, the solid residue dissolved in pyridine (30 ml.), and hydrogen sulfide was bubbled into the solution. Precipitation began after about 20 minutes. Water was then added and the product was filtered, washed with water and recrystallized from ethanol to yield 4.1 g. of yellow powder, m.p. 301-302° dec.; λ max (EtOH), 238 (ε, 5,540); 267 (ε, 4,850); 320 (ε, 14,860); 363 mμ (ε, 8,570).

Anal. Calcd. for $C_8H_{11}N_3OS_2$: C, 41.92; H, 4.84; N, 18.34; S, 27.93. Found: C, 42.05; H, 4.94; N, 18.17; S, 27.68.

(b) Cyclization of XXIhm to XIXhm.

Compound XXIhm (2.3 g.) was dissolved in 2% sodium hydroxide solution (100 ml.) and the solution then acidified with 10% hydrochloric acid. After the mixture had been cooled the precipitated product was collected by filtration and crystallized from dimethyl formamide to yield 1.55 g. (78%) of light yellow crystals, m.p. 323-325° dec.

Anal. Calcd. for $C_8H_9N_3OS$: C, 49.23; H, 4.65; N, 21.53; S, 16.40. Found: C, 48.98; H, 4.69; N, 21.25; S, 16.10.

4-Mercapto-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine Hydrochloride (XXIIh).

The acetyl derivative (XIXhm) (1.95 g.) was refluxed in 6 *N* hydrochloric acid (20 ml.) for 2 hours. The solution was evaporated under reduced pressure and the solid residue was recrystallized from 50% ethanol to yield yellow needles (1.4 g., 75%) which decomposed slowly above 330° without melting.

Anal. Calcd. for $C_6H_6ClN_3S$: C, 38.01; H, 4.25; N, 22.16; S, 16.88; Cl, 18.70. Found: C, 38.02; H, 4.27; N, 21.98; S, 16.92; Cl, 19.03.

A sample of the hydrochloride was converted to the free base by dilute aqueous ammonia. The compound crystallized from water as colorless cubes, m.p. 278-279° dec., which developed a light brown color when allowed to stand in the air. The results of nitrogen and sulfur determinations on this substance were not completely satisfactory.

Anal. Calcd. for $C_6H_7N_3S$: C, 47.05; H, 4.61; N, 27.44; S, 20.90. Found: C, 47.08; H, 4.60; N, 26.17; S, 21.96.

4-Mercapto-7-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine Hydrochloride (XXIIm).

The acetyl derivative XIXmm (2.1 g.) was hydrolyzed for 3 hours in 6 *N* hydrochloric acid (20 ml.). After evaporation and crystallization from 85% ethanol, 1.4 g., (79%) light yellow crystals, m.p. 291-292° dec., were obtained.

Anal. Calcd. for $C_7H_{10}ClN_3S$: C, 41.29; H, 4.95; N, 20.64; S, 15.71; Cl, 17.42. Found: C, 41.41; H, 5.01; N, 20.43; S, 15.56; Cl, 17.53.

6-Acetyl-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine (XXIIIm).

A stirred suspension of compound XIXhm (15 g.) and Raney nickel (30 g.) in water (200 ml.) was refluxed for 4 hours, then filtered and evaporated. The solid residue was crystallized from a small volume of ethanol to give 9.5 g. (76%) of colorless product, m.p. 142-143° dec.

Anal. Calcd. for $C_6H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.91; H, 5.60; N, 25.70.

1-Acetyl-3-pyrrolidone-4-thiocarboxamide (XIVhm).

A solution of 1-acetyl-4-cyano-3-pyrrolidone (Xhm) (15.2 g., 0.1 mole) and thioacetamide (15.3 g., 0.2 mole) in dimethylformamide saturated with hydrogen chloride (100 ml.) (14) was heated on a steam bath for 30 minutes. The solution was concentrated under reduced pressure to half the original volume and poured into cold water (100 ml.). After overnight refrigeration the product that precipitated was filtered and crystallized from ethanol to yield 12.3 g. (66%) of yellow crystals, m.p. 227-228° dec.; λ max (EtOH), 266 (ε, 10,000); 315 mμ (ε, 8,800).

Anal. Calcd. for $C_7H_{10}N_2O_2S$: C, 45.16; H, 5.41; N, 15.05; S, 17.19. Found: C, 45.10; H, 5.38; N, 14.87; S, 17.36.

Conversion of Compound XIVhm to XXIhm.

A solution of 1-acetyl-3-pyrrolidone-4-thiocarboxamide (XIVhm) (9.3 g., 0.05 mole) and ammonium formate (6.3 g., 0.1 mole) in ethanol (100 ml.) was refluxed for 6 hours. The dark solution was cooled overnight and the gray precipitate which separated was filtered out and crystallized twice from ethanol with the addition of charcoal for decolorization to yield 3.9 g. (42%) of 1-acetyl-3-amino-3-pyrroline-4-thiocarboxamide (XVIhm) as orange crystals, m.p. 244-245° dec.; λ max (EtOH), 278 (ε, 13,750); 334 mμ (ε, 17,150). Analytical values for nitrogen and sulfur appeared to indicate that this substance was impure.

Anal. Calcd. for $C_7H_{11}N_3OS$: C, 45.40; H, 5.99; N, 22.69; S, 17.28. Found: C, 45.23; H, 5.96; N, 20.75, 21.55; S, 18.48, 19.49.

A solution of this product (2 g.) in ethyl orthoformate (8 ml.) and acetic anhydride (8 ml.) was refluxed for 4 hours and the mixture was evaporated under reduced pressure. The black, oily residue was dissolved in pyridine (20 ml.) and hydrogen sulfide was bubbled into the solution. After one-half hour some solid precipitated. The solution was poured into water (100 ml.) and cooled. The precipitate (0.15 g.) melted at 300° and was found to be identical in infrared spectrum, melting point and mixed melting point to a sample of compound XXIhm obtained from compound Xhm as described above.

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(11) Taylor and Vroman (ref. 10) have discussed a possible mechanism for the analogous transformation to yield 6-mercaptopurine.

(12) Melting points are corrected. Microanalyses are by Drs. G. Weiler and F. B. Strauss, Oxford, England, and Galbraith Laboratories Inc., Knoxville, Tenn. Ultraviolet spectra were determined with a Cary recording spectrophotometer; infrared spectra were determined with a Perkin-Elmer Model 21 or Infracord spectrophotometers.

(13) In chloroform solution compound IIhm showed infrared bands at *ca.* 5.65 and 5.81 μ, as well as somewhat stronger absorptions at 5.97 μ and at 6.15 μ (broad). Broad absorption at *ca.* 3.00 μ was also evident. Presumably the bands at 5.65 and 5.81 μ correspond to the ketonic and ester carbonyls of the keto form, whereas the enol form is responsible for the absorptions at 3.00 μ (enolic hydroxyl), 5.97 μ (conjugated ester carbonyl) and 6.15 μ (combination of conjugated olefinic bond plus amide carbonyl). In a Nujol mull the bands at 5.65 and 5.81 μ disappear, strong bands remain at 5.91 μ and 6.21 μ (broad) and stronger enolic hydroxy absorption is seen at 2.89 and 3.15 μ (broad). Thus both tautomers seem to be present in chloroform solution with the enol probably predominating, but only the enol form is seen in the solid state as represented by the Nujol mull.

(14) This is the procedure of E. C. Taylor and J. A. Zoltewicz, *J. Am. Chem. Soc.*, 82, 2656 (1960), for the conversion of nitriles to thioamides.

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