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Aromaticity in Heterocyclic Systems. II. The Application of N.M.R. in a Study of the Synthesis and Structure of Certain Imidazo[1,2-c]Pyrimidines and Related Pyrrolo[2,3-d]Pyrimidines

By C. Wayne Noell and Roland K. Robins

Nuclear magnetic resonance spectra have been utilized in several instances to distinguish between ring closure to a derivative of imidazo[1,2-c]pyrimidine or pyrrolo[2,3-d]pyrimidine. N.m.r. studies have also been employed to select Vc as the most probable structure for 5-methylthio-2,7-imidazo[1,2-c]pyrimidinedione. Ultraviolet absorption spectra and n.m.r. studies in deuterium oxide support the conclusion that there is more aromaticity in the anion V g than in the neutral molecule. The present work describes several new synthetic routes to derivatives of imidazo[1,2-c]pyrimidine and pyrrolo[2,3-d]pyrimidine.

In connection with a general program designed to study aromaticity in nitrogen heterocyclic compounds, the syntheses of certain derivatives of imidazo[1,2-c]-pyrimidine (I) and pyrrolo[2,3-d]pyrimidine (II) were undertaken in our Laboratory.

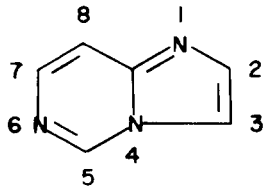
4-Amino-2-methylthio-6-pyrimidone (III) when treated with chloroacetylchloride in dimethylformamide gave 4-chloroacetylamino-2-methylthio-6-pyrimidone (IV). Treatment of IV with boiling dilute aqueous ammonia gave a product $C_7H_7N_3O_2S$, m.p. 295-298° C. It seemed probable that ring closure had occurred to yield either 2,7-dihydroxy-5-methylthioimidazo[1,2-c]pyrimidine (V) or 4,6-dihydroxy-2-methylthiopyrrolo[2,3-d]pyrimidine (VI). When this product was treated with phosphorus oxychloride, the corresponding dichloro derivative was obtained which was either 2,7-dichloro-5-methylthioimidazo[1,2-c]pyrimidine (VII) or 4,6-dichloro-2-methylthiopyrrolo[2,3-d]pyrimidine (XII).

The n.m.r. spectrum of this product in carbon tetrachloride showed a sharp singlet at 2.80 δ (3 protons) and two sharp singlets at 7.7 and 7.8 δ, respectively, which integrated for 1 proton each. No "N-H" absorption typical of the pyrrole ring was observed. Such a spectrum is consistent only with the structure of 2,7-dichloro-5-methylthioimidazo[1,2-c]-pyrimidine (VII). Therefore, cyclization of 4-chloroacetylamino-2-methylthio-6-pyrimidone (IV) had proceeded to give the bridgehead nitrogen derivative V.

Treatment of 4-chloroacetylamino-2-methylthio-6-pyrimidone (IV) with aluminum chloride at 180° was investigated as a possibility of obtaining the isomeric pyrrolo[2,3-d]pyrimidine (VI). Instead, a compound $C_6H_5N_3O_3$ was isolated, which indicated loss of the methylthio group. This compound (VIII) was treated with refluxing phosphorus oxychloride to give an excellent yield of 2,5,7-trichloroimidazo[1,2-c]pyrimidine (IX). The structural assignment for IX was readily made since in carbon tetrachloride two sharp singlets were observed (aromatic protons) at 7.4 and 7.6 δ, respectively. No "N-H" absorption typical of the pyrrole ring was detected. Thus, again ring closure must have occurred through the bridgehead nitrogen to yield the uric acid analog VIII.

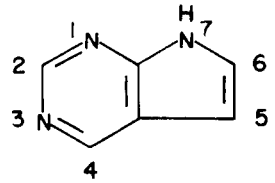
The possibility that 4-amino-2-methylthio-6-pyrimidone (III) had reacted with chloroacetylchloride in some anomalous fashion was considered since Pfleiderer and Strauss (2) had noted that 4-amino-1,3-dimethyluracil upon treatment with acetic anhydride gave 5-acetyl-4-amino-1,3-dimethyluracil. However, the n.m.r. spectrum of 4-chloroacetylamino-2-methylthio-6-pyrimidone (IV) in trifluoroacetic acid revealed the presence of a sharp singlet at 7.2 δ which could only be assigned to the proton at position 5. In deuterated dimethyl sulfoxide IV showed a singlet at 2.6 δ (SCH_3), a singlet at 4.25 δ ($-CH_2-$), a sharp singlet (1H) at 6.5 δ (H_5), a broad singlet at 8.6 δ (-NH-), and another broad singlet (1H) at 10.0 δ (-NH-). Furthermore, treatment of IV with phosphoryl chloride gave 6-chloro-4-chloroacetylamino-2-methylthiopyrimidine (X). When X was dissolved in carbon tetrachloride, the n.m.r. spectrum revealed sharp singlets at 2.5 δ (SCH_3), 4.2 δ ($-CH_2-$), and 7.8 δ (1H) which was assigned to the proton at position 5. In this instance absorption typical of an amide proton (1H) was found at 8.6 δ. Final proof of the structure of IV was obtained when aqueous ammonia converted 6-chloro-4-chloroacetylamino-2-methylthiopyrimidine (X) to 4-amino-6-chloro-2-methylthiopyrimidine (XI). This compound (XI) was identical to that obtained by treatment of 4-amino-2-methylthio-6-pyrimidone with phosphorus oxychloride (3). It is of interest that 4-chloroacetylamino-2-methylthio-6-pyrimidone (IV) ring closes to V with ammonia while the same treatment of 6-chloro-4-chloroacetylamino-2-methylthiopyrimidine (X) simply results in hydrolysis of the chloroacetyl function. A possible explanation can be found in a consideration of the mechanism of ring closure. In the presence of aqueous ammonia it is probable that IV exists in the anion form IVa which can also exist as the resonance form IVb. Nucleophilic attack of the anion at nitrogen 3 on the methylene carbon would result in ring closure to 5-methylthio-2,7-imidazo-[1,2-c]pyrimidinedione (V). In the molecule 6-chloro-4-chloroacetylamino-2-methylthiopyrimidine (X) no such anion can be formed. Indeed the presence of the chlorine atom at the 6-position effectively lowers the electron density so that hydrolysis is the preferred reaction.

In order to further verify the n.m.r. structural assignments of 2,7-dichloro-5-methylthioimidazo[1,2-



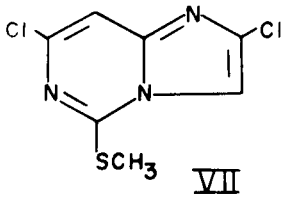
Imidazo[1,2-c]pyrimidine

I



pyrrolo[2,3-d]pyrimidine

II



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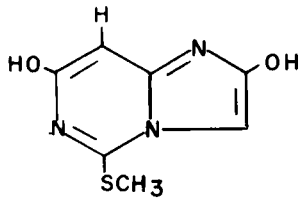
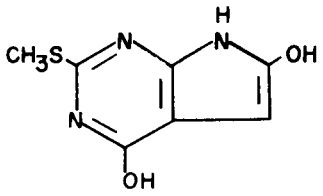


V



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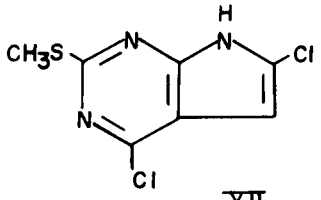
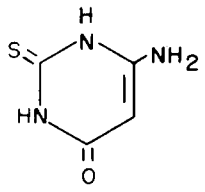
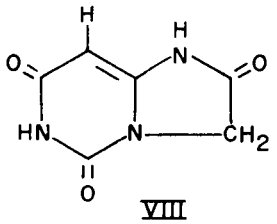


XII





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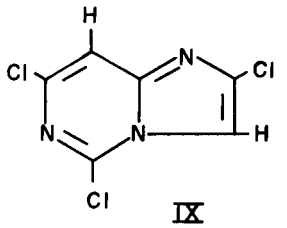

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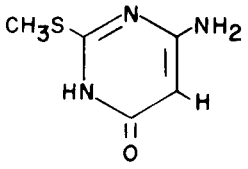

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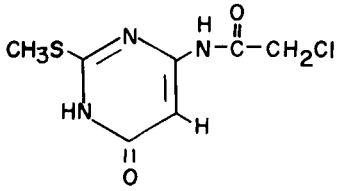

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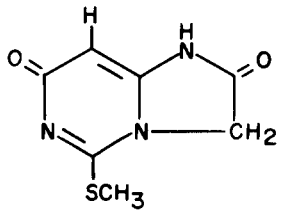

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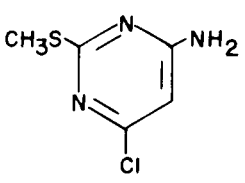

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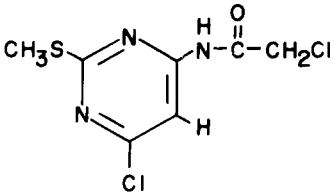

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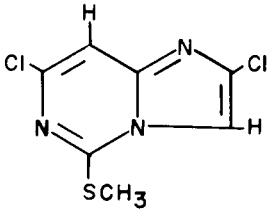

VII

V

VI

XII

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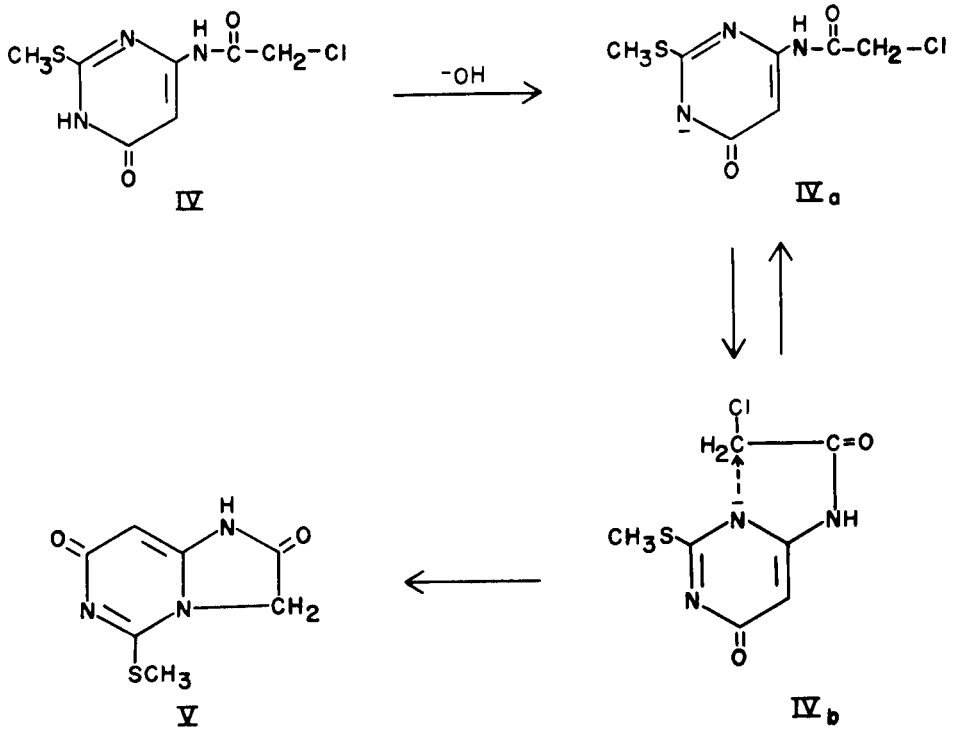
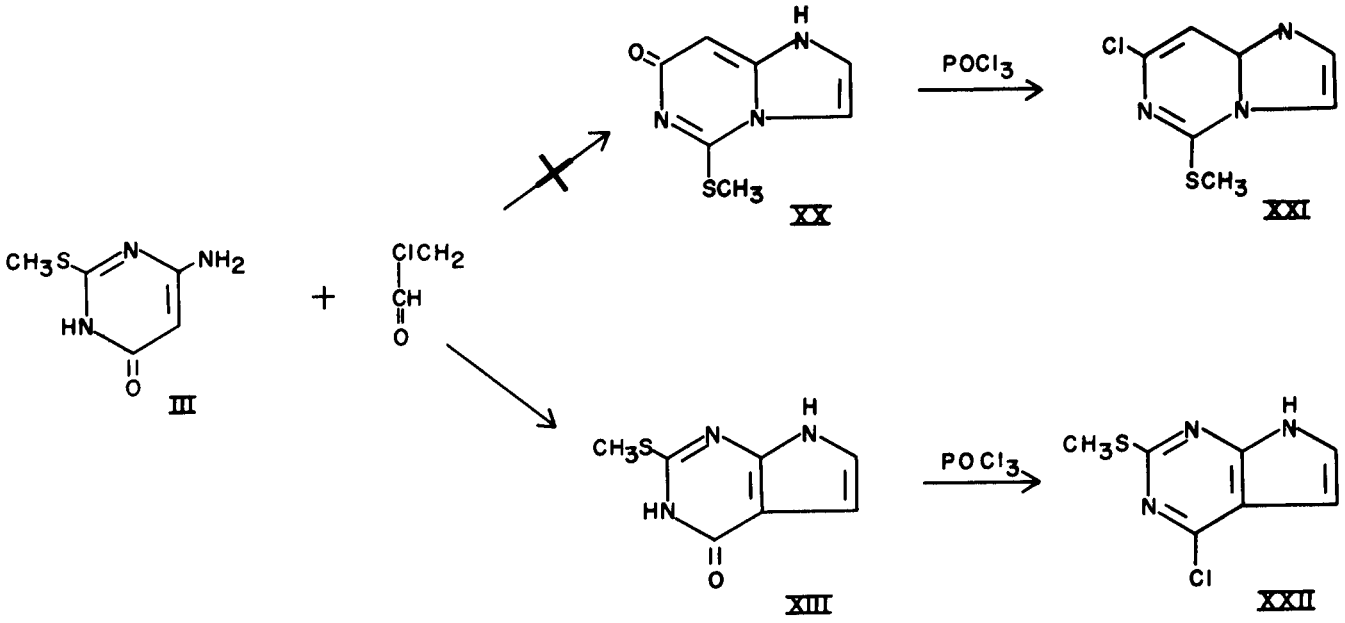
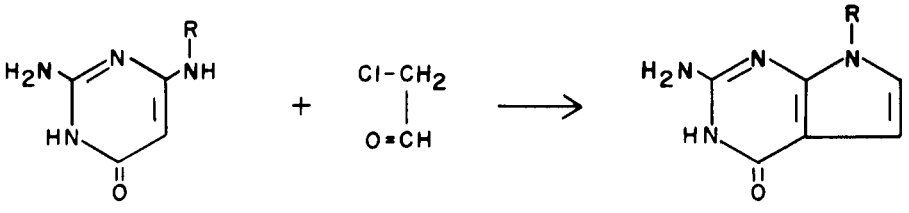
X

VII

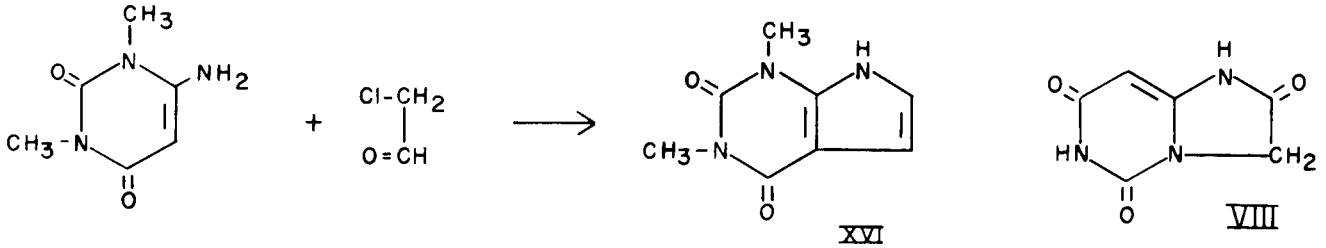




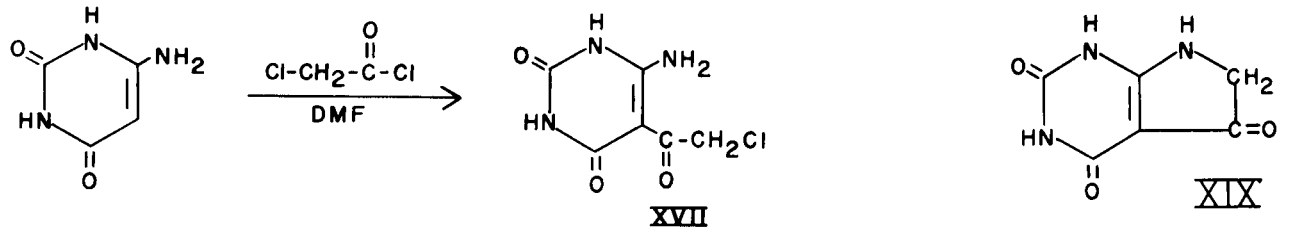


XIV, R = n-C_3H_7

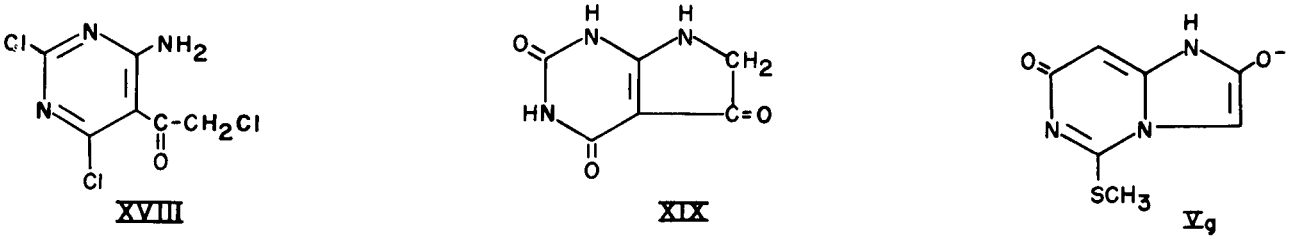
XV, R = $CH_2C_6H_5$



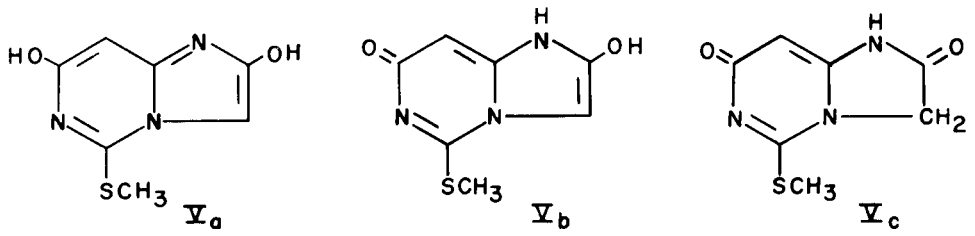
XVI VIII



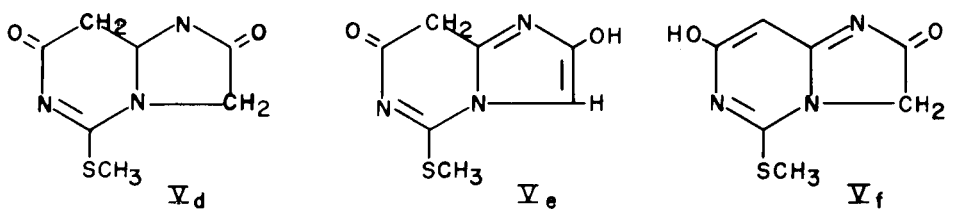
XVII XIX



XVIII XIX Vg



Va Vb Vc



Vd Ve Vf

Table I

Ultraviolet Absorption Spectra of Various Imidazo-[1,2-c]pyrimidines, Pyrrolo[2,3-d]pyrimidines and Related Compounds

No.	Name of Compound	EtOH λ_{max}, mμ	EtOH ε	pH 1 λ_{max}, mμ	pH 1 ε	pH 11 λ_{max}, mμ	pH 11 ε
V c	5-Methylthio-2,7-imidazo-[1,2-c]pyrimidinedione			234 276	17,400 12,200	232 289	35,800 16,600
VII	2,7-Dichloro-5-methylthiomidazo[1,2-c]pyrimidine	242 283 312	21,100 7,500 6,100				
VIII	2,5,7-Imidazo[1,2-c]-pyrimidinetrione			267	22,500	284	23,500
IX	2,5,7-Trichloroimidazo-[1,2-c]pyrimidine	230 280 304(s)	19,000 7,300 5,100				
X	6-Chloro-4-chloroacetylamino-2-methylthiopyrimidine	242 293	24,700 4,800				
XIII	2-Methylthio-4-pyrrolo-[2,3-d]pyrimidone			273	13,800	229 275	20,000 14,100
XIV	2-Amino-7-(*n*-propyl)-4-pyrrolo[2,3-d]pyrimidone			227 265	17,300 10,600	247 266	7,900 10,500
XV	2-Amino-7-benzyl-4-pyrrolo[2,3-d]pyrimidone			224 263	19,000 11,000	266	11,500
XVI	1,3-Dimethyl-2,4-pyrrolo-[2,3-d]pyrimidinedione			243 275	6,100 6,600	230 277	12,400 6,800
XVII	4-Amino-5-chloroacetyl-2,6-pyrimidinedione			260	14,400	228 279	12,600 20,000
XVIII	4-Amino-5-chloroacetyl-2,6-dichloropyrimidine	224 249 318	17,300 6,700 5,800				
XIX	2,4,5-Pyrrolo[2,3-d]-pyrimidinetrione			258	10,400	278	10,200
XXII	4-Chloro-2-methylthio-pyrrolo[2,3-d]pyrimidine	222 249 272(s) 310	10,100 28,900 6,600 7,200				

c]pyrimidine (VII) and 2,5,7-trichloroimidazo[1,2-c]-pyrimidine (IX), it seemed worthwhile to prepare several derivatives of the pyrrolo[2,3-d]pyrimidine ring system of known structure which would be soluble in carbon tetrachloride or deuterochloroform for a study of the n.m.r. spectra. In this regard 4-chloro-2-methylthiopyrrolo[2,3-d]pyrimidine was selected. Although the preparation of the requisite 2-methylthio-4-pyrrolo[2,3-d]pyrimidone (XIII) has previously been described in the literature (4), the route is somewhat lengthy. A more convenient synthesis, however, was suggested by a patent (5) which describes the reaction of chloroacetaldehyde and 4-aminouracil to give 2,4-pyrrolo[2,3-d]pyrimidinedione directly. This procedure was extended to the synthesis of 2-methylthio-4-pyrrolo[2,3-d]pyrimidone (XIII) from 4-amino-2-methylthio-6-pyrimidone (III) in excellent yield.

Once again it is conceivable that ring closure could take place to give either a derivative of imidazo[1,2-c]-pyrimidine or pyrrolo[2,3-d]pyrimidine. The product 5-methylthio-7-imidazo[1,2-c]pyrimidone (XX) was eliminated when 2-methylthio-4-pyrrolo[2,3-d]pyrimidone (XIII) was prepared by the method of Davoll (4) and shown to be identical to XIII by rigorous comparison of this authentic sample. Furthermore, inspection of the n.m.r. spectrum of 2-methylthio-4-pyrrolo-[2,3-d]pyrimidone (XIII) in deuterated dimethyl sulfoxide revealed the 5 and 6 aromatic protons at 6.4 δ and 6.9 δ (characteristically split), a sharp singlet at 2.6 δ (SCH_3), and the presence of two -NH- groups appearing as broad bands at 11.7 δ and 12.1 δ. This was further evidence supporting structure XIII, since structure XX would show only one NH proton. Treatment of 2-methylthio-4-pyrrolo[2,3-d]pyrimidone (XIII) with phosphorus oxychloride and N,N-diethylaniline readily gave 4-chloro-2-methylthiopyrrolo[2,3-d]pyrimidine (XXII). This compound in deuterated dimethyl sulfoxide exhibited a singlet at 2.6 δ (SCH_3), characteristic AB splitting (two doublets, J=2) at 7.6 and 6.5 δ due to the aromatic protons at positions 5 and 6, and a broad singlet (NH) at 12.35 δ. Such a spectrum eliminates the structure 7-chloro-5-methylthioimidazo[1,2-c]-pyrimidine (XXI) which would show another aromatic proton instead of the typical -NH- absorption. Thus, ring closure of III had indeed proceeded to yield the pyrrolo[2,3-d]pyrimidine ring. This type of ring closure was extended to the synthesis of 2-amino-7-(*n*-propyl)-4-pyrrolo[2,3-d]pyrimidone (XIV) and 2-amino-7-benzyl-4-pyrrolo[2,3-d]pyrimidone (XV) by treatment of the corresponding 2-amino-4-substitutedamino-6-pyrimidone with chloroacetaldehyde.

The most distinctive feature of these pyrrolo[2,3-d]-pyrimidine derivatives noted in the n.m.r. was the characteristic splitting pattern (AB type) of the 5 and 6 aromatic protons which for XIV appeared as two doublets (J=4) at 6.3 and 6.7 δ. The NH_2 absorption appeared at 6.1 δ (2H), and a broad NH proton was observed at 10.3 δ. Treatment of 4-amino-1,3-dimethyluracil and chloroacetaldehyde gave the theophylline analog 1,3-dimethyl-2,4-pyrrolo[2,3-d]pyrimidinedione (XVI). The fact that nitrogen atoms 1 and 3 are substituted precludes ring closure through a pyrimidine nitrogen atom. In dimethyl sulfoxide the appearance of two aromatic protons at 6.1 and 6.8 δ and the presence of -NH- at 11.7 δ is strong support for the structure XVI. It is interesting to note that the aromatic proton at 6.8 δ appears as a triplet (J=2) (proton at position 5), and the aromatic proton at 6.1 δ is split to a quartet (J=2) (proton at position 6) by the NH proton at position 7. The reaction of the aldehyde function at the 5 position of the appropriate pyrimidine would appear to be a most probable course of this ring closure reaction. Such similar condensations to give pyrido[2,3-d]pyrimidines have been previously reported (6). Indeed, synthesis of the appropriate pyrrolo[2,3-d]pyrimidine failed with chloroacetaldehyde and various pyrimidines such as 4,6-diaminopyrimidine, 6-amino-4-pyrimidone, and 4-amino-6-chlorpyrimidine which exhibit lower electron density at position 5.

When 4-aminouracil was treated with chloroacetylchloride in dimethylformamide, acylation at position 5 occurred preferentially to yield 4-amino-5-chloroacetyluracil (XVII). The structure of XVII was confirmed by the absence of the aromatic proton at C_5 (n.m.r.). Further confirmation of the structure assigned XVII was obtained by conversion of this derivative to 4-amino-5-chloroacetyl-2,6-dichloropyrimidine (XVIII) with phosphorus oxychloride. Examination of XVIII in the n.m.r. in dimethyl sulfoxide revealed a sharp singlet at 4.85 δ ($-CH_2-$) and a broader singlet at 8.15 δ ($-NH_2$, 2 protons). No absorption for C_5 proton was observed. Treatment of XVII with boiling aqueous ammonia resulted in cyclization to give 2,4,5-pyrrolo[2,3-d]pyrimidinetrione (XIX). In contrast to 2,5,7-imidazo[1,2-c]pyrimidinetrione (VIII), the compound XIX could not be converted to the aromatic 2,-4,5-trichloropyrrolo[2,3-d]pyrimidine with phosphorus oxychloride.

A number of the heterocyclic compounds described in this work present interesting structural problems. For instance, the compound V earlier referred to as 5-methylthio-2,7-imidazo[1,2-c]pyrimidinedione could conceivably possess any of the structures Va-Vf without considering possible polar structures.

Similar possibilities may also be written for the structure of 2,5,7-imidazo[1,2-c]pyrimidinetrione (VIII) or 2,4,5-pyrrolo[2,3-d]pyrimidinetrione (XIX). Examination of the n.m.r. spectrum of V in deuterated dimethyl sulfoxide at 100° showed absorption at 2.55 δ (SCH_3) (sharp singlet, 3 protons), a sharp singlet at 4.3 δ ($-CH_2-$, 2 protons), a sharp singlet at 5.1 δ (single aromatic proton), and a broad band (NH) at 7.2 δ (one proton). When the spectrum was run in trifluoroacetic acid, there was observed a singlet at 2.85 δ (SCH_3), a singlet at 4.7 δ (CH_2), and a singlet at 6.5 δ (one proton). These data readily eliminate structures Va and Vb from consideration since these structures require the presence of two different aromatic type protons. Likewise, structure Vd is eliminated, which predicts two different methylene groups. Of the remaining structures Vc, Ve, and Vf which predict one methylene group and one aromatic proton, only structure Vc is consistent with the -NH- proton observed at 7.2 δ in the amide region.

Similar examination of the n.m.r. spectrum of 2,-5,7-imidazo[1,2-c]pyrimidinetrione (VIII) in deuterated dimethyl sulfoxide revealed a sharp singlet (methylene, 2H) at 4.25 δ, a sharp singlet (1H) at 4.95 δ, a broad

peak (one proton, -NH- amide) at 7.4 δ, and another broad peak (-NH- cyclic aromatic amide, one proton) at 10.5 δ. Such data are consistent only with structure VIII. Examination of 2,4,5-pyrrolo[2,3-d]pyrimidinetrione (XIX) in deuterated dimethyl sulfoxide at 120° revealed only one sharp singlet at 4.5 δ. 2,4,5-Pyrrolo[2,3-d]pyrimidinetrione (XIX) (deuterated dimethyl sulfoxide) at 60° showed a methylene group at 4.7 δ (2H) as a sharp singlet, a weak broad band (-NH-) (1H) at 6.1 δ, and another broad band (two -NH- groups, 2 protons) at 7.6 δ. This is strong support for structure XIX. When the solution (deuterated dimethyl sulfoxide) was quickly cooled to room temperature and the n.m.r. spectrum run before any appreciable solid appeared, the previous sharp singlet at 4.7 δ (2H) split into a doublet at 4.45 δ and 4.55 δ. Such splitting of the methylene protons is due to the -NH- proton at position 7 at this temperature and provides additional evidence for structure XIX.

Additional information of interest may be obtained from ultraviolet absorption data (Table I). When 5-methylthio-2,7-imidazo[1,2-c]pyrimidinedione (Vc) was examined, it was found to possess λ max (*p*H 1) 276 mμ, ε 12,200 and λ max (*p*H 11) 289 mμ, ε 16,600. Such a combined hyperchromic and bathochromic shift strongly suggests additional resonance in the anion. Structure Vg is thus proposed for this anion.

When the compound Vc was dissolved in deuterium oxide in the presence of sodium peroxide and the n.m.r. spectrum examined. Instead of the methylene singlet observed (deuterated dimethyl sulfoxide) at 4.38 δ and the previously observed sharp singlet (1H) at 5.1 δ, there appeared two singlets of equal intensity (1H each) at 5.35 δ and 5.55 δ. One of the methylene protons at position 3 had been removed by base, and the remaining proton had shifted further down field. Such data are strong support for structure Vg and suggest more aromaticity in the anion than the neutral molecule. The formation of the anion Vg in base gives the molecule considerable stability in the imidazole ring and prevents hydrolysis which would otherwise be predicted from the amide structure Vc.

The ultraviolet absorption spectra of other compounds discussed in the present work may be found in Table I.

It is abundantly clear from the present work that nuclear magnetic resonance spectra can be of considerable assistance in the chemistry of nitrogen heterocyclic compounds, not only in following various ring closure reactions but also in the study of the actual structure which a heterocyclic compound may possess. It is quite apparent from this and a similar previous study (7) that often the simplest most aromatic type structure which can be drawn for a condensed heterocyclic system is not necessarily the preferred structure of the molecule.

EXPERIMENTAL (8)

4-Amino-5-chloroacetyl-2,6-pyrimidinedione (XVII).

To 25 g. of 4-aminouracil in 200 ml. of dimethylformamide (dried over silica gel) was added, with vigorous stirring, in one portion 22.25 g. of chloroacetylchloride. The reaction was exothermic, and the temperature rose to approximately 60°. Stirring was continued for approximately 20 min., and the mixture was then poured into 500 ml. of acetone and stirred for 20 min. The precipitate was filtered, washed with acetone, and dried at 70° for 2 hr. to give 40 g. of the desired product. After two recrystallizations from dimethylformamide, a purified sample, m.p. >300°, was obtained.

Anal. Calcd. for $C_6H_6ClN_3O_3$: C, 35.4; H, 3.0; N, 20.7. Found: C, 35.2; H, 2.5; N, 20.8.

2,4,5-Pyrrolo[2,3-d]pyrimidinetrione (XIX).

4-Amino-5-chloroacetyl-2,6-pyrimidinedione (10 g.) was dissolved in 300 ml. of water to which 10 ml. of 28% aqueous ammonia had been added. This mixture was boiled for 5 min.; decolorizing carbon was added, and the solution was filtered. The hot filtrate was adjusted to *p*H 6 with glacial acetic acid and allowed to stand about 30 min. with occasional stirring. The precipitate was then filtered, washed with acetone, and dried at 100° to give 4.7 g. of product which was recrystallized from aqueous acetic acid for analysis.

Anal. Calcd. for $C_6H_6N_3O_3$: C, 42.8; H, 3.6; N, 25.0. Found: C, 43.1; H, 3.7; N, 25.0.

4-Chloroacetylamino-2-methylthio-6-pyrimidone (IV).

To 50 g. of 4-amino-2-methylthio-6-pyrimidone (III) (3) in 200 ml. of dimethylformamide (dried over silica gel) was added in one portion 38.75 g. of chloroacetylchloride. The reaction was exothermic, and the temperature rose to about 55-60°. This mixture was stirred for 30 min.; after a precipitate appeared, 600 ml. of acetone was added. The resulting mixture was stirred for an additional 30 min., and the product was filtered and washed with acetone and then with ether to yield 46 g. of crude product, m.p. 208-214°. Recrystallization of a small sample from water yielded an analytical sample, m.p. 220-222°.

Anal. Calcd. for $C_7H_8ClN_3O_2S$: C, 35.6; H, 3.4; N, 17.8. Found: C, 36.1; H, 3.4; N, 18.1.

2,5,7-Imidazo[1,2-c]pyrimidinetrione (VIII).

4-Chloroacetylamino-2-methylthio-6-pyrimidone (20 g.) and 22.6 g. of anhydrous aluminum chloride were fused in an oil bath at 180° for 5 min. The mass was then allowed to cool; 900 ml. of water was carefully added followed by 50 ml. of glacial acetic acid. The resulting mixture was allowed to stand a few hours and was finally boiled on a hot plate for 20 min. Decolorizing carbon was then added, and the mixture was filtered and the filtrate allowed to cool. The precipitate that formed was filtered, washed with water followed by acetone, and dried at 100° *in vacuo* to give 8.7 g. of crude product. Recrystallization from aqueous acetic acid gave 4.8 g. of chromatographically pure product.

Anal. Calcd. for $C_6H_5N_3O_3$: C, 43.2; H, 3.0; N, 25.2. Found: C, 42.9; H, 3.3; N, 25.2.

2,5,7-Trichloroimidazo[1,2-c]pyrimidine (IX).

2,5,7-Imidazo[1,2-c]pyrimidinetrione (VIII, 30 g.) was added to 600 ml. of phosphorus oxychloride. The solution was refluxed for 4 hr., and the excess phosphorus oxychloride was then removed by vacuum distillation with a steam bath as the source of heat. The residue was poured with stirring onto a mixture of chopped ice and water. This mixture was then extracted 4 times with 500-ml. portions of ether, and the combined ethereal extracts were washed with water and dried over anhydrous sodium sulfate. The ether was removed by distillation, and the crude product was recrystallized from cyclohexane to yield 16 g. of product, m.p. 127°.

Anal. Calcd. for $C_6H_2Cl_3N_3$: C, 32.4; H, 0.9; N, 18.9. Found: C, 32.4; H, 1.3; N, 18.5.

1,3-Dimethyl-2,4-pyrrolo[2,3-d]pyrimidinedione (XVI).

Chloroacetaldehyde dimethyl acetal (13 g.) was placed in 30 ml. of water, and 2 ml. of concentrated hydrochloric acid was added. The resulting mixture was stirred at near boiling until a homogeneous solution was obtained (approx. 10 min.) and sodium acetate (8 g.) was then added (*p*H 6). This mixture was added to a stirred solution (temp. 90°) consisting of 10 g. of 4-amino-1,3-dimethyluracil (9) and 4 g. of sodium acetate in 50 ml. of water. At first all solid material dissolved; then after 5 min. a precipitate formed which was filtered and washed with water and then acetone. The crude product was dried at 100° to give 5.5 g. of the desired product, m.p. turns brown at ~280° and then melts at 292-294°. Recrystallization from water gave a pure product, m.p. 296° dec.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.6; H, 5.0; N, 23.5. Found: C, 53.8; H, 5.2; N, 23.2.

2-Amino-7-(*n*-propyl)-4-pyrrolo[2,3-d]pyrimidone (XIV).

Chloroacetaldehyde dimethyl acetal (11.2 g.) was placed in 50 ml. of water, and 2 ml. of concentrated hydrochloric acid was added. The resulting mixture was heated with stirring at near boiling for 15 min. to obtain a homogeneous mixture, and sodium acetate (10 g.) was then added. This solution was added (in one portion) to a mixture of 10 g. of 2-amino-4-(*n*-propyl)amino-6-pyrimidone (10) and 5 g. of sodium acetate in 100 ml. of hot water. The resulting mixture was allowed to stir on the steam bath for 20 min., and the precipitate was filtered and washed with water followed by acetone to yield 6.1 g. of product, m.p. 290-300° dec. The product was purified by precipitation from hot dilute hydrochloric acid with aqueous ammonia.

Anal. Calcd. for $C_9H_{12}N_4O$: C, 56.2; H, 6.3; N, 29.2. Found: C, 55.8; H, 6.2; N, 29.4.

2-Amino-7-benzyl-4-pyrrolo[2,3-d]pyrimidone (XV).

Chloroacetaldehyde dimethyl acetal (6.5 g.) was added to 50 ml. of water and 2 ml. of concentrated hydrochloric acid. The mixture was heated at near boiling for 15 min., and then 10 g. of sodium acetate was added. The resulting solution was added in one portion to a mixture of 10 g. of 2-amino-4-benzylamino-6-pyrimidone (10) and 5 g. of sodium acetate in 100 ml. of hot water. The mixture was allowed to stir on a steam bath for 20 min., and the precipitate was filtered and washed with water and then acetone, and dried at 100° to yield 5.1 g. of product. This product was purified in a manner similar to that employed for the purification of XIV.

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 65.0; H, 5.0; N, 23.3. Found: C, 65.4; H, 5.1; N, 23.5.

2-Methylthio-4-pyrrolo[2,3-d]pyrimidone (XIII) (4).

To 10 g. of 4-amino-2-methylthio-6-pyrimidone (3) and 10.5 g. of sodium

acetate in 150 ml. of hot water (80°) was added 13 g. of 40% chloroacetaldehyde (in water). The resulting mixture was stirred at 80° for 20 min. and then cooled to room temperature. The precipitate was filtered and washed with water followed by acetone to yield 6.3 g. of crude material which was recrystallized from water to give a product, m.p. 269-270°. The ultraviolet absorption and infrared spectra were identical to those exhibited by an authentic sample prepared by the method of Davoll (4).

Anal. Calcd. for $C_7H_7N_3OS$: C, 46.4; H, 3.9; N, 23.2. Found: C, 46.2; H, 3.5; N, 23.0.

4-Amino-5-chloroacetyl-2,6-dichloropyrimidine (XVIII).

4-Amino-5-chloroacetyl-2,6-pyrimidinedione (XVII, 20 g.) was added to 500 ml. of phosphorus oxychloride and 100 ml. of N,N-diethylaniline. The resulting solution was refluxed for 2 hr., and the excess phosphorus oxychloride was removed *in vacuo* with a steam bath as the source of heat. The residue was poured on chopped ice, and the mixture was allowed to stand a few minutes and then was extracted 4 times with 150-ml. portions of ether. After washing the combined ether extracts with a small amount of ice water, the ethereal solution was dried over anhydrous sodium sulfate. The ether was removed by distillation, and the residue was recrystallized from benzene to give 5 g. of product, m.p. 170°.

Anal. Calcd. for $C_6H_4Cl_3N_3O$: C, 29.8; H, 1.7; N, 17.5. Found: C, 29.8; H, 2.1; N, 17.4.

5-Methylthio-2,7-imidazo[1,2-c]pyrimidinedione (V).

4-Chloroacetyl-2-methylthio-6-pyrimidone (IV, 46 g.) was placed in 1000 ml. of hot (95°) water, and to afford complete solution (*p*H 14) the solid material was dissolved by addition of 28% aqueous ammonia. The solution was boiled with decolorizing carbon and filtered, and the filtrate was acidified to *p*H 5 with glacial acetic acid. The precipitate was filtered, washed with water followed by acetone, and dried at 100° to give 19 g. of product. A reprecipitation from boiling, dilute, aqueous ammonia with glacial acetic acid gave a pure product, m.p. 295-298° dec.

Anal. Calcd. for $C_7H_7N_3O_2S$: C, 42.6; H, 3.6; N, 21.3. Found: C, 42.3; H, 3.5; N, 21.1.

2,7-Dichloro-5-methylthioimidazo[1,2-c]pyrimidine (VII).

5-Methylthio-2,7-imidazo[1,2-c]pyrimidinedione (V, 30 g.) was added to 500 ml. of phosphorus oxychloride, and the resulting mixture was refluxed for 1.5 hr. The excess phosphorus oxychloride was removed *in vacuo* on a steam bath, and the residue was poured over chopped ice with stirring. The precipitate that formed was filtered, washed with ice water, and then dissolved in 900 ml. of ether. The ethereal solution was washed with water and then dried over anhydrous sodium sulfate. Removal of the ether by distillation gave slightly yellow needles which were triturated in 200 ml. of petroleum ether (30-60°). The petroleum ether was filtered to yield 30 g. of product, m.p. 147°. Recrystallization from cyclohexane did not alter the melting point.

Anal. Calcd. for $C_7H_5Cl_2N_3S$: C, 35.9; H, 2.1; N, 18.0. Found: C, 35.9; H, 2.3; N, 17.7.

6-Chloro-4-chloroacetylamino-2-methylthiopyrimidine (X).

4-Chloroacetylamino-2-methylthio-6-pyrimidone (IV, 5 g.) was added to 200 ml. of phosphorus oxychloride, and the resulting solution was refluxed for 3 hr. The excess phosphorus oxychloride was removed, and the residue was poured with stirring over chopped ice. The aqueous mixture was extracted with ether (three 200-ml. portions), and the combined ethereal extracts were washed with water and dried over anhydrous sodium sulfate. After the ether had been removed by distillation, the crude compound was crystallized from cyclohexane. This compound (2 g.) was recrystallized from cyclohexane to give a product, m.p. 100°.

Anal. Calcd. for $C_7H_7Cl_2N_3OS$: C, 33.4; H, 2.8; N, 16.7. Found: C, 33.7; H, 3.1; N, 16.9.

4-Chloro-2-methylthiopyrrolo[2,3-d]pyrimidine (XXII).

2-Methylthio-4-pyrrolo[2,3-d]pyrimidone (10 g.) was added to 500 ml. of phosphorus oxychloride and 20 ml. of N,N-diethylaniline. The resulting solution was refluxed for 4 hr.; the excess phosphorus oxychloride was removed *in vacuo* on a steam bath, and the residue was poured with stirring onto chopped ice. The cold aqueous mixture was extracted with ether (four 400-ml. portions), and the combined extracts were washed with water and then dried over anhydrous sodium sulfate. The ether was removed by distillation to leave 6 g. of crude product which was recrystallized from cyclohexane-acetone to give 5.0 g. of compound, m.p. 210°.

Anal. Calcd. for $C_7H_6ClN_3S$: C, 42.2; H, 3.0; N, 21.1. Found: C, 41.9; H, 2.7; N, 21.5.

Acknowledgment.

The authors wish to acknowledge the many helpful suggestions and assistance of Leroy B. Townsend relative to this work.

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Received October 24, 1963 Tempe, Arizona