Aust. J. Chem., 1975, **28**, 2435–46

The Hydrazinolysis of Heterocyclic Compounds. II* 6-Amino-4-hydroxy-1-methylpyrimidine-2(1*H*)-thione and Related Compounds

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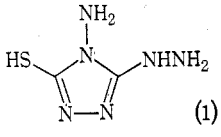
Abstract

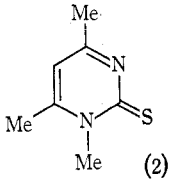
The reaction of 6-amino-4-hydroxy-1-methylpyrimidine-2(1*H*)-thione (3) with hydrazine is shown to follow at least three pathways to give 4-amino-5-hydrazino-1,2,4-triazole-3-thiol (1), 5-hydrazinopyrazol-3-ol (5; R = NH_2), (4-amino-5-mercapto-1,2,4-triazol-3-yl)acetohydrazide (4) and triaminoguanidine (6). Similarly, 4,6-dihydroxy-1-methylpyrimidine-2(1*H*)-thione (18) yields (1) and malonyl dihydrazide (19), and (4). By contrast 4,6-diamino-1-methylpyrimidine-2(1*H*)-thione (21) does not follow any of these pathways. Formation of (4) represents a new type of ring transformation of pyrimidines. Mechanisms of the reactions are discussed.

Introduction

Hydrazine has been shown[1] to produce (*inter alia*) 4-amino-5-hydrazino-1,2,4-triazole-3-thiol (1) from open-chain and heterocyclic compounds containing a thioureido group. Part I[2] of this series examined the reaction of 1,4,6-trimethylpyrimidine-2(1*H*)-thione (2) and related compounds as substrates with a view to elucidating the competing reactions and substituent effects on this general transformation. It was concluded that nucleophilic attack at the 4- and 6-positions promoted the pathway to the triazole (1), whilst that at the 2-position led to the major competing reaction which involved displacement of sulphur.



(1)



(2)

We report in this paper our investigation of the hydrazinolysis of 1-methylpyrimidine-2(1*H*)-thione derivatives having hydroxy† or amino groups in the 4- and 6-positions. The electronic effect of these substituents is similar to that of

* Part I, *Aust. J. Chem.*, 1975, **28**, 859.

† Although hydroxy and mercapto groups are well known to adopt the tautomerically favourable oxo and thioxo forms respectively (Katritzky, A. R., and Lagowski, J. M., *Advan. Heterocycl. Chem.*, 1963, **1**, 339) for simplicity of nomenclature (and structure) the former system is used, whatever the evidence for the predominant tautomer.

[1] Dickinson, R. G., and Jacobsen, N. W., *Anal. Chem.*, 1969, **41**, 1324.
[2] Dickinson, R. G., Jacobsen, N. W., and Gillis, R. G., *Aust. J. Chem.*, 1975, **28**, 859.

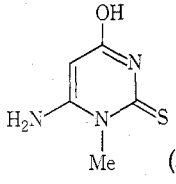
methyl groups at the same positions.[2] Such electron-releasing groups discourage the attack of nucleophiles at the electron-deficient 4- and 6-centres. Furthermore, amino groups, and more unexpectedly hydroxy groups, unlike alkyl groups, have been found to undergo nucleophilic substitution by hydrazine, thereby reducing the production of the triazole (1).

The Pyrimidines and Their Hydrazinolysis

6-Amino-4-hydroxy-1-methylpyrimidine-2(1H)-thione

6-Amino-4-hydroxy-1-methylpyrimidine-2(1*H*)-thione (3) was prepared from *N*-methylthiourea and ethyl cyanoacetate.[3] Predominance of the oxo–thioxo tautomer in the solid state was indicated by absence of a weak mercapto stretching vibration at 2550–2600 cm^{-1} and the presence of an amide carbonyl absorption at 1671 cm^{-1} in the infrared spectrum. The lability of the C 5 proton was reflected by its exchange with solvent protons in acidic and alkaline media in the p.m.r. spectrum.

The pyrimidine, when allowed to react with excess hydrazine hydrate at 100°, gave a complex reaction mixture [δ (CF_3COOH) 4·36 (s), 3·77 (s), 4·62 (s), 3·21 (s)] from which the major components (4-amino-5-mercapto-1,2,4-triazol-3-yl)acetohydrazide (4) (23%) (δ 4·36) and 4-amino-5-hydrazino-1,2,4-triazole-3-thiol (1) (11%) were isolated. Attempts to separate and identify the minor components apparent in the p.m.r. spectrum (δ 3·77, 4·62, 3·21) were unsuccessful. 5-Aminopyrazol-3-ol (5; R = H), the expected coproduct of the triazole (1),[2] was not detected.



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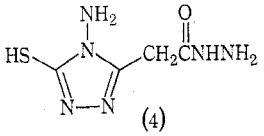

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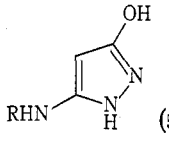

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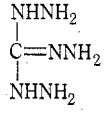


(6)

The composition of the reaction mixture (excluding 4-amino-5-hydrazino-1,2,4-triazole-3-thiol which is known to be formed slowly[4]) as indicated by the p.m.r. spectrum was not altered significantly when the reaction time was reduced to 20 min. However, when the reaction was carried out at room temperature (7 days), two new products, 5-hydrazinopyrazol-3-ol (5; R = NH_2) (22%) and triaminoguanidine (6) (10%), were isolated in addition to lesser amounts of (1) (4%) and (4) (5%). Both (5; R = NH_2) and (6) were shown to be unstable in hot hydrazine solution. The structure of (5; R = NH_2) was confirmed by its formation from 5-aminopyrazol-3-ol (5; R = H)[5] by gentle hydrazinolysis. A carbonyl absorption at 1683 cm^{-1} in the i.r. spectrum indicated predominance of the cyclic amide tautomer in the solid state.

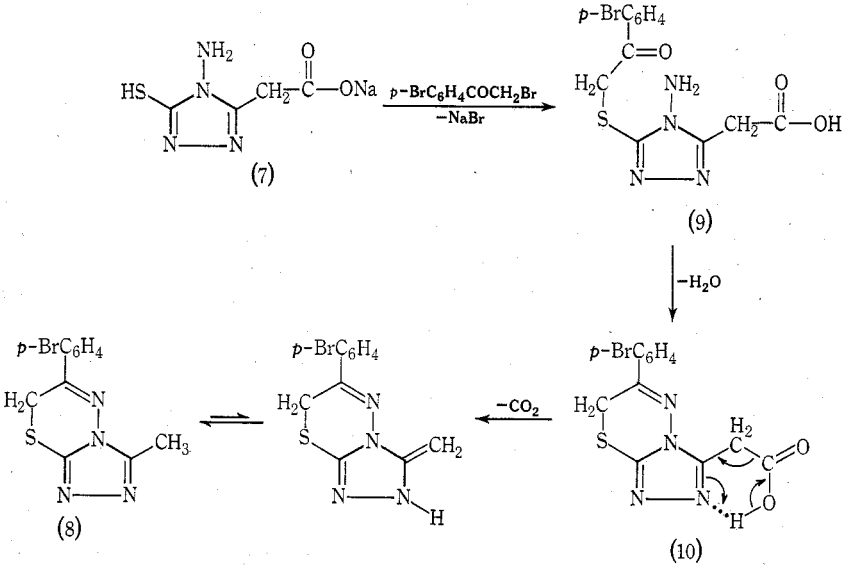
The triazolylacetohydrazide structure (4) was consistent with the analytical and spectroscopic properties. The thioamide tautomer was indicated in the solid state by absence of the mercapto stretching band at 2550–2600 cm^{-1} in the i.r. spectrum.

[3] Traube, W., and Winter, F., *Arch. Pharm.* (Weinheim), 1906, **244**, 11 (*Chem. Zentralbl.*, 1906, **1**, 1336).

[4] Dickinson, R. G., and Jacobsen, N. W., unpublished data.

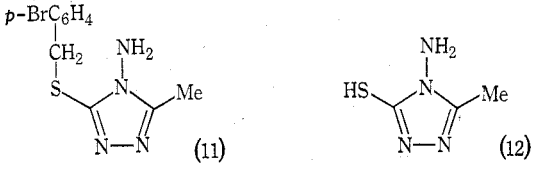
[5] Ishimaru, T., *Yakugaku Zasshi*, 1957, **77**, 796 (*Chem. Abstr.*, 1957, **51**, 17892i).

The assigned structure was confirmed by degradation of the acetohydrazide side chain. Hydrolysis in acid or alkali afforded (4-amino-5-mercapto-1,2,4-triazol-3-yl)-acetic acid (7) and hydrazine. Structure (7) was supported by analytical and spectroscopic data. To aid in the integration of its p.m.r. spectrum, the triazolylacetic acid (7) (as its sodium salt) was phenacylated with *p*-bromophenacyl bromide. Instead of the expected[6,7] thioether (9) the product obtained was its cyclization product 6-*p*-bromophenyl-3-methyl-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine (8) (see Scheme 1). This subsequent cyclization of the *S*-phenacyl derivative (9) of the triazole to the



Scheme 1

triazolothiadiazine (10) is in agreement with the reported[8] formation of 5-phenyl-1,3,4-thiadiazine derivatives from the reaction of phenacyl bromide with compounds containing the H_2N–N–C–SH system. Decarboxylation of the 3-substituent in these mild conditions occurred most likely through a six-centre transition state involving intramolecular hydrogen bonding. That decarboxylation occurred after formation of (9) was evident when it was shown in a separate experiment that (7) itself failed to decarboxylate under identical conditions. A similar reaction was observed with *p*-bromobenzyl bromide where *S*-benzylation and decarboxylation occurred to yield 4-amino-3-*p*-bromobenzylthio-5-methyl-1,2,4-triazole (11).



The structures of (8) and (11) were confirmed by synthesis from the known[6] 4-amino-5-methyl-1,2,4-triazole-3-thiol (12) and the respective phenacyl or benzyl

[6] Beyer, H., and Kroger, C.-F., *Justus Liebigs Ann. Chem.*, 1960, **637**, 135.
[7] Hoggarth, E., *J. Chem. Soc.*, 1952, 4811.
[8] Bose, P. K., and Nandi, B. K., *J. Indian Chem. Soc.*, 1930, **7**, 733, and preceding papers.

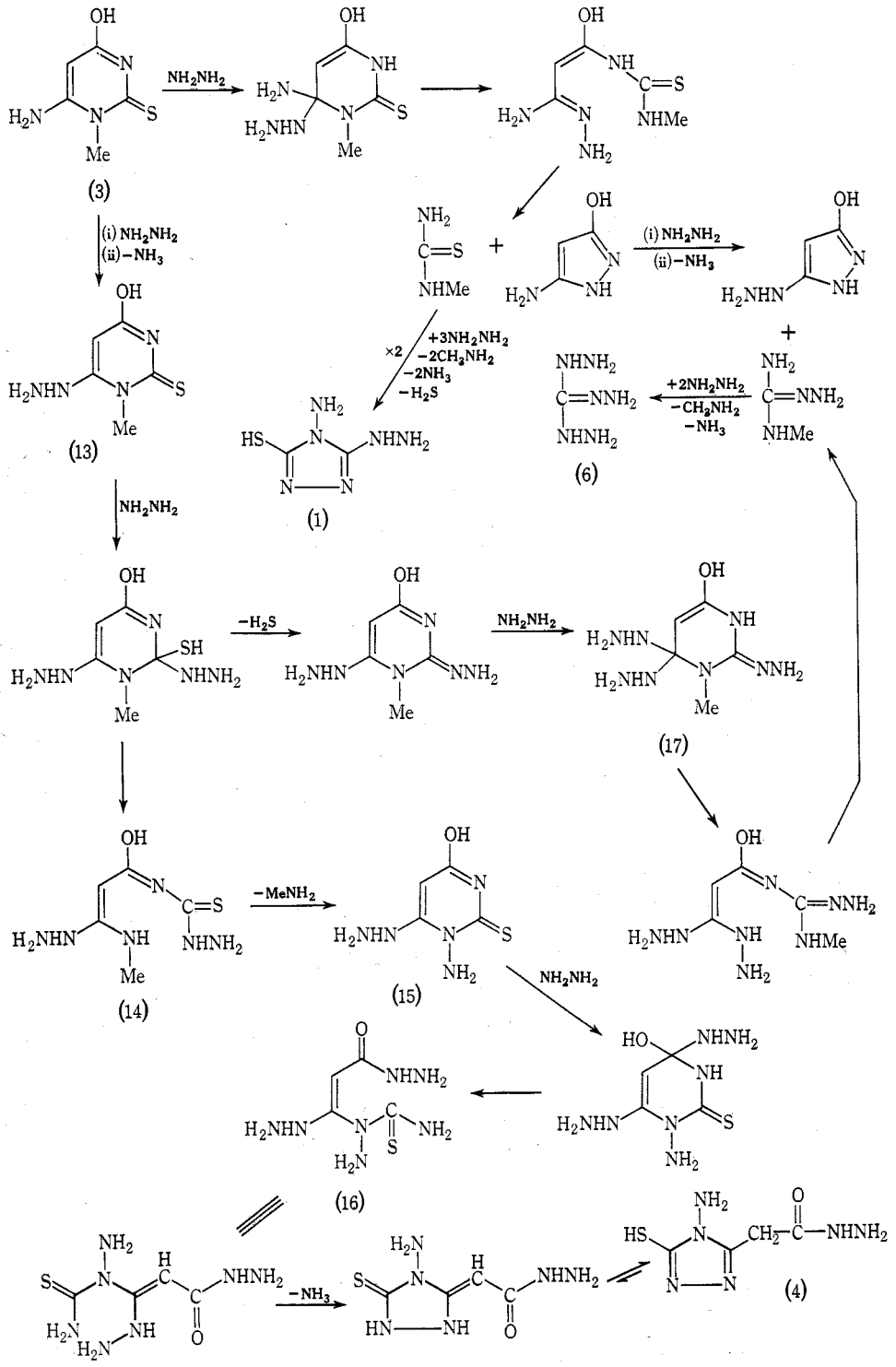
bromide. Further evidence confirming the structure of (4-amino-5-mercapto-1,2,4-triazol-3-yl)acetohydrazide (4) was the formation of a monobenzylidene derivative of (7) and direct decarboxylation of (7) to (12) by pyrolysis at 185°.

Plausible reaction pathways, outlined in Scheme 2, account for the observed products, but must be regarded as simplifications of an obviously complex system. Formation of the triazole (1) (11% yield) from the pyrimidine substrate (3) was expected to be analogous to that proposed for 1,4,6-trimethylpyrimidine-2(1*H*)-thione.[2] Here an initial nucleophilic attack of hydrazine at the 6-(or 4-)position with scission of the 1,6-(or 3,4-)bond and cyclization to the aminopyrazole (5; R = H) would expel *N*-methylthiourea, a known precursor of the triazole (1) under these conditions[1] (Scheme 2). Subsequent hydrazinolysis of the aminopyrazole (5; R = H) would yield the hydrazinopyrazole (5; R = NH_2) as shown by separate experiment. Alternatively, hydrazinolysis of the 6-amino group of (3) prior to cleavage of the ring could occur. At higher than ambient temperatures, decomposition of (5; R = NH_2) was quite facile.

The nucleophilic attack of hydrazine, initiating the sequence leading to the major product (4-amino-5-mercapto-1,2,4-triazol-3-yl)acetohydrazide (4), was postulated at the 6-position of the substrate (3) with subsequent displacement of ammonia to yield the 6-hydrazino derivative (13). A second attack at the 2-position, cleavage of the 1,2-bond to (14), and cyclization with expulsion of methylamine would yield the transient *N*-aminopyrimidine (15), which by a 3,4-addition of hydrazine and scission of the 3,4-bond would yield the acyclic intermediate (16). Rotation about the 1,6-bond and cyclization with loss of ammonia would give the triazolylacetohydrazide product (4). Alternative cyclizations of the intermediates (14) and (16) could yield the pyrazole ring with expulsion of the thioureido moiety, and these must be deemed significant competitors to the sequence leading to (4). Several alternative pathways, differing in the order of the steps or in the structures of the intermediates, could also be considered viable. Verification of any one or more selected sequence was not experimentally possible. However, one feature of all possible routes was an intermediate of the *N*-aminopyrimidine type (15). Conversion of authentic *N*-aminopyrimidines into 1,2,4-triazoles has been observed recently by Jacobsen and McCarthy.[9]

The triaminoguanidine (6), the fourth product from the hydrazinolysis of 6-amino-4-hydroxy-1-methylpyrimidine-2(1*H*)-thione (3), was isolated only when the reaction was carried out at room temperature. This fact is in keeping with the known instability[10] of triaminoguanidine in hot basic solution. The origin of this single carbon product was most certainly the C2 moiety of the substrate, and therefore its formation was in competition to that of the triazole (1), whose carbon atoms are also known to originate solely from the C2 moiety.[1] However, formation of triaminoguanidine from an expelled C2 thioureido fragment was unlikely since the base was not formed from either *N*-methylthiourea or thiocarbohydrazide under similar reaction conditions. Thus displacement of sulphur must have occurred whilst the pyrimidine ring was intact. Support for this proposal was the isolation of triaminoguanidine from the hydrazinolysis of 1,4,6-trimethylpyrimidine-2(1*H*)-thione[2] where it was also established that acyclic guanidine derivatives readily yielded triaminoguanidine in hydrazine solution. In the present instance, elimination of

[9] Jacobsen, N. W., and McCarthy, B. L., unpublished data.
[10] Scott, E. S., and Audrieth, L. F., *J. Org. Chem.*, 1954, **19**, 1231.

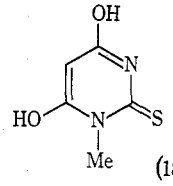


Scheme 2

hydrogen sulphide following attack of hydrazine at the 2-position of (13) was considered the likely pathway. Further attack of hydrazine at the 6-(or 4-)position of the resultant 2-hydrazonopyrimidine (17) with scission of the 1,6-(or 3,4-)bond would yield an acyclic guanidine intermediate. Ring closure to the product 5-hydrazinopyrazol-3-ol (5; R = NH_2) would expel the precursor of triaminoguanidine (6).

4,6-Dihydroxy-1-methylpyrimidine-2(1H)-thione

This pyrimidine (18) was prepared in excellent yield from diethyl malonate and *N*-methylthiourea. Its structure in the solid state was not clearly indicated from the infrared spectrum. Medium intensity bands at 1670, 1664, 1633 cm^{-1} were consistent with amide carbonyl frequencies observed in similar heterocyclic systems[11,12] and suggested a mixture of hydrogen-bonded oxo–thioxo tautomers. A broad band at 2400–3250 cm^{-1} assigned as a hydrogen-bonded hydroxyl absorption supported this assumption, although contribution from the dioxo–thioxo tautomer could not be excluded. The p.m.r. spectrum in trifluoroacetic acid solvent [δ 3·72 (s, 3H, NCH_3), 4·01 (s, 2H, ring CH_2)] indicated the C5 methylene tautomer, whilst the anionic species in sodium deuteroxide [δ 3·67 (s, 3H, NCH_3), 5·12 (s, 1H, ring CH)] showed a normal C5 'aromatic' proton which slowly underwent deuteration presumably through an enolization sequence.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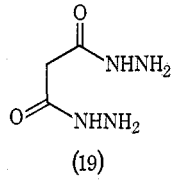
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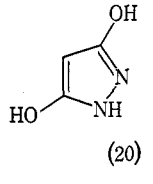
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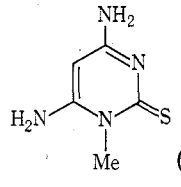

(21)

Hydrazinolysis of the pyrimidine (18) at 100° gave a tarry residue from which 4-amino-5-hydrazino-1,2,4-triazole-3-thiol (1) (49%) and (4-amino-5-mercapto-1,2,4-triazol-3-yl)acetohydrazide (4) (4%) were readily isolated. The p.m.r. spectrum of the residual tarry product in deuterium oxide solvent showed a resonance at δ 3·24 with smaller signals at δ 3·17, 3·41. The major component was malonyl dihydrazide (19). The minor components were of similar origin since they were shown by p.m.r. spectroscopy to be formed with (19) when diethyl malonate was refluxed with hydrazine in sodium ethoxide solution. Pyrazole-3,5-diol (20), the expected coproduct of the triazole (1), was not detected. This was not surprising since pyrazoles of this type cannot be prepared by condensation of hydrazines and malonic esters in basic conditions, more reactive malonyl substrates being required.[13]

Formation of the triazole (1) from the substrate (18) was expected to be analogous to the route outlined in Scheme 2 except that displacement of the thioureido moiety resulted from addition of a second hydrazine molecule, rather than from an intramolecular cyclization leading to pyrazole-3,5-diol (20). The formation of the triazolylacetohydrazide (4) was significant in this instance since it involved the

[11] Katritzky, A. R., and Tanner, A. P., in 'Physical Methods in Heterocyclic Chemistry' (Ed. A. R. Katritzky) Vol. 10, p. 252 (Academic: New York 1962).
[12] Tanner, E. M., *Spectrochim. Acta*, 1956, **8**, 9.
[13] Woodruff, M., and Polya, J. B., *Aust. J. Chem.*, 1975, **28**, 133, and references therein.

relatively unfavourable nucleophilic substitution of the 6-hydroxy substituent by hydrazine. The relative ease of hydrazinolysis of the 6-amino and 6-hydroxy substituents is reflected in the yields of the triazolylacetohydrazide (4) from (3) (23%) and (18) (4%). Formation of (4) from the dihydroxypyrimidine (18) was expected to be similar to its formation from (3) (Scheme 2). However, in this case, the hydrazide (4) was isolated free of the contaminating coproducts which accompanied its formation from the amino hydroxy analogue suggesting that substitution of the 6-hydroxy group by hydrazine was not the initial step in the transformation, but occurred at a stage sufficiently advanced to assure formation only of (4).

*4,6-Diamino-1-methylpyrimidine-2(1*H*)-thione*

Preparation of this pyrimidine (21) from malononitrile and *N*-methylthiourea under the usual conditions resulted in poor yields (20–25%). Significantly higher yields (35%) were achieved by pyrolysing the acylic condensation product of the reactants at 160°.

Hydrazinolysis of the diaminopyrimidine at 100° gave a hygroscopic product which did not contain the customary 4-amino-5-hydrazino-1,2,4-triazole-3-thiol (1), nor the expected triazolylacetohydrazide (4). The p.m.r. spectrum in deuterium oxide solvent revealed major resonances at δ 2·90, 4·25 and minor resonances at δ 3·63, 4·21. Acidic and alkaline hydrolysis failed to alter the product composition and attempts to prepare derivatives of functional amino groups were unsuccessful. The major product(s) thus remain as yet unidentified.

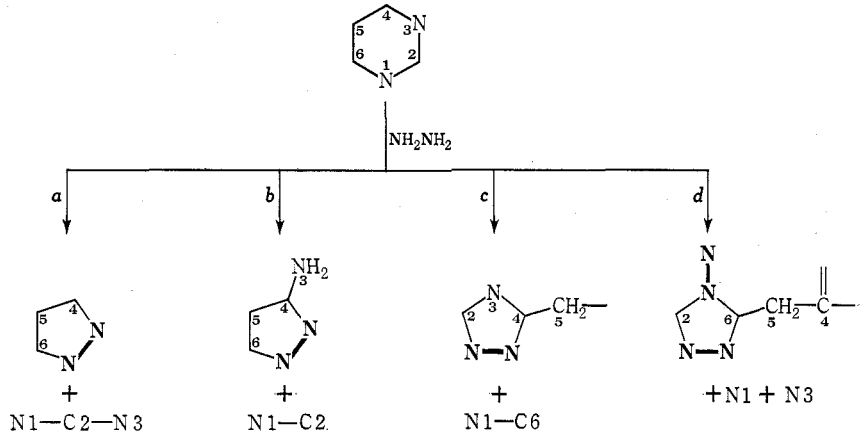
Discussion

Open-chain and heterocyclic compounds having a thioureido moiety have, with few exceptions, been shown[1] to form 4-amino-5-hydrazino-1,2,4-triazole-3-thiol (1) upon reaction with hydrazine. Using the 1-methylpyrimidine-2(1*H*)-thione as the basic unit, we have examined this reaction in order to analyse the effects of substituents on the behaviour of the pyrimidine ring. In this paper, the attachment of the electron-releasing hydroxy and amino groups at the 4- and 6-positions of the ring has been shown to be significant in their effects upon the formation of the triazole (1).

With 4,6-dihydroxy substituents (18), the yield of the triazole (1) was large (49%) compared to those from the 6-amino-4-hydroxy analogue (3) (11%) and the 4,6-diaminopyrimidine analogue (21) (0%). Meaningful analysis of these substituent effects on the mode of hydrazinolysis was difficult due to the variety and complexity of the reaction pathways, but some points could be noted.

The route to the triazole (1) is initiated by hydrazine attack at the 6-(or 4-)position of the ring. Ring-opening at the 1,6-(or 3,4-)bond is facilitated in the case of the dihydroxypyrimidine substrate (18) by the reluctance of the alternative reaction of displacement of the hydroxy group. In contrast, facile substitution of the 6-amino group of the aminohydroxypyrimidine (3) promotes the pathway to the major competing reaction yielding the triazolylacetohydrazide (4). It is unlikely that steric differences between the amino and hydroxy groups play any major role in determining the course of the reaction. Formation of triaminoguanidine from the 6-amino-4-hydroxypyrimidine (3) involves simple hydrazinolysis of the 2-thioxo substituent, and exemplifies a competing reaction shown to be of importance with 1,4,6-trimethyl-

pyrimidine-2(1*H*)-thione.[2] Detectable amounts of the triazole (1) are not obtained from the diaminopyrimidine (21), but unfortunately no comment can be made here without knowledge of the products. Thus (21) represents an exception to the thioureido test,[1] as does the triazolylacetohydrazide (4). That (4) is unaffected even by prolonged boiling with hydrazine indicates the unusual stability of the 1,2,4-triazole ring to nucleophilic attack.



Scheme 3

Formation of (4-amino-5-mercapto-1,2,4-triazol-3-yl)acetohydrazide (4) represents a new type of pyrimidine ring transformation by hydrazine. Several such ring transformations may be distinguished (Scheme 3). The most common of these is ring contraction to a pyrazole with loss of the N1–C2–N3 moiety[14] (path *a*). Other ring transformations recognized are loss of the N1–C2 moiety and incorporation of N3 in an exocyclic amino group of the pyrazole ring[15] (path *b*), and loss of the C6–N1 moiety with C5 being incorporated in an exocyclic substituted methyl group of a 1,2,4-triazole ring[14,16] (path *c*). The present transformation involves loss of the N1 and N3 fragments, with the C4–C5 moiety being incorporated in an exocyclic acetohydrazide group of the 1,2,4-triazole ring (path *d*).

Experimental

Melting points were determined in an electrically heated silicone oil bath (Buchi) and are uncorrected. Infrared spectra (Nujol mulls) were recorded on a Perkin–Elmer 247 spectrophotometer. P.m.r. spectra were recorded on either a Varian A60 or a Jeol MH-100 spectrometer using tetramethylsilane ($SiMe_4$) or sodium trimethylsilylpropanesulphonate ($Me_3Si(CH_2)_3SO_3Na$) as internal standard. Purity of products and progress of reactions were checked by paper chromatography with Whatman No. 1 paper; development was by ascending flow with solvent systems *A* [butanol/acetic acid/water (60 : 15 : 25 by weight)] and *B* [aqueous ammonium chloride (3% by weight)]; visualization was by u.v. irradiation or by immersion in iodine vapour. Microanalyses were performed either by the University of Queensland Microanalytical Service or by the Australian

[14] Plas, H. C., van der, and Jongejan, H., *Rec. Trav. Chim. Pays-Bas*, 1968, **87**, 1065, and references therein.

[15] Biffin, M. E. C., Brown, D. J., and Porter, Q. N., *Tetrahedron Lett.*, 1967, 2029; *J. Chem. Soc., C*, 1968, 2159.

[16] Plas, H. C., van der, and Jongejan, H., *Tetrahedron Lett.*, 1967, 4385.

Microanalytical Service. Unless otherwise stated, 98–100% hydrazine hydrate was used for all hydrazinolysis experiments.

6-Amino-4-hydroxy-1-methylpyrimidine-2(1H)-thione (3)

Following the directions of Traube and Winter,[3] *N*-methylthiourea (9 g, 0·1 mol) and ethyl cyanoacetate (11·3 g, 0·1 mol) were refluxed in ethanolic sodium ethoxide (2·3 g sodium in 60 ml absolute EtOH) for 4 h. The ethanol was then removed by evaporation under reduced pressure and the residue treated with excess 2M acetic acid. The crude product collected and recrystallized from water gave the pyrimidine (3) as colourless needles (14·3 g, 91%), m.p. 271–272° (dec.). P.m.r. (CF_3COOH, $SiMe_4$) δ 4·00 (s, NMe); [$(CD_3)_2SO$, $Me_3Si(CH_2)_3SO_3Na$] δ 3·74 (s, 3H, NMe), 5·07 (s, 1H, C5–H); [NaOD in D_2O, $Me_3Si(CH_2)_3SO_3Na$] δ 3·81 (s, NMe). ν_{max} 3320, 3245, 3155 (NH); 3048 (C5–H); 1671 (C=O); 1622, 1517 (NH) cm^{-1}.

Hydrazinolysis of 6-Amino-4-hydroxy-1-methylpyrimidine-2(1H)-thione (3)

(i) *At 100°*.—The procedure described below is an adaptation of the best of many experiments aimed at an optimal separation of the products. The pyrimidine (3) (3·14 g, 0·02 mol) and hydrazine hydrate (15 g, 0·3 mol) were heated on a steam bath for 2 h. After *c.* 10 min, the solution boiled with evolution of amine gases and sulphurous fumes. The mixture was evaporated under reduced pressure and the tarry residue stirred with water (10 ml) to an even suspension. The insoluble residue was collected by filtration (product (A)) and the mother liquors acidified to pH 6 with conc. hydrochloric acid. After standing at room temperature for 1 h, the precipitate was collected by filtration (product (B)) and the mother liquors were refrigerated overnight. The further precipitate (product (C)) was collected and the mother liquors discarded.

Product (A) was extracted with boiling water (8 ml) and filtered. The residue recrystallized from water (100 ml, activated charcoal) gave colourless needles of 4-amino-5-hydrazino-1,2,4-triazole-3-thiol (1) (0·16 g, 11%), m.p. 231–233° (dec.) (R_F (*A*), 0·25; R_F (*B*), 0·63). The filtrate was ice-cooled and the precipitate collected and combined with product (B).

Product (C) was successively extracted with boiling water (5 × 4 ml), the extracts cooled in ice, and the precipitated solids collected separately. The solids from extracts 4 and 5 were combined with product (B). The solids from extracts 1–3 were combined (0·35 g) and shown by p.m.r. spectroscopy to be a multicomponent mixture [(CF_3COOH, $SiMe_4$) δ 4·36 (s) ≡ product (B); 3·77 (s); 4·62 (s); 3·21 (s)] (R_F (*A*), one spot 0·23; R_F (*B*), one spot 0·58). Attempts to separate the components of this mixture were unsuccessful.

Combined product (B) recrystallized twice from water (2 × 25 ml, activated charcoal) gave colourless needles of *(4-amino-5-mercapto-1,2,4-triazol-3-yl)acetohydrazide* (4) (0·84 g, 23%), m.p. 249–250° (dec.) (Found: C, 25·3; H, 4·5; N, 44·3; S, 16·7. $C_4H_8N_6OS$ requires C, 25·5; H, 4·3; N, 44·7; S, 17·0%). R_F (*A*), 0·23; R_F (*B*), 0·58. P.m.r. (CF_3COOH, $SiMe_4$) δ 4·36 (s, $-CH_2-$). ν_{max} 3308, 3300, 3255sh, 3100, 3045 (NH); 1659 (C=O); 1652 (C=N); 1640, 1622, 1590, 1551, 1505 (NH) cm^{-1}.

(ii) *At room temperature*.—The pyrimidine (3) (3·14 g, 0·02 mol) and hydrazine hydrate (15 g, 0·3 mol) were stirred at room temperature (20–25°) in a loosely stoppered flask for 7 days. The substrate slowly dissolved and then precipitated as the hydrazine salt which was consumed during the first 5 days with evolution of amine gases. The mixture was then evaporated to near dryness at room temperature under reduced pressure, and the tarry residue stirred with water (10 ml) to an even suspension. The insoluble material was collected by filtration and washed with minimum ice-water. Recrystallization from 90% aqueous ethanol (activated charcoal) gave 5-hydrazinopyrazol-3-ol (5; R = NH_2) as light brown *needles* (0·5 g, 22%), m.p. 183–185° (dec.) (Found: C, 31·3; H, 5·4; N, 49·3. $C_3H_6N_4O$ requires C, 31·6; H, 5·3; N, 49·1%). P.m.r. (CF_3COOH, $SiMe_4$) δ 5·93 (s, CH_2); (D_2O) no signal, exchange. ν_{max} 3270, 3250, 3175, 3135 (NH); 3055 (C4–H); 1683 (C=O); 1642 (C=C); 1583, 1577, 1536 (NH) cm^{-1}.

The reaction mother liquors were cooled in ice and then neutralized to pH 6 with conc. hydrochloric acid. The cream precipitate was collected by filtration and recrystallized from water to yield 4-amino-5-hydrazino-1,2,4-triazole-3-thiol (1) as colourless needles (0·06 g, 4%), m.p. 231–233° (dec.).

The reaction mother liquors on refrigeration overnight deposited small colourless needles which were collected and recrystallized from 90% aqueous ethanol to yield triaminoguanidine hydro-

chloride (6) as colourless needles (0·3 g, 10·5%), m.p. 234–235° (dec.) [no depression with an authentic sample[17]].

The reaction mother liquors on further refrigeration for several days deposited a brown solid which was collected by filtration and successively extracted with boiling water (5 × 2 ml). The extracts were ice-cooled and the precipitated solids collected by filtration. The solids from extracts 3–5 were combined and recrystallized from water to give (4-amino-5-mercapto-1,2,4-triazol-3-yl)-acetohydrazide (4) as colourless needles (0·15 g, 4·5%), m.p. 249–250° (dec.). The solids from extracts 1 and 2 were combined and analysed by p.m.r. spectroscopy, which showed a mixture of compounds [CF_3COOH, $SiMe_4$) δ 4·36 (s) ≡ triazolylacetohydrazide (4); 3·77 (s), 4·62 (s), 3·21 (s)], similar in composition to that from the 100° reaction (i) above.

5-Hydrazinopyrazol-3-ol (*5*; *R* = NH_2)

Cyanoacetohydrazide[18] was refluxed in sodium methoxide solution to give 5-aminopyrazol-3-ol[19] (5; R = H) in 55% yield. The pyrazole (5; R = H) (0·99 g, 0·01 mol) and hydrazine hydrate (7·5 g, 0·15 mol) were stirred at room temperature (20–25°) for 48 h. The substrate dissolved readily yielding a yellow solution from which ammonia gas was evolved after *c.* 30 min. The yellow colour was transformed to a deep orange-red colour over the reaction period. The hydrazine was removed by evaporation at room temperature under reduced pressure, and the residue stirred with water (5 ml) to an even suspension. The brown solid was collected by filtration and washed with a minimum of ice-water. Recrystallized from 90% aqueous ethanol, it gave the pyrazole (5; R = NH_2) as light brown needles (0·6 g, 52%), m.p. 183–185° (dec.). The product was identical (mixed m.p., i.r., p.m.r.) to that obtained from the pyrimidine reaction (ii) above.

Hydrolysis of (*4-Amino-5-mercapto-1,2,4-triazol-3-yl)acetohydrazide* (*4*)

The triazolylacetohydrazide (4) (1·88 g, 0·01 mol) was refluxed in 2M sodium hydroxide solution (20 ml) for 2 h. The solution was acidified to pH 5–6 with conc. hydrochloric acid and evaporated to dryness under vacuum to give *sodium* (*4-amino-5-mercapto-1,2,4-triazol-3-yl)acetate* as colourless needles (1·6 g, 83%), m.p. 246–249° (dec.). The sodium salt (0·98 g, 5 mmol) was triturated with 2M hydrochloric acid (2·5 ml, 5 mmol) and the precipitated free acid collected by filtration and vacuum dried ($CaCl_2$). Recrystallization from ethyl acetate gave (*4-amino-5-mercapto-1,2,4-triazol-3-yl)acetic acid* (7) as colourless needles (0·64 g, 74%), m.p. 181·5–183° (dec.) (Found: C, 27·9; H, 3·7; N, 31·9; S, 18·4. $C_4H_6N_4O_2S$ requires C, 27·6; H, 3·6; N, 32·2; S, 18·4%). P.m.r. (CF_3COOH, $SiMe_4$) δ 4·33 (s, $-CH_2-$). ν_{max} 3300–2500 (OH, acid, H-bonded); 3254, 3220, 3140 (NH); 3003sh (CH); 1718 (C=O, acid); 1618sh (C=N); 1610, 1570 (NH) cm^{-1}. The triazolylacetohydrazide (4) was also hydrolysed by refluxing in 2M hydrochloric acid for 4 h.

(4-Benzylideneamino-5-mercapto-1,2,4-triazol-3-yl)acetic Acid

Benzaldehyde (0·48 g, 4·5 mmol) in ethanol (2 ml) was added dropwise with stirring over 5 min to (4-amino-5-mercapto-1,2,4-triazol-3-yl)acetic acid (7) (0·53 g, 3 mmol) in conc. hydrochloric acid (10 ml). The mixture was stirred for a further 5 min, cooled in ice, and the copious white precipitate collected by filtration and dried under vacuum ($CaCl_2$). Recrystallization from chloroform gave the *hydrochloride* of (4-benzylideneamino-5-mercapto-1,2,4-triazol-3-yl)acetic acid as small white needles (0·77 g, 78%), m.p. 185–186° (dec.) (Found: C, 44·2; H, 3·7; Cl, 11·9; N, 18·8; S, 10·7. $C_{11}H_{11}ClN_4O_2S$ requires C, 43·9; H, 3·4; Cl, 12·4; N, 18·5; S, 10·6%). P.m.r. (CF_3COOH, $SiMe_4$) δ 4·32 (s, 2H, $-CH_2-$), 7·54–8·07 (m, 5H, Ph), 9·49 (s, 1H, –CH=).

*6-p-Bromophenyl-3-methyl-7*H*-1,2,4-triazolo*[*3,4-*b][*1,3,4*]*thiadiazine* (*8*)

(i) *From* (*4-amino-5-mercapto-1,2,4-triazol-3-yl)acetic acid* (*7*).—The triazolylacetic acid (7) sodium salt (0·2 g, 1 mmol) was dissolved in water (1 ml). To this solution (pH 6) was added ethanol (5 ml) and *p*-bromophenacyl bromide (0·25 g, 0·9 mmol), and the mixture refluxed for 4 h. The ethanol was evaporated under reduced pressure and the residue stirred with water (10 ml)

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and cooled in ice. The crude product was separated by filtration and recrystallized from 5% aqueous ethanol to yield *6*-p-*bromophenyl-3-methyl-7*H-*1,2,4-triazolo*(*3,4*-b)-*1,3,4-thiadiazine* (8) as minute cream needles (0·26 g, 84%), m.p. 222–224° (Found: C, 43·0; H, 3·1; Br, 26·4; N, 17·9; S, 10·3. $C_{11}H_9BrN_4S$ requires C, 42·7; H, 3·0; Br, 25·9; N, 18·1; S, 10·4%). P.m.r. ($CDCl_3$, $SiMe_4$) δ 2·58 (s, 3H, CMe), 3·95 (s, 2H, $-CH_2-$), 7·72 (AB quartet, 4H, *J* 9 Hz, δ_A 7·66, δ_B 7·78, *p*-C_6H_4).

(ii) *From 4-amino-5-methyl-1,2,4-triazole-3-thiol* (*12*).—The triazole (12) (0·26 g, 2 mmol) [prepared from thiocarbohydrazide and acetic acid[6]] and *p*-bromophenacyl bromide (0·55 g, 2 mmol) were refluxed in 70% aqueous ethanol (15 ml) for 4 h. The solution was then evaporated to dryness under reduced pressure. The residue purified as in (i) above gave the triazolothiadiazine (8) (0·54 g, 87%), m.p. 222–224° [identical (mixed m.p., i.r., p.m.r.) to the product in (i) above].

*4-Amino-3-*p-*bromobenzylthio-5-methyl-1,2,4-triazole* (*11*)

(i) *From* (*4-amino-5-mercapto-1,2,4-triazol-3-yl*)*acetic acid* (*7*).—The triazolylacetic acid (7) sodium salt (0·2 g, 1 mmol) and *p*-bromobenzyl bromide (0·24 g, 0·95 mmol) were allowed to react in 80% aqueous ethanol (6 ml) as for the *p*-bromophenacyl bromide case (i) above. The product isolated and purified in similar manner gave *4-amino-3-*p-*bromobenzylthio-5-methyl-1,2,4-triazole* (11) as white microcrystals (0·25 g, 83%), m.p. 164–166° (Found: C, 40·4; H, 3·7; Br, 27·3; N, 18·3; S, 10·6. $C_{10}H_{11}BrN_4S$ requires C, 40·2; H, 3·7; Br, 26·7; N, 18·7; S, 10·7%). P.m.r. (CF_3COOH, $SiMe_4$) δ 2·78 (s, 3H, CMe), 4·46 (s, 2H, $-CH_2-$), 7·41 (AB quartet, 4H, *J* 9 Hz, δ_A 7·31, δ_B 7·51, *p*-C_6H_4).

(ii) *From 4-amino-5-methyl-1,2,4-triazole-3-thiol* (*12*).—The triazole (12) (0·26 g, 2 mmol) and *p*-bromobenzyl bromide (0·5 g, 2 mmol) were refluxed in 70% aqueous ethanol (15 ml) for 4 h. The solution was then evaporated to dryness and the residue purified as in (i) above. The product triazole (11) (0·47 g, 78%), m.p. 164–166°, was identical (mixed m.p., i.r., p.m.r.) to that in (i) above.

Pyrolysis of (*4-Amino-5-mercapto-1,2,4-triazol-3-yl*)*acetic Acid* (*7*)

The triazolylacetic acid (7) (0·35 g, 2 mmol) was heated in a glass tube in a metal sublimation block at 185°. The compound decomposed with liberation of carbon dioxide gas. After the initial reaction had subsided (*c.* 10 min), the tube was evacuated to *c.* 2 mmHg pressure. Sublimation of the decomposition mixture was continued for 1 h. The sublimate, colourless needles, was collected and resublimed at 185° at 1 mmHg pressure to yield 4-amino-5-methyl-1,2,4-triazole-3-thiol (12) as colourless needles (0·17 g, 65%), m.p. 209–210° (dec.) [undepressed by an authentic sample[6]].

4,6-Dihydroxy-1-methylpyrimidine-2(*1*H)-*thione* (*18*)

Diethyl malonate (16 g, 0·1 mol) and *N*-methylthiourea (9 g, 0·1 mol) were refluxed in sodium ethoxide solution (4·6 g sodium in 80 ml absolute EtOH) for 4 h. The sodium salt of the product precipitated steadily during the reaction time. The mixture was evaporated under reduced pressure and cooled in ice. Ice (100 g) was added and then excess conc. hydrochloric acid (40 ml) with stirring. The precipitate was collected by filtration, washed with cold water, and dried under vacuum. Recrystallization from ethyl acetate gave *4,6-dihydroxy-1-methylpyrimidine-2*(*1*H)-*thione* (18) as slightly pink needles (13·0 g, 82%), m.p. 195–196° (dec.) (Found: C, 28·0; H, 3·9; N, 17·4; S, 20·2. $C_5H_6N_2O_2S$ requires C, 28·0; H, 3·8; N, 17·7; S, 20·3%). P.m.r. (CF_3COOH, $SiMe_4$) δ 3·72 (s, 3H, NMe), 4·01 (s, 2H, $-CH_2-$); (NaOD in D_2O $Me_3Si(CH_2)_3SO_3Na$) 3·67 (s, 3H, NMe), 5·12 (s, 1H, –CH=, exch.). ν_{max} 2400–3250 br (OH, H-bonded); 3109 (NH); 1670, 1644sh, 1633 (C=O); 1525 (NH); 1465 (CH) cm^{-1}.

Hydrazinolysis of 4,6-Dihydroxy-1-methylpyrimidine-2(*1*H)-*thione* (*18*)

The pyrimidine (18) (3·16 g, 0·02 mol) and hydrazine hydrate (15 g, 0·3 mol) were heated on a steam bath for 3 h. The substrate dissolved readily yielding a yellow solution from which amine gases were evolved after *c.* 20 min. The hydrazine was evaporated under reduced pressure, and the residue treated with boiling water (10 ml) and filtered. The residue recrystallized from water gave 4-amino-5-hydrazino-1,2,4-triazole-3-thiol (1) as colourless needles (0·71 g, 49%), m.p. 231–233° (dec.). The filtrate on further cooling (3 h) deposited a cream solid which, separated by filtration and twice recrystallized from water (2×4 ml, activated carbon), gave (4-amino-5-mercapto-1,2,4-

triazol-3-yl)acetohydrazide (4) as colourless needles (0·15 g, 4%), m.p. 249–250° (dec.), identical (mixed m.p., i.r., p.m.r.) with the product from the pyrimidine (3).

The reaction mother liquors were evaporated under reduced pressure at 100°. P.m.r. of the residual tar (D_2O, $Me_3Si(CH_2)_3SO_3Na$) showed resonances at δ 3·17, 3·24, 3·41. Paper chromatography: R_F (*B*) 0·94, 0·89, 0·85. Successive extractive crystallizations with absolute ethanol (4 × 50 ml) gave malonyl dihydrazide (19) as colourless needles (0·08 g, 3%), m.p. 153–154° (no depression with an authentic specimen[20]).

4,6-Diamino-1-methylpyrimidine-2(1H)-thione (21)

(i) *Direct method.*—Malononitrile (6·6 g, 0·1 mol) and *N*-methylthiourea (9 g, 0·1 mol) were refluxed in sodium ethoxide solution (4·6 g sodium in 70 ml absolute EtOH) for 6 h. The sodium salt of the product precipitated steadily from the dark red-brown reaction mixture over the reflux period. The mixture was then evaporated to dryness under reduced pressure and cooled in ice. Water (30 ml) was added and the pH of the solution was adjusted to 9 with conc. hydrochloric acid (22 g, 0·2 mol). The mixture was refrigerated overnight and the brown solid collected by filtration and washed with cold water. Recrystallization from water (activated charcoal) gave *4,6-diamino-1-methylpyrimidine-2(1H)-thione* (21) as colourless needles (3·4 g, 23%), m.p. 249–251° (dec.) (Found: C, 38·7; H, 5·2; N, 35·0; S, 20·5. $C_5H_8N_4S$ requires C, 38·5; H, 5·2; N, 35·9; S, 20·5%). P.m.r. (CF_3COOH, $SiMe_4$) δ 3·99 (s, 3H, NMe), 5·73 (br s, 1H, C5–H). ν_{max} 3380, 3305, 3260sh, 3185 (NH); 3085 (C5–H); 1655sh, 1648, 1603, 1594 (NH) cm^{-1}.

(ii) *Stepwise method.*—Malononitrile (6·6 g, 0·1 mol) was added with stirring over 5 min to *N*-methylthiourea (9 g, 0·1 mol) in sodium propoxide solution (4·6 g sodium in 100 ml propan-1-ol) heated on a steam bath. The resultant suspension was stirred a further 5 min and then cooled in ice (1 h). The solid was separated by filtration, washed with cold propan-1-ol, and dried under vacuum ($MgSO_4$). This compound [m.p. 148–153° (dec.); p.m.r. (CF_3COOH, $SiMe_4$) δ 3·12 (s, 3H, NMe), 3·88 (s, 2H, $-CH_2-$)] was consistent with a primary condensation product of type $N{\equiv}CCH_2C(NH_2){=}N{-}CSNHCH_3$. The crude dry product (14·5 g) was heated at 160° at atmospheric pressure for 20 min, during which time it melted and then resolidified. The temperature was raised to 180° to ensure complete reaction and the mixture then cooled. The crude product recrystallized from water (activated charcoal) gave the pyrimidine (21) as colourless needles (5·5 g, 35%), m.p. 249–251° (dec.) [identical (mixed m.p.) to the product in (i) above].

Hydrazinolysis of 4,6-Diamino-1-methylpyrimidine-2(1H)-thione (21)

The pyrimidine (21) (1·56 g, 0·01 mol) and hydrazine hydrate (7·5 g, 0·15 mol) were heated on a steam bath for 2 h. The reactant dissolved slowly yielding a deep orange solution from which amine gases were steadily evolved. The mixture evaporated to dryness gave a hygroscopic light brown solid (1·42 g). P.m.r. (D_2O, $Me_3Si(CH_2)_3SO_3Na$) δ 2·90 (s), 3·63 (s), 4·21 (s), 4·25 (s), integrating as 17 : 1·5 : 2·5 : 6. Paper chromatography: R_F (*A*) 0·18, 0·52, 0·61; R_F (*B*) 0·88, 0·78, 0·65. The product was readily soluble in water, and adjustment of the pH with cooling gave no precipitate. The crude product was extracted with boiling ethanol (50 ml) and filtered. Addition of excess ethanolic picric acid solution gave an amorphous yellow precipitate which, after several recrystallizations from absolute ethanol, gave a yellow powder, m.p. 227–230° (dec.) (Found: C, 33·8; H, 3·2; N, 30·9; S, 7·6%). No reasonable structure was compatible with this data, and identification of the components of the product mixture was not achieved.

Acknowledgment

We thank the Rural Credits Development Fund for a grant for the support of R.G.D.

Manuscript received 12 June 1975

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