1,2,3,4,6-Penta-azaindenes (8-Azapurines). Part VII.[1,2] Degradation by Acid of the 6-Methylthio-derivatives of 8-Azapurines and Purines to Thiol Esters such as 4-Amino-5-(methylthio)carbonyl-1,2,3-triazole (IIIa) and the Corresponding Imidazole

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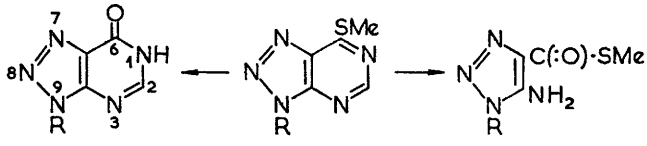
6-Methylthio-8-azapurine (IIa) in boiling N-hydrochloric acid was rapidly degraded to 4-amino-5-(methylthio)-carbonyl-1,2,3-triazole (IIIa) in 90% yield; the 7-, 8-, and 9-methyl- and 9-benzyl-derivatives behaved similarly. Physical properties, *e.g.* the strong absorption at *ca.* 900 cm.$^{-1}$ (:C–S· stretch), showed that these were RS·CO· (and not RO·CS·) esters. At a lower temperature, 9-methyl-6-methylthio-8-azapurine gave the intermediate 4-amino-3-methyl-1,2,3-triazol-5-yl(methylthio)methyleneiminium hydrochloride (Xb). Mechanisms are discussed for the above reactions and for the alternative decomposition, by weaker acid, to 8-azapurin-6(1*H*)-ones (I). The mercaptocarbonyl esters were converted into the corresponding amides and methylamides. One of the latter, 4-amino-3-methyl-1,2,3-triazole-5-carboxymethylamide, gave 1,9-dimethyl-8-azapurin-6(1*H*)-one in hot formamide. Aqueous sodium carbonate hydrolysed 4-amino-3-methyl-5-(methylthio)carbonyl-1,2,3-triazole to 4-amino-3-methyl-1,2,3-triazole-5-carboxylic acid, which was decarboxylated to 4-amino-3-methyl-1,2,3-triazole in boiling butanol.

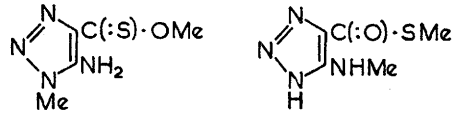
Acid degradation of 6-methylthiopurine (and its 9-methyl derivative) gave 4-amino-5-(methylthio)carbonyl-imidazole (and its 3-methyl derivative, respectively). New syntheses of 7-methyl- and 9-methyl-6-methylthiopurine are described.

Ionisation constants, and u.v. and n.m.r. spectra are discussed.

VERY little is known about the action of acid on the γ-methylthio-derivatives * of *N*-heteroaromatics, although (mineral) acid-catalysed hydrolysis of an α-methylthio- to an α-hydroxy-group * is a standard preparative reaction (ref. 3 gives early examples in the pyrimidine series). It will be shown here that acids attack 6-methylthio-derivatives of 8-azapurine † (II) in two mutually exclusive ways which give either (*a*) the 6-hydroxy-analogue (I), or (*b*) the thiol ester (III) produced by opening the pyrimidine ring. Increased strength of acid favours the latter course.



(I) a; R = H b; R = Me c; R = CH_2Ph (II) a; R = H b; R = Me c; R = CH_2Ph (III) a; R = H b; R = Me c; R = CH_2Ph



(IV) (V)

Products from 8-Azapurines.—9-Methyl-6-methylthio-8-azapurine [4] (IIb), heated under reflux with N-acetic acid for 64 hr., gave much 6-hydroxy-9-methyl-8-azapurine (Ib). This and unchanged starting material together accounted for 95%, but no thiol ester (IIIb) could be detected. The same methylthio-compound (IIb), heated under reflux with N-hydrochloric acid for 15 min., was converted almost completely into the thiol ester, 4-amino-3-methyl-5-(methylthio)carbonyl-1,2,3-triazole ‡ (IIIb); but none of the hydroxy-compound (Ib) was formed.

The structure (IIIb) follows from the conversion of the product (in aqueous ammonia at 20°) into the known 4-amino-3-methyl-1,2,3-triazole-5-carboxamide [4] (with evolution of methanethiol), and from spectral evidence. The i.r. spectra of thiol esters are highly characteristic; [5] *e.g.* that of *S*-butyl thiobenzoate which has two equally prominent peaks, 915 (:C–S· str.) and 1665 (C=O str.) cm.$^{-1}$ (*cf.* the C=O stretch of butyl benzoate, 1725 cm.$^{-1}$). Consonant with the proposed mercaptocarbonyl structure for compound (IIIb), the two most prominent i.r. absorption peaks were found at 900 and 1630 cm.$^{-1}$, equal in strength. For the isomeric methoxy(thiocarbonyl) structure (IV), the C=S stretch is likely to be near 1100 cm.$^{-1}$ and much less intense.[6]

The ^{1}H n.m.r. spectrum of the *S*-methyl ester (IIIb), obtained in a mixture of perdeuteriodimethyl sulphoxide and deuterium oxide, showed only two peaks, 6·23 (3H) and 7·68 (3H), which are assigned to *N*-CH_3 and *S*-CH_3 respectively. Any *O*-CH_3 peak would occur at *ca.* 6·0 near the *N*-CH_3 peak. The *S*-methyl ester (IIIb) absorbs in the u.v. region at $\lambda_{max.}$ 287 nm. (see Table)

* In this paper, α and γ mean that the substituent is located (with reference to ring-nitrogen atoms) as in 2- and 4-methylthiopyrimidine, respectively.

† '8-Azapurine' is permitted as a trivial name for 1,2,3,4,6-penta-azaindene.

‡ The amino-group of aminotriazoles is consistently numbered 4 in this series. The position of 'indicated hydrogen' (*e.g.*, 3*H*) is identical with that of the alkyl-group in nuclear alkylated triazoles, and is unknown for non-alkylated triazoles.

[1] Part VI, A. Albert, W. Pfleiderer, and D. Thacker, *J. Chem. Soc.* (*C*), 1969, 1084.

[2] Preliminary reports, A. Albert, *Angew. Chem.*, 1969, **81**, 115; *Chem. Comm.* 1969, 500.

[3] H. L. Wheeler and H. F. Merrian, *Amer. Chem. J.*, 1903, **29**, 478; H. L. Wheeler and G. S. Jamieson, *ibid.*, 1904, **32**, 342.

[4] A. Albert, *J. Chem. Soc.* (*C*), 1969, 152.

[5] R. A. Nyquist and W. J. Potts, *Spectrochim. Acta*, 1959, **15**, 514.

[6] L. J. Bellamy, in 'Organic Sulphur Compounds,' ed. N. Kharasch, Pergamon Press, Oxford, 1961, **1**, 55.

(unusually high for a triazole), comparable with that of simple aromatic thiobenzoates.[7] Whereas hydroxy(thiocarbonyl) esters are readily isomerized by heat [8] to mercaptocarbonyl esters, compound (IIIb) is unaltered below its m.p. (213°).

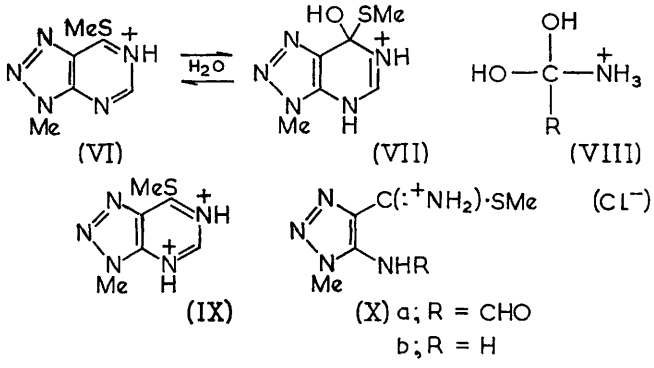
This evidence makes it certain that 9-methyl-6-methylthio-8-azapurine is converted by hydrochloric acid into the mercaptocarbonyl ester (IIIb) and not to the isomeric hydroxy(thiocarbonyl) ester (IV). Moreover, it is not the isomeric mercapto(carbonyl) ester (V) (arising froma Dimroth rearrangement [4]) because (*a*) it undergoes diazotisation and couples with 2-naphthol to give a deep red azo-compound, and (*b*) it lacks acid properties whereas the isomer (V) must be an acid of pK_a *ca.* 8. No other heteroaromatic *o*-amino-mercaptocarbonyl esters are known.

Further examples were similarly made, namely: 4-amino-5-(methylthio)carbonyl-1,2,3-triazole (IIIa), and its 3-benzyl (IIIc), 2-methyl-, and 1-methyl-derivatives from 6-methylthio-8-azapurine [4] (IIa), and its 9-benzyl- [4] (IIc), 8-methyl-,[9] and 7-methyl-[10] derivatives respectively. The position of the alkyl group had no apparent effect on the reaction. The benzyl-azapurine (IIc) required addition of an organic solvent (*e.g.* acetic acid) to bring it into solution in the boiling hydrochloric acid, to permit the reaction to proceed quickly enough to avoid contamination with the hydroxy-compound (Ic) formed by the alternative slow reaction.

All the mercaptocarbonyl esters were formed as large, colourless, odourless crystals in nearly quantitative yields. They were converted by ammonia into the known carboxylic amides, with loss of methanethiol (see Experimental section). All the mercaptocarbonyl esters were stable for many months at 25°, and were resistant when boiled with N-hydrochloric acid (in general, thiol esters are stable to dilute acids [11]). The melting point of the 3-methyl isomer was much higher than those of the 1- and 2-methyl isomers, an effect attributable to steric interference by the 3-substituent with intramolecular hydrogen bonding between the 4- and 5-substituents. The corresponding methylamides (in which –NHMe replaced –SMe) were prepared from the mercaptocarbonyl esters and aqueous methylamine; here again the 3-methyl derivative melted very much higher than its 1-methyl isomer.

Mercaptocarbonyl esters with an N-alkyl substituent were easily converted by aqueous sodium carbonate into the corresponding carboxylic acids, but 4-amino-5-(methylthio)carbonyl-1,2,3-triazole (IIIa) gave, in addition, some polymeric material, apparently by self acylation because 4-amino-1,2,3-triazole-5-carboxylic acid was found to be unaffected by alkali. 4-Amino-3-methyl-1,2,3-triazole-5-carboxylic acid, from compound (IIIb) was decarboxylated in boiling butanol to 4-amino-3-methyl-1,2,3-triazole, the hydrochloride of which had been obtained by another route.[12]

4-Amino-3-methyl-1,2,3-triazole-5-carboxymethylamide was cyclised to 1,9-dimethyl-8-azapurin-6-one when heated with formamide at 220°. Although that solvent evolves ammonia freely above 200°, no 9-methyl-8-azapurin-6-one [9] was formed by exchange with the methylamino-group in the starting material. The latter azapurine is distinguishable by having an acidic group and a N–H stretching band near 3000 cm.$^{-1}$; the u.v. spectra of both azapurines are very similar (see Table). This reaction should prove useful for making other 1-alkyl-6-oxo-8-azapurines.



Reaction Mechanisms.—Two mutually exclusive reactions are distinguishable for the action of acids on 6-methylthio-8-azapurines (II). The first of these, to be referred to as following ' course (A) ', is very slow, leads to the corresponding 6-hydroxy-derivative (I), and is effected by N-acetic acid. The second reaction [which follows ' course (B) '] is rapid, leads to the corresponding mercaptocarbonyl ester (III), and is effected by stronger acids, *e.g.* N-hydrochloric acid. Because the 6-methylthio-derivatives are unaffected by long periods in boiling water, it is reasonable to assume that course (A) starts with formation of the monocation,[13] *e.g.* (VI).* The first basic pK_a of 9-methyl-6-methylthio-8-azapurine was found to be —0·78 at 20° (see Table), equivalent to *ca.* —0·4 at 100°.[14] The average pH during the acetic acid-catalysed reaction was 3; therefore *ca.* 0·04% of the substrate existed as monocation, at equilibrium under these conditions. The retardation is more likely to depend on the next step, namely a slow, reversible, hydration to structure (VII) followed by rapid loss of methanethiol to give the product (Ib). This mechanism is analogous to that accepted for the acid-catalysed hydrolysis (bimolecular)

* The proton is considered to be on *N*-1 to take advantage of the 4-aminopyridinium-type resonance, in which the charge is shared with *N*-9 (ref. 13).

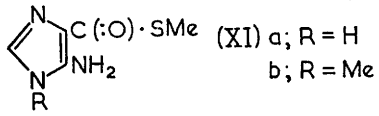
[7] H. P. Koch, *J. Chem. Soc.*, 1949, 387.
[8] S. A. Karjala and S. M. McElvain, *J. Amer. Chem. Soc.*, 1933, **55**, 2966.
[9] A. Albert, *J. Chem. Soc.* (*C*), 1968, 2076.
[10] A. Albert and K. Tratt, *J. Chem. Soc.* (*C*), 1968, 344.
[11] O. Wallach and H. Bleibtreu, *Ber.*, 1879, **12**, 1061.
[12] C. Pedersen, *Acta Chem. Scand.*, 1959, **13**, 888.
[13] A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 1948, 2240.
[14] D. D. Perrin, *Austral. J. Chem.*, 1964, **17**, 484.

of esters and amides,[15a] and of imidates and amidines,[15b] namely through slowly formed hydrated intermediates, such as (VIII) for amides. The percentage of the covalent hydrate (VII) present at any instant must be very small, because it is established that a γ-substituent sterically hinders the hydration of a six-membered nitrogen-containing ring.[16]

Course (B), which needs stronger acid, may require a dication such as (IX). The substrates (II) were too labile in very strong acid for the second basic ionisation constant to be found, but it must be very low (*cf.* −6·3 and −5·5 for the second ionisation constant of pyrimidine and quinazoline respectively). The two positively charged nitrogen atoms, of the dication (IX), make the 1,2- and 2,3-bonds highly electron-deficient and hence fragile. By conducting the reaction at a lower temperature, the intermediate (Xb) was isolated in good yield. Hence the nitrogen atom (*N*-1) initially remained with the carbon atom attached to the methylthio-group. The speed of course (B) is attributed mainly to typical acid-catalysed (irreversible) deformylation [(Xa) ⟶ (Xb)]; in less acidic solutions, when the formyl-derivative (Xa) cannot be removed in this way, the equilibrium (Xa) ⇌ (IX) is expected to favour the starting material (IX). Deposition of the product (IIIb) from boiling solution is not a major influence, because a high percentage of mercaptocarbonyl ester was found in supersaturated solution before deposition began. Some other reactions that undergo a change in rate-determining step with increasing concentration of general acid or base catalyst have been investigated kinetically.[15b,c]

The intermediate (Xb) is an example, rare in heterocyclic chemistry, of a thioimidate (examples from the benzene series are reviewed in ref. 17). The thioimidate (Xb), a somewhat stronger base than aniline (see Table), was stable as the hydrochloride at room temperature, but was rapidly and quantitatively converted into the mercaptocarbonyl ester (IIIb) when boiled with N-hydrochloric acid, thus justifying its postulated role as a key intermediate in course (B). The free base of the thioimidate, liberated at pH 7 by cold aqueous sodium hydrogen carbonate, was shown by paper chromatography to be undecomposed; but when boiled with water, it was transformed into 4-amino-5-cyano-3-methyl-1,2,3-triazole, identical with a specimen obtained by dehydrating 4-amino-3-methyl-1,2,3-triazole-5-carboxamide.

The action of alkalies on 6-methylthio-8-azapurines led to many products.[4] In a reinvestigation, mercaptocarbonyl esters were not found prominent.



(XI) a; R = H
b; R = Me

Products from Purines.—6-Methylthiopurines were found to give similar products on acid degradation, but the lower inductive (−*I*) effect of the fused imidazole (compared to the triazole) ring greatly retarded the production of mercaptocarbonyl esters. Thus, it was necessary to heat 6-methylthiopurine with N-hydrochloric acid under reflux for 4 hr. to achieve the maximum yield of 4-amino-5-(methylthio)carbonylimidazole (XIa), whereas only 15 min. was required for the reaction (IIa) ⟶ (IIIa). However with an increase in the strength of acid to 7N, the purine gave the maximum yield of (XIa) in 15 min. With 9-methyl-6-methylthiopurine, the *N*-alkylation further lowered the inductive effect of the five-membered ring so that, in boiling N-hydrochloric acid, much 6-hydroxy-9-methylpurine accompanied the mercaptocarbonyl ester (XIb). 7-Methyl-6-methylthiopurine was so rapidly destroyed by acid that neither the mercaptocarbonyl ester nor the hydroxypurine was obtainable.

The 9-methyl- and 7-methyl-6-methylthiopurine were made by new methods; the former by heating 5-amino-4-methylamino-6-methylthiopyrimidine with ethyl orthoformate (previously it had been prepared[18] by methylating 6-mercapto-9-methylpurine which is not easily accessible). The 7-methyl isomer was synthesised by stirring 4-amino-5-formamido-6-methylthiopyrimidine[19] (obtained by an improved formylation of the corresponding diamine) with methyl iodide and potassium carbonate in dimethylformamide; the subsequent ring closure was accomplished by heating the mixture. This application of a general method of Montgomery and Hewson[20] is much more convenient than the usual preparation[21] from 2-chloro-7-methyl-6-mercaptopurine.

The proof of structure of the two imidazole mercaptocarbonyl esters rests on the similarity of their n.m.r., i.r., and u.v. spectra to those of their triazole analogues. In addition, 4-amino-5-(methylthio)carbonylimidazole (XIa), was converted by ammonia to the known[22] 4-aminoimidazole-5-carboxamide. Since they were more basic than the corresponding triazoles (see Table), the imidazole mercaptocarbonyl esters required a higher pH for isolation from the reaction mixture.

Ionisation Constants and U.v. Spectra.—These are given in the Table. The pK_a value of 4-amino-3-methyl-1,2,3-triazole (2·27) which is the simplest

[15] (*a*) C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' G. Bell, London, 1953, pp. 770, 786; (*b*) E. S. Hand and W. P. Jencks, *J. Amer. Chem. Soc.*, 1962, **84**, 3503; D. W. Robinson and W. P. Jencks, *ibid.*, 1967, **89**, 7088; (*c*) R. B. Martin, R. I. Hedrick, and A. Purcell, *J. Org. Chem.*, 1964, **29**, 3197; B. A. Cunningham and G. L. Schmir, *J. Amer. Chem. Soc.*, 1967, **89**, 917; A. J. Kirby and W. P. Jencks, *ibid.*, 1965, **87**, 3217.

[16] A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1; W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc.*, 1965, 5360.

[17] V. Grignard, 'Traité de Chimie organique,' Masson et Cie, 194, Paris, XIII, 644.

[18] R. K. Robins and H. H. Lin, *J. Amer. Chem. Soc.*, 1957, **79**, 490.

[19] R. Denayer, *Bull. Soc. chim. France*, 1962, 1358.

[20] J. A. Montgomery and K. Hewson, *J. Org. Chem.*, 1961, **26**, 4469.

[21] E. Fischer, *Ber.*, 1898, **81**, 431.

[22] E. Shaw and D. W. Woolley, *J. Biol. Chem.*, 1949, **181**, 89; W. Shive, W. W. Ackermann, M. Gordon, M. E. Getzendaner and R. E. Eakin, *J. Amer. Chem. Soc.*, 1947, **69**, 725.

amino-1,2,3-triazole so far examined (*cf.* pK_a 1·17 for 1,2,3-triazole, and 1·25 for 1-methyl-1,2,3-triazole, at 20°),[23] shows that the resonance-aided exaltation of basic strength, so common in the α-amino-derivatives of six-membered nitrogen-containing rings [23] but little investigated in five-membered rings, does not operate here.

4-Amino-3-methyl-1,2,3-triazole-5-carboxylic acid has only one pK_a (4·08) below pK_a 11; thus the compound is not the isomer, 4-methylamino-1,2,3-triazole-5-carboxylic acid (if produced by a Dimroth rearrangement [24]), which would require a second acidic pK_a at *ca.* 7·5 (*N*-3).

Only those mercaptocarbonyl esters lacking an *N*-alkyl-group have acidic properties; the imidazole example is, as expected, a much weaker acid than the 1,2,3-triazole.

A basis for considering the u.v. spectra is provided by 1,2,3-triazole which has only one absorption peak [210 nm. in ethanol (log ε 3·64)]; the cation has an identical spectrum.[25] It can be seen that the amino-group in 4-amino-3-methyl-1,2,3-triazole has introduced a large bathochromic shift; this shift is not abolished in the cation, showing that protonation does not take place on the primary amino-group.

Other discussions of pK_a values and u.v. spectra occur in the main text.

EXPERIMENTAL

M.p.s are uncorrected. Yields refer to material sufficiently pure to give only one spot in chromatography on two Whatman No. 1 papers [one developed with 3% aqueous ammonium chloride, and one with butanol–5N-acetic acid (7 : 3)] viewed, in turn, in 365 and 254 nm. light. Specimens were applied to these papers in aqueous pyridine. Microanalyses were by Dr. J. E. Fildes and her staff. Ionisation constants, obtained by the methods described (ref. 26), were determined by Mr. D. T. Light and Miss M. D. Basell under supervision of Dr. D. D. Perrin.

U.v. spectra, maxima confirmed with an Optica manual instrument, were measured by Mr. I. Pavelić under supervision of Dr E. Spinner, who also recorded (on a Perkin-Elmer model 21 instrument) those i.r. spectra marked 'KBr'. The other i.r. spectra were obtained on a Unicam SP 200 instrument in Nujol (also in hexachlorobutadiene). Spectra (of mercaptocarbonyl esters) obtained both in KBr discs and in Nujol on the respective instruments showed similar resolution. N.m.r. spectra were obtained by Mr. S. Brown, supervised by Dr. T. J. Batterham, with a Perkin-Elmer model R10 instrument, operating at 33·5° and 60 Mc./sec., with tetramethylsilane as internal standard.

Action of Acetic Acid.—9-Methyl-6-methylthio-8-azapurine (IIb) [4] (0·36 g., 0·002 mole) and N-acetic acid (4 ml.) were heated under reflux for 64 hr. (became clear at 16 hr.); the mixture was then taken to dryness at 65°. The residue was boiled with ethanol (5 ml.), which, filtered at 20°, gave

Ionisation constants and u.v. spectra

Compd.	Ionisation in water (20°) Species [a]	pK_a	Spread ±	Conc. (M)	A.w. 1 [b] (nm.)	Spectroscopy in water [c] λ$_{max.}$ (nm.)	log ε	pH
1,2,3-Triazole								
4-Amino-5-(methylthio)carbonyl	0					237, 293	3·75, 4·06	5·0
	− [d]	7·12	0·02	10^{-4}	325	211, *231*, *255*, 300	4·05, *3·67*, *3·48*, 4·03	10·0
1-Methyl derivative	0					*232*, 256, 312	*3·62*, 3·63, 3·96	E [e]
2-Methyl derivative	0					247, 307	3·48, 3·95	M
3-Methyl derivative	0					239, 287	3·77, 4·13	E
4-Amino-3-methyl	0					238	3·73	7·0
	+	2·27	0·02	10^{-4}	265	259	3·63	−0·2
4-Amino-3-methyl-5-carboxy	−	4·08 [f]	0·03	10^{-4}	280			
4-Amino-3-methyl-5-(methylthio)-methyleneiminium	0					245, 273	3·95, 3·94	7·5
	+	5·47	0·01	0·005	P	222, 256, 318	4·05, 3·83, 4·10	3·0
4-Amino-5-cyano-3-methyl	0					225, 251	3·95, 3·78	M
Imidazole								
4-Amino-5-(methylthio)carbonyl	0					235, 306	3·60, 4·25	7·0
	+	3·38 [g]	0·04	10^{-5}	325	243, 300	3·74, 4·24	1·0
	−	10·45 [g]	0·04	10^{-5}	335	*230*, 318	*3·72*, 4·23	13·0
3-Methyl derivative	0					239, 305	3·59, 4·22	7·0
	+	3·08	0·04	10^{-5}	328	247, 302	3·67, 4·21	1·0
Other								
6-Methylthiopurine	+	1·63 [h]	0·01	10^{-4}	310			
9-Methyl-6-methylthio-8-azapurine	+	−0·78	0·03	10^{-4}	325			
1,9-Dimethyl-8-azapurin-6-one	0					*215*, 257 [j]	*4·03*, 3·92	7·0

[a] Neutral species (0), anion (−), cation (+). [b] Analytical wavelength for spectrometric determinations; P means that determination was potentiometric. [c] Inflections in italics. [d] Acidic pK_a of *N*-3; *cf.* 7·79 for pK_a of 4-amino-5-carbamoyl-1,2,3-triazole (ref. 10). [e] In ethanol (E), or methanol (M). [f] No other acidic pK up to 11. [g] These values resemble those for 4-carbamoylimidazole (3·7 and 11·8), *cf.* E. Rogers, *Science*, 1952, 116, 253. [h] This value must replace '0' in A. Albert and D. J. Brown, *J. Chem. Soc.*, 1954, 2060 (the anionic pK of 8·47 in this reference is correct). [i] For u.v. spectrum, see ref. 4. [j] *Cf.* 6-hydroxy-9-methyl-8-azapurine: 254 nm. (log ε 3·98) in ref. 9.

[23] A. Albert in 'Physical Methods in Heterocyclic Chemistry,' ed. A. R. Katritzky, Academic Press, New York, 1963, **1**, pp. 98, 31.

[24] D. J. Brown in 'Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Wiley, New York, 1968, vol. 1, p.209.

[25] D. Dal Monte, A. Mangini, R. Passerini, and C. Zauli, *Gazzetta*, 1958, **88**, 977.

[26] A. Albert and E. P. Serjeant, 'Ionization Constants of Acids and Bases,' Methuen, London, 1962.

70% of 6-hydroxy-9-methyl-8-azapurine (Ib), m.p. 301° (lit.,[4] 305°). Evaporation of the ethanol produced pure starting material (0·09 g.); no mercaptocarbonyl ester (IIIb) was detectable by paper chromatography. When boiled with water for 64 hr. the starting substance was unchanged.

Action of Hydrochloric Acid.—9-Methyl-6-methylthio-8-azapurine [2] (1·62 g., 0·009 mole) and N-hydrochloric acid (18 ml., 2 equiv.) were heated under reflux for 15 min. Crystals usually began to separate after 1 min. The mixture, chilled and filtered, gave *4-amino-3-methyl-5-(methylthio)carbonyl-1,2,3-triazole* (IIIb) (94%), m.p. 213—215° (from 85 parts of water) [Found (for material dried at 80°/0·01 mm.): C, 34·9; H, 4·6; N, 32·2; S, 18·7. $C_5H_8N_4OS$ requires C, 34·9; H, 4·7; N, 32·5; S, 18·6%], $\nu_{max.}$ (KBr disc) 3400, 3310, 3230 (all m), 1630s,br (C=O str.), 1570, 1515, 1370, 1310, 1210, 1000 (all m), and 900s (·C–S str.) cm.$^{-1}$. It is soluble in cold 10N- (but not in N-)hydrochloric acid, insoluble in 0·1N-sodium hydroxide, almost insoluble in boiling chloroform.

6-Methylthio-8-azapurine [27] (IIa) (6·4 g.) and N-hydrochloric acid (80 ml.) were heated under reflux for 15 min. Sodium hydrogen carbonate was added to the solution to raise its pH to 2. The mixture was chilled and filtered to give *4-amino-5-(methylthio)carbonyl-1,2,3-triazole* (90%), m.p. 202° (from 19 parts of water) [Found (for material dried at 60°/0·01 mm.): C, 30·3; H, 3·7; N, 35·7. $C_4H_6N_4OS$ requires C, 30·4; H, 3·8; N, 35·4%], $\nu_{max.}$ (KBr disc) 3000s, 2795s, 2780s, and 1640s (C=O), 1500m, 1325m, 1265m, and 910s (·C–S) cm.$^{-1}$.

9-Benzyl-6-methylthio-8-azapurine [4] (IIc) (0·42 g.), dissolved in acetic acid (3·5 ml.; anhydrous) and N-hydrochloric acid (3·5 ml., 2 equiv.) were heated under reflux for 5 min. and chilled. *4-Amino-3-benzyl-5-(methylthio)-carbonyl-1,2,3-triazole* (85%), m.p. 220° (from 180 parts of methanol) [Found (for material dried at 110° in air): C, 53·3; H, 4·8; N, 22·8. $C_{11}H_{12}N_4OS$ requires C, 53·2; H, 4·9; N, 22·6%], $\nu_{max.}$ 3150m, 1645s, 1625s (C=O), 1565m, 1505s, 930m, and 890s (·C–S) cm.$^{-1}$.

8-Methyl-6-methylthio-8-azapurine [9] (1·07 g., 0·006 mole) and N-hydrochloric acid (12 ml.), heated under reflux for 2 min., chilled and filtered, produced *4-amino-2-methyl-5-(methylthio)carbonyl-1,2,3-triazole* (94%), m.p. 108° [from 24 parts of light petroleum (b.p. 60—80°)] [Found (for material sublimed at 80°/0·01 mm.): C, 34·8; H, 4·8; N, 32·4%], $\nu_{max.}$ 3475m, 3305s, 1660s, 1620s (C=O), 1540s, 1505s, 1340m, 1285s, and 915s (·C–S) cm.$^{-1}$.

Similarly 7-methyl-6-methylthio-8-azapurine [10] when heated with N-hydrochloric acid for 7 min. gave *4-amino-1-methyl-5-(methylthio)carbonyl-1,2,3-triazole* (70%) m.p. 132° (from 15 parts of water) [Found (for material dried at 110° in air): C, 34·9; H, 4·7; N, 32·6%], $\nu_{max.}$ 3400m, 3275s, 3175s, 1610s (C=O), 1535s, 1450s, 1315m, 1195s, and 910s (·C–S) cm.$^{-1}$.

Preparation of Amides.—4-Amino-1-methyl-5-(methylthio)carbonyl-1,2,3-triazole (0·17 g., 0·001 mole) and 14N-aqueous ammonia (3 ml.) were stirred at 21—24° for 2 days; the mixture was taken to dryness at 60° to give 4-amino-1-methyl-1,2,3-triazole-5-carboxamide (90%), m.p. 173° (lit.,[10] 174°). The isomeric 2-methyl mercaptocarbonyl ester similarly furnished 4-amino-2-methyl-1,2,3-triazole-5-carboxamide (90%), m.p. 193° (lit.,[9] 193°), $\nu_{max.}$ 3400s, 3305s, 3180s, 1655 (C=O str.), 1610s, 1545s, 1310 , 1195m, and 695m cm.$^{-1}$. Similarly, the isomeric 3-methyl mercaptocarbonyl ester produced 4-amino-3-methyl-1,2,3-triazole-5-carboxamide,* m.p. 243—244° (lit.,[9] 244°). 4-Amino-3-benzyl-5-(methylthio)carbonyl-1,2,3-triazole (0·2 g.) and saturated ethanolic ammonia (5 ml.) heated at 120° for 3 hr. and taken to dryness gave 4-amino-3-benzyl-1,2,3-triazole-5-carboxamide * (95%), m.p. 232—233° (lit.,[28] 233—235°). 4-Amino-5-(methylthio)carbonyl-1,2,3-triazole (0·32 g.) dissolved in 14N-aqueous ammonia was set aside at 25° for several days until a test showed that no mercaptocarbonyl ester remained (when this was not done, the activated 4-amino-group in the anion of the amide was acylated by unused ester to give a polymeric substance). Concentration of the solvent to 4 parts, and filtration while hot, gave (on cooling) 4-amino-1,2,3-triazole-5-carboxamide (90%), m.p. 225—226° (lit.,[28] 224—225°).

Methylamides.—The appropriate mercaptocarbonyl ester (0·56 g.) and 40% aqueous methylamine (10 ml.) were stirred at 20—25° for 2 days; the mixture was then taken to dryness at 55° to give the following compounds. *4-Amino-2-methyl-1,2,3-triazole-5-carboxymethylamide* (97%), m.p. 105° (from benzene) [Found (for material dried at 60° and 0·01 mm.): C, 38·7; H, 6·2; N, 45·1. $C_5H_9N_5O$ requires C, 38·7; H, 5·9; N, 45·1%], $\nu_{max.}$ 3335s, 1645s (C=O str.), 1595s, 1565s, 1305m, and 1185m cm.$^{-1}$. *4-Amino-3-methyl-1,2,3-triazole-5-carboxymethylamide* * (96%), m.p. 234—235° (from 14 parts of water) [Found (for material dried in air at 110°): C, 38·5; H, 6·0; N, 45·1%], $\nu_{max.}$ 3275s, 3105s, 1650, 1640, 1620s (C=O), 1575, 1555s, 1430m, 1300m, 1235s, 1150m, and 1010m cm.$^{-1}$.

4-Amino-3-benzyl-5-(methylthio)carbonyl-1,2,3-triazole (0·24 g.) and 35% ethanolic methylamine (5 ml.) (Fluka), heated at 120° for 3 hr., produced *4-amino-3-benzyl-1,2,3-triazole-5-carboxymethylamide* * (80%), m.p. 155° (from 8 parts of ethanol) [Found (for material dried in air at 110°): C, 57·2; H, 5·95; N, 30·4. $C_{11}H_{13}N_5O$ requires C, 57·1; H, 5·7; N, 30·3%], $\nu_{max.}$ (KBr disc) 3420m, 3300m, 1635s (C=O), 1575s, 1460, 1285, and 1240 (all m) cm.$^{-1}$.

4-Amino-5-(methylthio)carbonyl-1,2,3-triazole (0·32 g., 0·002 mole) dissolved in 50% aqueous methylamine (6 ml.), set aside for 40 hr. at 24° and taken to dryness at 50°, gave *4-amino-1,2,3-triazole-5-carboxymethylamide* (90%), m.p. 194° (from nitromethane) [Found (for material dried at 110° and 0·01 mm.): C, 34·2; H, 5·1; N, 49·3. $C_4H_7N_5O$ requires C, 34·0; H, 5·0; N, 49·6%], $\nu_{max.}$ 3260s, 3100s, 1640s (C=O str.), 1570s,br, 1520, 1415, 1355, 1275, 1200, 1185, and 820 all m, cm.$^{-1}$.

Action of Sodium Carbonate on Mercaptocarbonyl Esters.—4-Amino-3-methyl-5-(methylthio)carbonyl-1,2,3-triazole (IIIb) (0·17 g., 0·001 mole) and N-sodium carbonate (2 ml.), heated under reflux for 1 hr., cooled, clarified from a little starting material, then acidified (pH 2·5), deposited *4-amino-3-methyl-1,2,3-triazole-5-carboxylic acid* (80%) (from 60 parts of water), m.p. 178° (if inserted at 165°) [Found (for material dried at 60° and 0·01 mm.): C, 34·0; H, 4·3; N, 39·3. $C_4H_6N_4O_2$ requires C, 33·8; H, 4·3; N, 39·4%], $\nu_{max.}$ 3100m,br, 1670s ($ArCO_2H$), 1625s,br ($ArCO_2^-$), 1580m,br, 1520s, 1440m, 1375m, 1320m, 1215s,br, and 1120m, cm.$^{-1}$.

* When diasotised in 5N-hydrochloric acid, it coupled (scarlet) with alkaline 2-naphthol, showing that Dimroth-type isomerisation had not occurred.

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[28] J. R. E. Hoover and A. R. Day, *J. Amer. Chem. Soc.*, 1956, **78**, 5832.

4-Amino-2-methyl-5-(methylthio)carbonyl-1,2,3-triazole similarly gave 4-amino-2-methyl-1,2,3-triazole-3-carboxylic acid (92%) (from ethanol), m.p. 174° (lit.,[9] 175°).

4-Amino-5-(methylthio)carbonyl-1,2,3-triazole (IIIa) similarly gave a precipitate (at pH 2·5) from which boiling water (1 ml.) extracted 4-amino-1,2,3-triazole-5-carboxylic acid (35% yield), m.p. 153° (eff.) (lit.,[9] 153°). The residue was poorly soluble in common solvents, tended to form gels, and lacked sulphur, $\nu_{max.}$ 3250s,br, 1680s + 1620s,br (C=O strs.), 1520s, 1365m, 1215s, and 975m cm.$^{-1}$; the bands 1680 and 1620 cm.$^{-1}$ were not changed after contact with triethylamine (absence of CO_2H).

4-Amino-3-methyl-1,2,3-triazole.— 4-Amino-3-methyl-1,2,3-triazole-5-carboxylic acid (0·28 g., 0·002 mole) and butanol (2·8 ml.) were heated under reflux for 3 hr. The solvent was removed under reduced pressure. The residue was dissolved in cold ethanol (0·2 ml.) and toluene (2 ml.) was added. The mixture, set aside for two days at −12°, gave *4-amino-3-methyl-1,2,3-triazole** (65%), m.p. 77°, very soluble in cold water [Found (for material dried at 24° and 0·01 mm.): C, 37·0; H, 6·3; N, 56·9. $C_3H_6N_4$ requires C, 36·7; H, 6·2; N, 57·1%], τ ([$^2H_6$]Me_2SO) 3·22 (1H, CH), 4·60 (broad, 2H, NH_2), 6·29 (3H, CH_3), the band at 4·6 disappeared when D_2O was added.

1,9-Dimethyl-8-azapurin-6(1H)-one.— 4-Amino-3-methyl-1,2,3-triazole-5-carboxymethylamide (0·155 g., 0·001 mole) and formamide (1 g.) were heated in an *open* flask at 225° (bath temp.) for 90 min.; the mixture was cooled, diluted with ethanol (1 ml.), and refrigerated. The precipitate, washed with a little acetone, gave *1,9-dimethyl-8-azapurine-6(1H)-one* (75%), m.p. 207° (from ethanol) [Found (for material dried at 110° in air): C, 43·5; H, 4·2; N, 42·2. $C_6H_7N_5O$ requires C, 43·6; H, 4·3; N, 42·4%], $\nu_{max.}$ 1700s (C=O str.), 1565s, 1320, 1275, 1100, 990, 785 all m, cm.$^{-1}$.

Intermediate in Acid Hydrolysis of 9-Methyl-6-methylthio-8-azapurine.—The azapurine (0·36 g., 0·002 mole) dissolved in 10N-hydrochloric acid (2·5 ml., 10 equiv.) at 24°, was set aside for 22 hours. Acetone (12 ml.) was then added to the mixture, and the whole was set aside at 0° for 2 days. The crystals of 4-amino-3-methyl-1,2,3-triazol-5-yl(methylthio)-methyleneiminium hydrochloride (Xb) (65%) were filtered off. After dissolution in 6 parts of water and reprecipitation with acetone, the m.p. (207°) was unchanged [Found (for material dried at 24° and 0·01 mm.): C, 28·95; H, 4·9; N, 33·65; S, 15·4. $C_5H_{10}ClN_5S$ requires C, 28·9; H, 4·85; N, 33·7; S, 15·4%], $\nu_{max.}$ 3400m, 3150s, 3000s, 2500m,brs, 1640m (C=N$^+$H str.), 1585m, 1537m, 1360m, and 865m cm.$^{-1}$; τ([$^2H_6$]Me_2SO) 7·27 (3H, SMe), 6·19 (3H, NMe), 1·9 broad (2H, 4-NH_2), 1·62, 2·56, 3·51 all sharp (0·67H each; N^+H_2, *i.e.* a N–H coupled triplet,[29] these last four peaks disappeared when a trace of D_2O was added. The free base, liberated in aqueous solution at pH 7, evolved methanethiol at 160°; the residue had m.p. 226—228°. After being heated under reflux with water (7 parts) for 1 hr., the free base deposited 4-amino-5-cyano-3-methyl-1,2,3-triazole (77%), m.p. 229—230° (from 30 parts of methanol) identical with material prepared as follows.

4-Amino-5-cyano-3-methyl-1,2,3-triazole.—To 4-amino-3-methyl-1,2,3-triazole-5-carboxamide [9] (0·14 g., 0·001 mole) and dimethylformamide (0·5 ml.), stirred in an ice-bath, was added phosphoryl chloride (0·17 ml., 0·002 mole). The solution and its container were placed in an 80° bath for 10 min. and cooled. N-Hydrochloric acid (1 ml.) was added to the mixture which was then boiled for 5 min. and refrigerated to give *4-amino-5-cyano-3-methyl-1,2,3-triazole* (80%), m.p. 229—230° (from 25 parts of water) [Found (for material dried in air at 110°): C, 39·2; H, 3·9; N, 56·5. $C_4H_5N_5$ requires C, 39·0; H, 4·1; N, 56·9%], $\nu_{max.}$ 3340 + 3150, 2210 (C≡N str.), 1660, 1595, 1315, 1235, and 1030 (all m) cm.$^{-1}$.

Acid Hydrolysis of the Iminium-Hydrochloride (Xb).—The hydrochloride (0·10 g., 0·0005 mole) in 1N-hydrochloric acid (1 ml.) was heated under reflux for 15 min.; it was then refrigerated. The solid formed was pure 4-amino-3-methyl-5-(methylthio)carbonyl-1,2,3-triazole (97%), m.p. 213—215°, identical with material described above.

4-Amino-5-(methylthio)carbonylimidazole.— 6-Methylthiopurine [30] (1·02 g., 0·006 mole) and N-hydrochloric acid (12 ml., 2 equiv.) were heated under reflux for 4 hr.; the mixture was then cooled. The pH was raised to 7·3 with sodium hydrogen carbonate (*ca.* 1·5 g.). After refrigeration, the solid was filtered off and crystallised from 20 parts of 0·1M-borax and then from 36 parts of water; *4-amino-5-(methylthio)carbonylimidazole* was obtained as needles (65%), m.p. 226° (with effervescence and resolidification) [Found (for material dried at 80° and 0·01 mm.): C, 38·1; H, 4·7; N, 26.9 $C_5H_7N_3OS$ requires C, 38·2; H, 4·5; N, 26·7%], τ([$^2H_6$]Me_2SO) 2·86 (1H, CH), 3·85 (2H, NH_2; exchanges with D_2O), 7·77 (3H, SCH_3), $\nu_{max.}$ (KBr), 3410m, 3370m, 3120m, 1637s, 1620s, 1610s (C=O str.), 1560s, 1515m, 1457m, 1375s, 1333m, 1307m, and 890s (:C–S str.) cm.$^{-1}$. Acidification of the alkaline filtrates and recrystallisation of the precipitate from 70 parts of water gave 6-hydroxypurine (25%), found to be identical with an authentic specimen by i.r. spectroscopy and chromatography. The mercaptocarbonyl ester, stirred with 3N-ethanolic ammonia (100 parts) for 1 week at 25°, gave 4-aminoimidazole-5-carboxamide (80%), m.p. 169—170° (decomp.) (lit.,[22] 170—171°).

9-Methyl-6-methylthiopurine.— 5-Amino-4-methylamino-6-methylthiopyrimidine [31] (1·7 g., 0·01 mole), freshly distilled ethyl orthoformate (7·5 ml.), and acetic anhydride (7·5 ml.) were heated under reflux for 3 hr. The volatile components were at once removed at 75° under reduced pressure. The residue was heated under reflux with methanol (20 ml.) for 30 min. and was then refrigerated to give 9-methyl-6-methylthiopurine (90%), m.p. 169—170° (lit.,[18] 171—172°).

4-Amino-3-methyl-5-(methylthio)carbonylimidazole.— 9-Methyl-6-methylthiopurine (0·18 g., 0·001 mole) and N-hydrochloric acid (2 ml.) were heated under reflux for 2 hr.; the mixture was then cooled in ice while the pH was raised to 12 with N-sodium hydroxide. The precipitated *4-amino-3-methyl-5-(methylthio)carbonylimidazole* (30%), recrystallised from 175 parts of water, had m.p. 268° [Found (for material dried at 110° in air): C, 41·8; H, 5·5; N, 24·7. $C_6H_9N_3OS$ requires C, 42·1; H, 5·3; N, 24·6%], $\nu_{max.}$ 3400m, 3130m, 1640s, 1620s (C=O str.), 1560s, 1520m, 1420m, 1195m, 1055m, and 880s (:C–S) cm.$^{-1}$. Acidification of the alkaline filtrate gave 6-hydroxy-9-methylpurine (55%), identical with an authentic specimen.[32]

7-Methyl-6-methylthiopurine.—4,5-Diamino-6-methylthiopyrimidine [33] (1·0 g.) and formic acid (2 ml.) were boiled vigorously for 5 min. The excess of acid was removed at

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55°/25 mm., and the residue triturated with 2N-aqueous ammonia until the pH rose to 5. The solid, filtered off, recrystallised from 120 parts of ethanol, and dried at 25°, yielded 4-amino-5-formamido-6-methylthiopyrimidine (70%), m.p. 220° (lit.,[19] 222°); the mixed m.p. with 6-methylthiopurine (m.p. 218°), which was a possible product of hydrolysis and ring-closure, was 195°, $\nu_{max.}$ 3150m, 1650s (C=O str.), 1570s, and 1520m, cm.$^{-1}$. To this pyrimidine (0·54 g., 0·003 mole), dissolved in dry dimethylformamide (25 ml.), was added dried potassium carbonate (0·42 g., 2 equiv.) and methyl iodide (0·42 g., 1 equiv.). The mixture was stirred for 44 hr., with exclusion of moisture, and was then heated under reflux for 90 min. The residue, after removal of the solvent at 80°, was added to boiling water (3 ml.) which, when chilled, furnished 7-methyl-6-methylthiopurine (70%), m.p. 208—209° (lit.,[21] 207—208°) [Found (for material dried at 110° in air): C, 46·5; H, 4·6; N, 31·45. Calc. for $C_7H_8N_4S$: C, 46·7; H, 4·5; N, 31·1%].

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