Reactions of 2-, 6-, and 8-Monosubstituted 1- and 3-Methylpurines with Hydroxide Ions in Water

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The reactions of 2-, 6-, and 8-monochloro- (or methylthio-)1-(and 3-)methylpurines towards N-sodium hydroxide have been examined. 1-Methyl-2- and -6-methylthiopurine underwent normal nucleophilic displacement to give the hydroxypurines, but 1-methyl-8-methylthiopurine underwent ring fission to give 5-amino-2-methylthioimidazole-4-carbaldehyde. 3-Methyl-6-methylthiopurine afforded 5-methylaminoimidazole-4-carbaldehyde predominantly, and some 6-hydroxy-3-methylpurine; and 3-methyl-8-methylthiopurine underwent ring opening like its 1-methyl isomer. 7-(and 9-)Methyl-2-methylthiopurines (for comparison) gave 4-amino-5-methylamino- and 5-amino-4-methylamino-2-methylthiopyrimidines, respectively. 6-Chloro-3-methylpurine gave 5-methylaminoimidazole-4-carbonitrile and some 6-hydroxy-3-methylpurine; but 8-chloro-3-methylpurine was consumed without forming 8-hydroxy-3-methylpurine.

REACTIONS of 2-, 6-, and 8-chloro- and methylsulphonyl-7-(and 9-)methylpurines with hydroxide ions have been recorded previously.[1] The nucleophilic displacement and ring-opening reactions of some 2-, 6-, and 8-monochloro-(or methylthio-)1-(and 3-)methylpurines towards hydroxide ions have now been examined. A number of purines [2] and purinium salts [3,4] alkylated in the pyrimidine ring are known to undergo ring opening under alkaline conditions to give imidazoles; the products from 3-methyl-6,8-bismethylthiopurine (1) with hydroxide ions were not identified.[5]

In the present work 1-methyl-2- and -6-methylthiopurines were heated with N-sodium hydroxide on a steam-bath, giving 2- and 6-hydroxy-1-methylpurine,

(1)

respectively, as the only products, but 1-methyl-8-methylthiopurine (2) under the same conditions underwent a two-step process as indicated by the u.v. spectra

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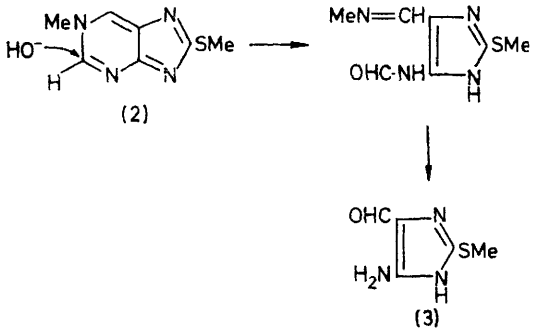
to give ultimately 5-amino-2-methylthioimidazole-4-carbaldehyde (3), together with a gaseous base, assumed to be methylamine. The reaction presumably proceeded by nucleophilic attack by hydroxide ion at C-2.



A check of the stability of 2-, 6-, and 8-hydroxy-1-(and 3-)methylpurines under the conditions of the hydrolysis revealed that they were stable. The structure of (3) was established by analysis, ^{1}H n.m.r. spectra, and its ring closure with formamide at 190—200 °C to give 8-methylthiopurine. Compound (3) shows an unusually long wavelength u.v. absorption maximum (at 330 nm).

3-Methyl-2-methylthiopurine was not available for study. 3-Methyl-6-methylthiopurine with N-sodium hydroxide underwent ring opening to give 5-methylaminoimidazole-4-carbonitrile predominantly, contrary to the findings of Jones and Robins,[6] and possibly a small amount of 6-hydroxy-3-methylpurine as shown by paper chromatography. This reaction is also envisaged as proceeding by hydroxide ion attack at C-2 followed by elimination of the methylthio-group; the mechanism is similar to that proposed in the pteridine and quinazoline series.[7] 3-Methyl-6-methylthiopurine with the stronger nucleophile, methoxide ion, underwent replacement only to give 6-methoxy-3-methylpurine. An attempt to oxidize 3-methyl-6-methylthiopurine to the corresponding sulphone with potassium permanganate in 8N-acetic acid gave only 6-hydroxy-3-methylpurine, formed presumably by hydrolysis of the methylsulphonyl group. Repetition of the work of Pal and Horton[2] under less severe conditions revealed that 6-amino-3-methylpurine and N-sodium hydroxide at 75—80 °C for 30 min gave mostly 6-hydroxy-3-methylpurine and no 5-methylaminoimidazole-4-carbonitrile.

3-Methyl-8-methylthiopurine with N-sodium hydroxide underwent ring opening like its 1-methyl isomer to give a product tentatively identified as 5-methylamino-2-methylthioimidazole-4-carbaldehyde on the basis of its ^{1}H n.m.r. and mass spectra and similarity in u.v. spectrum to compound (3).

For comparative purposes both 7- and 9-methyl-2-methylthiopurines with N-sodium hydroxide were examined, and gave respectively 4-amino-5-methylamino- and 5-amino-4-methylamino-2-methylthiopyrimidine. (Brown and Jones[8] found that 6,9-dimethyl-2-methylthiopurine with N-sodium hydroxide at 100 °C gave 5-amino-4-methyl-6-methylamino-2-methylthiopyrimidine.) 2-Dimethylamino-9-methylpurine under similar conditions did not undergo appreciable change, presumably owing to electron release by the substituent and relative stabilisation of the nucleus to nucleophilic attack. By contrast 7- and 9-methyl-2-methylsulphonylpurines with hydroxide ion underwent normal nucleophilic displacement,[1] and 2-chloro-7-methylpurine[1] gave a mixture of the hydroxypurine and 4-amino-2-chloro-5-methylaminopyrimidine.

Of the chloro-*N*-methylpurines examined in this work 6-chloro-3-methylpurine with N-sodium hydroxide at *ca.* 80 °C as described in the Experimental section gave 5-methylaminoimidazole-4-carbonitrile and also some 6-hydroxy-3-methylpurine; the reaction mixture from 8-chloro-3-methylpurine under comparable conditions revealed no evidence of 8-hydroxy-3-methylpurine on chromatographic and u.v. spectroscopic examination; and 2-chloro-9-methylpurine[9] gave two major products, one of which was shown by chromatography to be 2-hydroxy-9-methylpurine.

Preparation of Compounds.—Compounds required for this study but not described in the Experimental section were prepared as follows. 2-Hydroxy-1-methylpurine[10] was produced from 4-amino-2-hydroxypyrimidine through its 5-nitro-derivative,[11] 4-amino-1-methyl-5-nitropyrimidin-2-one,[12] 4,5-diamino-1-methylpyrimidin-2-one,[13] and its 5-formyl derivative.[10] 6-Hydroxy-1-methylpurine[14] was prepared from ethyl cyanoacetate and thiourea through 4-amino-6-hydroxy-2-mercaptopyrimidine,[15] its 5-nitro-derivative,[15] 4,5-diamino-6-hydroxy-2-mercaptopyrimidine,[15] its 5-formyl derivative,[15] 4-amino-5-formylamino-6-hydroxypyrimidine,[14] and its *N*(1)-methyl derivative.[14] 8-Hydroxy-1-methylpurine[16] came from 4-amino-6-hydroxypyrimidine through 4-amino-1-methylpyrimidin-6-one as described below, its 5-nitro-derivative,[17] 4,5-diamino-1-methylpyrimidin-6-one,[17] 6,8-dihydroxy-1-methylpurine,[17] and 8-hydroxy-6-mercapto-1-methylpurine.[16] 2-Hydroxy-3-methylpurine[18] was prepared from *N*-methylurea and ethyl nitrosocyanoacetate[19] through 4-amino-6-hydroxy-3-methyl-5-nitrosopyrimidin-2-one,[20] 4,5-diamino-6-hydroxy-3-methylpyrimidin-2-one,[21] 2,6-

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dihydroxy-3-methylpurine,[21] and 2-hydroxy-6-mercapto-3-methylpurine.[18] An alternative preparation of 2,6-dihydroxy-3-methylpurine [22] from 'sulphaminouracil' [22-25] (5-aminouracil-6-sulphonic acid) through its *N*-methyl derivative [22] was unsatisfactory because of difficulties associated with the methylation. 6-Hydroxy-3-methylpurine [18] was prepared from *N*-methylthiourea and ethyl cyanoacetate through 4-amino-6-hydroxy-3-methylpyrimidine-2-thione [26] and its 5-nitroso-derivative,[27] 5,6-diamino-4-hydroxy-1-methylpyrimidine-2-thione [27] and 6-hydroxy-2-mercapto-3-methylpurine.[18] 8-Hydroxy-3-methylpurine [18] was prepared from 5,6-diamino-4-hydroxy-1-methylpyrimidine-2-thione [27] through 5,6-diamino-4-mercapto-1-methylpyrimidine-2-thione [27] and 8-hydroxy-2,6-dimercapto-3-methylpurine.[27] 2-, 6-, Or 8-chloro-1-methyl- or 2-chloro-3-methyl-purine could not be prepared from the corresponding hydroxy-compounds with phosphoryl chloride and diethylaniline under a variety of conditions, nor could 2-chloro-1-methylpurine be prepared from the hydroxy-compound with the Bosshard reagent.[28-30] 8-Chloro-3-methylpurine was prepared, but in low yield, from 8-hydroxy-3-methylpurine with phosphoryl chloride and diethylaniline. Satisfactory analyses could not be obtained but the ^{1}H n.m.r. and mass spectra were consistent with its structure. 6-Chloro-3-methylpurine [31] (as hydrochloride) was prepared by the literature procedure [31] from 3-methyl-6-methylthiopurine.[18] 1-Methyl-2-methylthiopurine was prepared from 4,5-diamino-1-methyl-2-methylthiopyrimidinium iodide [32] through 4,5-diamino-1-methylpyrimidin-2-thione and 2-mercapto-1-methylpurine as described below. The preparation in aqueous sodium hydroxide was unsatisfactory owing to deformylation. An attempted preparation involving the quaternisation of 4,5-diamino-2-benzylthiopyrimidine with methyl iodide was unsatisfactory.

1-Methyl-6-methylthiopurine hydriodide was prepared according to a published method [33] and 1-methyl-8-methylthiopurine was obtained from its hydriodide.[34] Attempted preparation of the latter from 4,5-diamino-1-methylpyrimidinium chloride with thiourea gave instead 1,4-dihydro-4-imino-1-methyl-5-thioureidopyrimidine.

2-Mercapto-3-methylpurine could not be prepared from the 2-hydroxy-analogue by reaction with phosphorus pentasulphide in pyridine or tetralin. 3-Methyl-8-methylthiopurine was prepared by methylation of 8-methylthiopurine with diazomethane [4] (all four monomethyl isomers were obtained).

EXPERIMENTAL

All compounds were examined for impurities by paper chromatography on Whatman no. 1 paper with (*a*) aqueous 3% ammonium chloride, and (*b*) butan-1-ol–5N-acetic acid (7 : 3) as solvent, and by t.l.c. and were recrystallised to constant m.p.

Analyses were performed by the Australian National University Analytical Services Unit. Solids for analysis were dried at 100 °C unless otherwise stated and m.p.s were taken for samples in Pyrex capillaries. U.v. spectra were measured with a Unicam SP 1700 spectrophotometer. ^{1}H N.m.r. spectra were recorded at 60 MHz and 35 °C with a Varian T-60A spectrometer, with [$^2H_6$]dimethyl sulphoxide as solvent and tetramethylsilane as internal standard. I.r. spectra were determined for Nujol mulls. Mass spectra were measured by Dr. J. K. MacLeod with an A.E.I. MS9 instrument.

Hydrolysis experiments were conducted at 75—80 °C and also (for spectroscopic concentrations) at 20 °C; both gave similar results as shown by the spectra.

5-Aminouracil-6-sulphonic Acid.—This compound was prepared according to the literature procedures.[22-25] Methylation [24] of its sodium salt with methyl iodide gave a product apparently identical with that described by Nenitzescu,[24] which has a ^{1}H n.m.r. spectrum consistent with a ring-methylated structure {δ[$(CD_3)_2SO$] 3.2 (MeN) and 3.3 (s, Me_2N); δ(NaOD) 2.75 (Me_2N) and 3.2 (MeN)} rather than that of the trimethylammonio-compound.[24]

4-Amino-1-methylpyrimidin-6-one.—This compound was prepared by modification [35] of the reported methylation of 4-amino-6-hydroxypyrimidine with dimethyl sulphate in aqueous alkali.[36] By altering the concentrations and allowing the reaction mixture to cool slowly, a precipitate of pure 4-amino-1-methylpyrimidin-6-one (20—30%) yield was obtained. However extraction of the residue left after evaporation of the reaction mixture with chloroform yielded a mixture which also contained 1-methyl-4-methylaminopyrimidin-6-one (possibly formed by methylation, Dimroth rearrangement, and remethylation), identified by mixed m.p. and i.r. spectral comparison with an authentic specimen.[17]

2-Hydroxy-3-methylpurine.—3-Methyl-6-thioxanthine (3.6 g) was dissolved in 0.75N-sodium hydroxide (50 ml) and refluxed with Raney nickel (*ca.* 14 g wet) for 2.5 h. The nickel was filtered off and the filtrate adjusted to pH 6 with 10N-hydrochloric acid and evaporated to dryness. The residue was extracted several times with boiling ethanol and gave 2-hydroxy-3-methylpurine (1.18 g), δ[$(CD_3)_2SO$] 3.57 (MeN) and 8.10 and 8.61 (each s, 8- and 6-H); its u.v. spectrum corresponded with published data.[37] Bergmann and his co-workers [18] report a yield of 12%.

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[37] F. Bergmann, H. Kwietny, G. Levin, and D. J. Brown, *J. Amer. Chem. Soc.*, 1960, **82**, 598.

8-*Chloro*-3-*methylpurine*.—A mixture of 8-hydroxy-3-methylpurine (0.155 g), phosphoryl chloride (3.5 ml), and diethylaniline (0.4 ml) was refluxed with stirring for 2.5 h. Solid began separating after 0.5 h. The mixture was evaporated *in vacuo*, the dark oil was cooled in ice, water was added, and the solution was adjusted to pH 3 with ammonia and extracted with chloroform (3 × 20 ml). The product (contaminated with diethylaniline) was subjected to t.l.c. (alumina; chloroform) and the product recrystallised from cyclohexane to give 8-*chloro*-3-*methylpurine*, m.p. 140—145° (decomp.), δ($CDCl_3$) 4.26 (MeN) and 8.5 and 8.91 (2- and 6-H), M^+ 168/170.

4,5-*Diamino*-1-*methylpyrimidine*-2-*thione*.—To a solution of sodium ethoxide [from sodium (0.75 g) and ethanol (40 ml)] saturated with hydrogen sulphide was added a suspension of 4,5-diamino-1-methyl-2-methylthiopyrimidinium iodide [32] (4.6 g) in ethanol (40 ml). This mixture was heated under reflux for 1 h with hydrogen sulphide continuously bubbled through. A white solid which deposited was collected and recrystallised from ethanol to give 4,5-*diamino*-1-*methylpyrimidine*-2-*thione* (1.98 g), m.p. 265—267° (decomp.) (Found: C, 38.8; H, 5.2; N, 36.0. $C_5H_8N_4S$ requires C, 38.5; H, 5.2; N, 35.9%).

2-*Mercapto*-1-*methylpurine*.—(*a*) 4-Amino-5-formamido-1-methylpyrimidine-2-thione (0.43 g), *NN*-dimethylformamide (5.0 ml), and anhydrous potassium carbonate (0.43 g) were refluxed for 1.5 h. The mixture was diluted with water and adjusted to pH 7, and the product (0.33 g) was collected and recrystallised from water to give 2-*mercapto*-1-*methylpurine*, m.p. 285—290° (decomp.) (Found: C, 43.3; H, 3.9; N, 33.9. $C_6H_6N_4S$ requires C, 43.4; H, 3.7; N, 33.7%).

(*b*) 4,5-Diamino-1-methylpyrimidine-2-thione (0.040 g) and formamide (0.5 ml) were heated at 190 °C for 10 min. The mixture was cooled and the product collected and recrystallised from water; it was identical with that described in (*a*).

(*c*) 4,5-Diamino-1-methylpyrimidine-2-thione (0.25 g) and formic acid (98%; 5 ml) were heated under reflux for 6 h. The solution was evaporated to dryness *in vacuo* and the residue was heated under reflux with 2N-sodium hydroxide (6.0 ml) for 20 min, and acidified with acetic acid. The precipitate was collected and recrystallised from water to give 2-mercapto-1-methylpurine (0.095 g), m.p. 285—290° (decomp.). Repetition of the experiment gave a low yield of 2-mercapto-1-methylpurine and 4,5-diamino-1-methylpyrimidine-2-thione was recovered from the reaction mixture.

4-*Amino*-5-*formamido*-1-*methylpyrimidine*-2-*thione*.— A mixture of 4,5-diamino-1-methylpyrimidine-2-thione (0.500 g) and formic acid (10 ml) was refluxed for 1.5 h and then evaporated to dryness. The residue was diluted with water and adjusted to pH 6, and the solid collected and recrystallised from water to give the *formamidopyrimidine* (0.430 g), m.p. 270—275° (decomp.) (Found: C, 39.4; H, 4.2; N, 30.6. $C_6H_8N_4OS$ requires C, 39.1; H, 4.4; N, 30.4%).

1-*Methyl*-2-*methylthiopurine*.— 2-Mercapto-1-methylpurine (0.095 g) dissolved in 0.1N-sodium hydroxide (8.0 ml) was stirred vigorously with methyl iodide (0.2 ml) for 3 h. The product (0.090 g) was filtered off and recrystallised from water to give 1-*methyl*-2-*methylthiopurine*, m.p. 243—245° (Found: C, 46.5; H, 4.5; N, 31.4. $C_7H_8N_4S$ requires C, 46.6; H, 4.5; N, 31.1%).

4,5-*Diamino*-2-*benzylthiopyrimidine*.—Benzyl chloride (0.57 ml) was added dropwise with stirring over 1 h to a solution of 4,5-diamino-2-mercaptopyrimidine (0.5 g) in 2N-sodium hydroxide (4.25 ml) and stirring was continued for 3 h. The precipitate was collected and recrystallised from water to give 4,5-*diamino*-2-*benzylthiopyrimidine* (0.42 g), m.p. 151—153° (Found: C, 56.8; H, 5.3; N, 24.1. $C_{11}H_{12}N_4S$ requires C, 56.8; H, 5.2; N, 24.1%).

1-*Methyl*-8-*methylthiopurine*.— 1-Methyl-8-methylthiopurine hydriodide [34] (0.500 g) was converted into the hydrochloride by shaking with an excess of freshly prepared silver chloride. After filtration the solution of the hydrochloride was adjusted to pH 6 with 2N-sodium hydroxide and evaporated to dryness. The residue was extracted several times with boiling ethyl acetate and on concentration gave 1-*methyl*-8-*methylthiopurine* (0.150 g), m.p. 218—220° (Found: C, 46.75; H, 4.7; N, 31.2. $C_7H_8N_4S$ requires C, 46.6; H, 4.5; N, 31.1%).

1,4-*Dihydro*-4-*imino*-1-*methyl*-5-*thioureidopyrimidine*.— 4,5-Diamino-1-methylpyrimidinium chloride [32] (0.2 g) and thiourea (0.3 g) were fused at 185—190 °C for 15 min. The mixture was diluted with water, adjusted to pH 7, and evaporated to dryness. The residue was dissolved in N-sodium hydroxide and neutralised with acetic acid; the crystals which were slowly deposited were collected and recrystallised from ethanol to yield 1,4-*dihydro*-4-*imino*-1-*methyl*-5-*thioureidopyrimidine* (0.015 g) (Found: C, 39.4; H, 5.5; N, 37.6. $C_6H_{10}N_5S$ requires C, 39.1; H, 5.4; N, 38.0%), $\nu_{max.}$ 2 080 cm^{-1}.

Methylation of 8-*Methylthiopurine with Diazomethane*.— 8-Methylthiopurine [38] (1.5 g) was suspended in ether (50 ml) containing diazomethane (*ca.* 1.5 g) and the mixture stirred at room temperature for 20 h. The precipitate (0.800 g) was filtered off and subjected to t.l.c. [alumina; chloroform–ethanol (30 : 1)] to give, in order of descending R_F value, the 9-, 7-, 3-, and 1-methyl isomers. The 9-, 7-, and 1-methyl isomers were identified by i.r. and ^1H n.m.r. comparisons with authentic specimens,[1,39] and the 3-methyl isomer by m.p. and u.v. comparison with published data.[4] The filtrate from the preparation was evaporated and the product chromatographed on an alumina column. 9-Methyl-8-methylthiopurine was eluted first, and the solvent was changed to chloroform–ethanol (30 : 1) to give the 3-methyl isomer. The overall yields of isomers were 9- (0.41 g), 3- (0.255 g), 7- (0.150 g), and 1- (0.250 g).

Hydrolysis of 1-*Methyl*-2-*methylthiopurine*.—1-Methyl-2-methylthiopurine (0.01 g) and N-sodium hydroxide (1.0 ml) were warmed on a steam-bath for 20 min, cooled, and neutralised. Paper chromatography revealed one product only, identical with authentic 2-hydroxy-1-methylpurine,[10] and the u.v. spectra were also consistent with this product.[13]

Hydrolysis of 1-*Methyl*-6-*methylthiopurine*.—1-Methyl-6-methylthiopurine hydriodide (0.010 g) and N-sodium hydroxide (1.0 ml) were heated at 75—80 °C for 15 min, cooled, and neutralised. Paper chromatography showed one product only of the same R_F value as 1-methylhypoxanthine. The spot was eluted and the u.v. spectra were found consistent with published data for 1-methylhypoxanthine [14] [$\lambda_{max.}$ 249 nm (pH 0.0), 251 (5.0), and 260 (11.0)].

5-*Amino*-2-*methylthioimidazole*-4-*carbaldehyde*.— 1-Methyl-8-methylthiopurine (0.1 g) and N-sodium hydroxide (1.0 ml) were heated on a steam-bath for 20 min. The mixture was cooled and neutralised and the precipitate

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(0.023 g) collected and recrystallised from water to give *5-amino-2-methylthioimidazole-4-carbaldehyde*, m.p. 90—91° (Found, for sample dried at 70 °C and 20 mmHg: C, 38.4; H, 4.8; N, 26.3. $C_5H_7N_3OS$ requires C, 38.2; H, 4.5; N, 26.7%), δ[$(CD_3)_2SO$] 2.53 (MeS) and 9.01 (HCO), M^+ 157, $\lambda_{max.}$ (pH 12) 330 nm.

5-Methylaminoimidazole-4-carbonitrile.— 3-Methyl-6-methylthiopurine [18] (0.1 g) and N-sodium hydroxide (1.0 ml) were heated on a steam-bath for 30 min. The mixture was cooled and neutralised, and the solid collected and recrystallised from water to give *5-methylaminoimidazole-4-carbonitrile* (0.035 g), m.p. 222—223° (Found: C, 49.1; H, 4.8; N, 46.4. $C_5H_6N_4$ requires C, 49.2; H, 4.9; N, 45.9%), δ[$(CD_3)_2SO$] 2.83 (d, MeN) and 7.11 (2-H), $\nu_{max.}$ 2 220 cm^{-1} (C≡N), M^+ 122.

6-Methoxy-3-methylpurine.—A mixture of 3-methyl-6-methylthiopurine (0.08 g) and sodium methoxide (0.25N; 8 ml) was refluxed for 0.5 h, then cooled, and dry hydrogen chloride was passed through until precipitation was complete. The mixture was evaporated *in vacuo* and a solution of the residue in water was adjusted carefully to pH 9. The precipitate was collected and recrystallised from water to give 6-methoxy-3-methylpurine dihydrate, m.p. 160—162° (lit.,[31] 160—162°) (Found: C, 50.1; H, 5.3; N, 33.45. Calc. for $C_7H_8N_4O,0.2H_2O$: C, 50.1; H, 5.05; N, 33.4%).

Hydrolysis of 3-Methyl-8-methylthiopurine.—3-Methyl-8-methylthiopurine (0.020 g) and N-sodium hydroxide (2.0 ml) were warmed at 75—80 °C for 6 min. The mixture was then adjusted to pH 6 and extracted with chloroform. The product was subjected to t.l.c. (alumina; chloroform–ethanol) and the major spot eluted with chloroform, but on concentration it darkened to give a solid, m.p. 25—35°, M^+ 171 (Calc. for $C_6H_9N_3OS$: *M*, 171). The u.v. spectrum at pH 11—13 was similar to that for 5-amino-2-methylthioimidazole-5-carbaldehyde from 1-methyl-8-methylthiopurine.

Hydrolysis of 7-Methyl-2-methylthiopurine.—7-Methyl-2-methylthiopurine [1] (0.005 g) and N-sodium hydroxide (1.0 ml) were warmed at 75—80 °C for 0.5 h. The mixture was chilled and the solid (0.0032 g) was collected; it was identical with authentic 4-amino-5-methylamino-2-methylthiopyrimidine [40] [mixed m.p. 203—205° (lit.,[40] 202—204°); ^1H n.m.r., u.v., and i.r. spectroscopy]. Paper chromatography of the reaction mixture and the precipitate did not reveal any 2-hydroxy-7-methylpurine.[1]

Hydrolysis of 9-Methyl-2-methylthiopurine.—9-Methyl-2-methylthiopurine (0.010 g) and N-sodium hydroxide (1.0 ml) were heated at 75—80 °C for 0.5 h; the mixture was neutralised and evaporated to dryness. The product was identical {paper chromatography and ^1H n.m.r. [$(CD_3)_2SO$]} with authentic 5-amino-4-methylamino-2-methylthiopyrimidine (described below).

5-Amino-4-methylamino-2-methylthiopyrimidine.— 5-Amino-2-mercapto-4-methylaminopyrimidine [41] (0.5 g) dissolved in N-sodium hydroxide (8.0 ml) with methyl iodide (0.5 ml) was stirred vigorously at room temperature for 1 h. The solid which separated was collected, washed with a little cold ethanol, and recrystallised from warm water to give *5-amino-4-methylamino-2-methylthiopyrimidine* (0.27 g), m.p. 108—110° (Found, for compound dried at 70° and 20 mmHg: C, 42.6; H, 5.9; N, 33.4. $C_6H_{10}N_4S$ requires C, 42.35; H, 5.9; N, 32.9%), δ[$(CD_3)_2SO$] 2.35 (MeS), 2.75 (d, MeN, *J* 5 Hz), 4.37br (HN), and 7.38 (6-H).

Hydrolysis of 2-Dimethylamino-9-methylpurine.—2-Dimethylamino-9-methylpurine [42] (0.001 g) and N-sodium hydroxide (0.5 ml) were heated at 75—80 °C. Paper chromatography after 30 min revealed only starting material; however after 1.5 h another product had been formed but it was not 2-hydroxy-9-methylpurine.[42]

Hydrolysis of 6-Chloro-3-methylpurine.—6-Chloro-3-methylpurine hydrochloride [31] (0.015 g) and N-sodium hydroxide (1.0 ml) were warmed at 75—80 °C for 20 min. The mixture was adjusted to pH 7 and on paper chromatography showed two spots, the major one corresponding to 5-methylaminoimidazole-4-carbonitrile (see above) and the other to 3-methylhypoxanthine.[18]

8-Mercaptopurine.—(*a*) 1,4-Dihydro-4-imino-1-methyl-5-thioureidopyrimidine (0.005 g) was fused at 200—210 °C for 0.5 h. The mixture was diluted with water and filtered, and the filtrate evaporated to dryness; the 8-mercaptopurine, was identified by comparison (u.v. and i.r. spectra) with an authentic sample (Pfaltz and Bauer Inc.).

(*b*) 4,5-Diamino-1-methylpyrimidinium chloride [32] (0.4 g) and thiourea (0.65 g) were fused at 200—210 °C for 0.5 h. The solid obtained after cooling was recrystallised from water to yield 8-mercaptopurine (0.16 g), identified by its spectra.

8-Methylthiopurine.— 5-Amino-2-methylthioimidazole-4-carbaldehyde (0.015 g) and formamide (1.5 ml) were heated at 190—200 °C for 0.5 h. The solution was subjected to t.l.c. (cellulose; butanol–acetic acid, 7 : 3) and the spot of R_F corresponding to authentic 8-methylthiopurine [38,43] was removed and eluted with water. Evaporation of the extract gave 8-methylthiopurine (0.003 g), which was further characterised by its i.r. and u.v. spectra.

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