161. *Selective Thiation of Hydroxypurines by Phosphorus Pentasulphide.*

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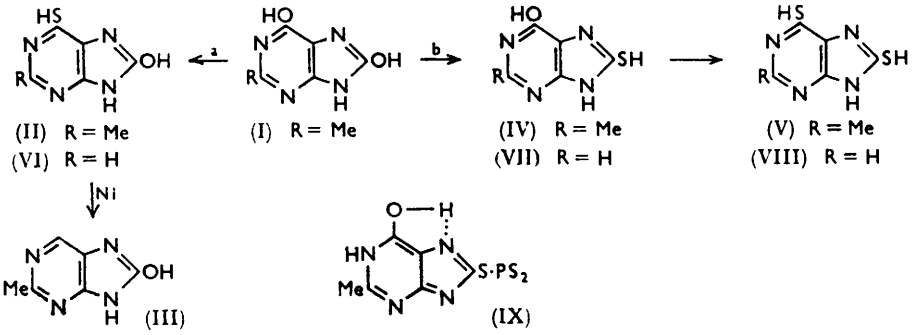
6,8-Dihydroxy-2-methylpurine gives as main thiation product 6,8-dimercapto-2-methylpurine (V), whereas the 6-monomercapto-compound (II) is obtained only in minute quantities. The latter product is not an intermediate in the formation of the former, which originates from the 8-mercapto-compound (IV). In the thiation of 6,8-dihydroxypurine and uric acid the 6-mercapto-derivatives are the main products, and the 6,8-dimercapto-compounds are formed as by-products through the 8-monomercapto-intermediates. Thiation of the 8-carbonyl group is possible only if oxygen is present at position 6.

Beaman [1] first observed that in xanthine only the 6-carbonyl group is substituted by phosphorus pentasulphide. This selective reaction has proved of great value in the synthesis of purines which otherwise are accessible only with difficulty, notably derivatives

[1] Beaman, *J. Amer. Chem. Soc.*, 1954, **76**, 5633.

of 2-hydroxypurine.[2,3] The usefulness of the thiation was extended considerably by the recent findings that in 4,5-diaminouracils [4] and in 6,8-dihydroxypurine [5] sulphur is again introduced only at position 6.



(II) R = Me (VI) R = H (I) R = Me (IV) R = Me (VII) R = H (V) R = Me (VIII) R = H (III) (IX)

In an attempt to use the latter reaction for the synthesis of the unknown 8-hydroxy-2-methylpurine (III), the annexed route was examined, starting from the known 6,8-dihydroxy-2-methylpurine.[6] The 2-methyl derivative (I) was recovered practically unaffected by phosphorus pentasulphide in boiling pyridine for 2 hours but in 6 hours, as in the case of 6,8-dihydroxypurine,[5] gave a 52% yield of the 6,8-dimercapto-derivative [6] (V) and a small amount of 8-hydroxy-6-mercapto-2-methylpurine (II), $\lambda_{max.}$ (pH 8·0) 242 and 333 mμ, that was separated by paper chromatography. The latter was identical with a sample obtained by condensing 4,5-diamino-6-mercapto-2-methylpyrimidine with urea. The 8-mercapto-isomer (IV), which was synthesised from 4,5-diamino-2-methyl-6-oxopyrimidine and thiourea, was quite different from the above minor product.

Thiation of the methylpurine (I) differs sharply from that of its parent 6,8-dihydroxypurine.[5] If the 6-mercapto-derivative (II) were the intermediate in the formation of the dimercapto-derivative (V) the second thiation step must be much faster than the first one to explain our failure to isolate more than traces of monomercapto-compound. However, the 6-mercapto-derivative resisted attack by phosphorus pentasulphide, so that dithiation occurs by the alternative path (b). Indeed, 6-hydroxy-8-mercapto-2-methylpurine (IV) reacts smoothly with the reagent, conversion into (V) being quantitative in 3—4 hr. Thus (b) is the main path and only a very small amount of thiation occurs at position 6, this reaction stopping at that point.

The 2-methyl group can produce this change in the thiation of 6,8-dihydroxypurine by deactivation of the 6-carbonyl group or by activation of the 8-carbonyl group. Deactivation can be demonstrated, independently of the second effect, by comparison of the thiation of 4,5-diamino-6-hydroxypyrimidine and its 2-methyl derivative: the former gives a 50% yield of the corresponding 6-mercaptopyrimidine after 2 hours' refluxing, the 2-methyl homologue being recovered after 6 hours. Similarly, 2-methylhypoxanthine resists thiation in boiling pyridine, although it has been reported [7] that under forced conditions (near 200°) about 60% of 6-mercapto-2-methylpurine can be obtained. This deactivation may be ascribed to transmission of the inductive effect of the methyl group through the conjugated chain Me·C:N·C:C·C:O in the pyrimidine ring, thus reducing the electrophilic character at position 6.

These considerations do not explain, however, why thiation now proceeds at position 8 with measurable speed. Direct activation of $C_{(8)}$ by the 2-methyl group cannot be

[2] Kalmus and Bergmann, *J.*, 1960, 3679.
[3] Bergmann and Tamari, *J.*, 1961, 4468.
[4] Levin, Kalmus, and Bergmann, *J. Org. Chem.*, 1960, **25**, 1752.
[5] Bergmann and Kalmus, *J. Org. Chem.*, 1961, **26**, 1660.
[6] Noell and Robins, *J. Org. Chem.*, 1959, **24**, 320.
[7] Robins, Jones, and Lin, *J. Org. Chem.*, 1956, **21**, 695.

demonstrated, as both 8-hydroxypurine and its 2-methyl derivative are refractory towards phosphorus pentasulphide. This result parallels our previous failure to thiate 2,8-dihydroxypurine.[5]

New light was shed on this problem by the following observation. 6-Hydroxy-8-mercaptopurine (VII) reacts smoothly with phosphorus pentasulphide in pyridine,[8] but 8-hydroxy-6-mercaptopurine (VI) is resistant under the same conditions. This result led us to re-investigate the thiation of 6,8-dihydroxypurine. After removal of the main product (VI), described previously,[5] the presence of traces of 6,8-dimercaptopurine [9] (VIII) resulting undoubtedly from the intermediate (VII), was proved by paper chromatography. Clearly, here the relative rates of reaction by paths (a) and (b) are reversed.

It is now evident that thiation at position 8 succeeds only if oxygen is present at position 6 and is prevented by a 6-thione group. A possible explanation may be sought in the formation of a hydrogen bridge between the 6-oxo- and the 7-imino-group. This unusual type of hydrogen bonding, which is strengthened by the inductive effect of the 2-methyl group on the 6-carbonyl group, has been discussed by Brown and Mason [10] on the basis of infrared spectroscopy. We suggest tentatively that this hydrogen bonding enhances enolisation at position 8, thus activating the latter towards formation of an intermediate (IX).

Elion, Müller, and Hitchings [11] reported that uric acid and phosphorus pentasulphide give a mixture of 6-thiouric and a smaller amount of 6,8-dithiouric acid. In conformity with this and with the above discussion, we find that 8-thiouric acid reacts readily with phosphorus pentasulphide, while 6-thiouric is refractory. It is thus evident that 6-thiouric acid is not an intermediate in the formation of 6,8-dithiouric acid, and that uric acid behaves similarly to 6,8-dihydroxypurine.

Experimental

Ultraviolet spectra were measured in a Beckman UV spectrophotometer. R_F values were determined on Whatman paper No. 1 by the descending method. Spots were located under a Mineralight ultraviolet lamp, emitting light of about 255 mμ.

Thiation of 6,8-*Dihydroxy-2-methylpurine* (I).—To a suspension of 6,8-dihydroxy-2-methylpurine [6] (4 g.) in dry pyridine (350 ml.) phosphorus pentasulphide (20 g.) was added slowly, with stirring, and the mixture was refluxed for 4 hr. The solvent was removed *in vacuo* and the residue decomposed by water (70 ml.) at 70° for 30 min. The water-insoluble portion was dissolved in cold N-sodium hydroxide (charcoal), and the filtrate acidified with glacial acetic acid. Reprecipitation gave yellow rods (2·5 g., 52%), R_F (solvent B) 0·69, $\lambda_{max.}$ 245, 273, and 339 mμ at pH 8 and 242, 270, and 335 mμ at pH 11·0. While the two higher absorption maxima are close to the values reported by Noell and Robins,[6] these authors did not record the short-wave maximum. The product proved to be identical with the dimercapto-derivative (V), obtained by thiation of 2-methyl-6-hydroxy-8-mercaptopurine (see below), thus establishing its structure.

The filtrate from the dimercapto-derivative was concentrated, to yield a small second crop of crystals (~0·1 g.), which, as shown by paper chromatography, contained a mixture of the dimercapto-compound (V) and 8-hydroxy-6-mercapto-2-methylpurine (II), $\lambda_{max.}$ 314 mμ at pH 11·0 (see below).

8-*Hydroxy*-6-*mercapto*-2-*methylpurine* (II).—An intimate mixture of 4,5-diamino-6-mercapto-2-methylpyrimidine [12] (0·5 g.) and urea (0·8 g.) was heated at 180—185° for 30 min. The cake was dissolved in N-sodium hydroxide (25 ml.), and the solution filtered and acidified by glacial acetic acid. Crystallisation from water gave the pure *purine* (II) as rods (85%) (Found: C, 39·4; H, 3·0; N, 30·4. $C_6H_6N_4OS$ requires C, 39·6; H, 3·3; N, 30·8%).

[8] Elion, Goodman, Lange, and Hitchings, *J. Amer. Chem. Soc.*, 1959, **81**, 1898, reported this thiation as occurring in boiling tetralin.
[9] Ishidate and Yuki, *Pharm. Bull.* (*Japan*), 1957, **5**, 240.
[10] Brown and Mason, *J.*, 1957, 682.
[11] Elion, Müller, and Hitchings, *J. Amer. Chem. Soc.*, 1959, **81**, 3042.
[12] Albert, Brown, and Wood, *J.*, 1954, 3832.

Compound (II) was recovered unchanged after interaction with phosphorus pentasulphide for 5 hr.

6-*Hydroxy*-8-*mercapto*-2-*methylpurine* (IV).—A mixture of 4,5-diamino-6-hydroxy-2-methylpyrimidine [13] (1 g.) and thiourea (1·8 g.) was heated at 180—185° for 45 min. The cake was dissolved in N-sodium hydroxide, the solution filtered and acidified with glacial acetic acid. Purification was effected by dissolving the purine in concentrated ammonia and reprecipitating with acetic acid. Prismatic blocks of decomp. >300° (0·7 g., 54%) (Found: N, 30·85%) were obtained.

TABLE 1.

Physical properties of 2-methylpurines.

Purine	$\lambda_{max.}$ (mμ) at pH: 1·0	8·0	11·0	R_F [a]	Solvent	Fluorescence	Ref.
6,8-Dihydroxy		261		0·28	A	Violet	
2-methyl- (I)	255	259	273	0·38	A	Violet	6
8-Hydroxy-6-mercapto- (VI)	238	237	237	0·46	A	Light blue	8
	333	311	310				
2-methyl- (II)	243	242	246	0·52	A	Violet	
	336	333	314				
6-Hydroxy-8-mercapto- (VII)	233	235	233	0·42	A	Violet	8
	288	294	289				
2-methyl- (IV)		238		0·48	A	Violet	
		295					
6,8-Dimercapto- (VIII)	270	272	241	0·65	B	Yellow	8
	357	358	260				
			333				
2-methyl- (V)	270	273	270	0·69	B	Yellow	6
	360	339	335				
8-Hydroxy		280		0·59	A	Violet	
2-methyl- (III)		282		0·64	A	Violet	

[a] Determined by the descending method. Solvent A, 95% EtOH–AcOH–H_2O (85 : 5 : 10); B, Pr^iOH–NMe_2·CHO–25% aq. NH_3 (65 : 25 : 10).

Thiation of 6-*Hydroxy*-8-*mercapto*-2-*methylpurine* (IV).—A mixture of the purine (IV) (1 g.) and phosphorus pentasulphide (5 g.) in pyridine (50 ml.) was refluxed during 4 hr., then was worked up as above to yield 0·6 g. (55%) of yellow rods, exhibiting $\lambda_{max.}$ of 242, 270, 335 mμ at pH 11·0. The compound (V) thus proved to be identical with the main product, isolated after thiation of (I) (see above).

By-product of the Thiation of 6,8-*dihydroxypurine*.—This thiation was carried out as described previously.[5] Concentration of the mother-liquor and subsequent paper chromatography revealed a mixture of two products: (*a*) R_F 0·45 in solvent A; $\lambda_{max.}$ 311 mμ at pH 8·0. This is 8-hydroxy-6-mercaptopurine (VI). (*b*) R_F 0·65 in solvent A; $\lambda_{max.}$ 358 mμ at pH 8·0. This is 6,8-dimercaptopurine (VIII), identical with the product, described below.

Thiation of 6-*Hydroxy*-8-*mercaptopurine* (VII).—This reaction, which had been carried out previously in tetralin,[8] proceeded also in pyridine, to give a 45% yield of 6,8-dimercaptopurine (VIII) within 90 min. The product was obtained as yellow prisms, decomp. >300°. Its spectral properties were in agreement with those reported by Elion *et al.*[8]

6,8-*Dithiouric Acid*.—(a) *By thiation of* 8-*thiouric acid*. 8-Thiouric acid [14] (2 g.) and phosphorus pentasulphide (6 g.) were refluxed in dry pyridine (600 ml.) for 40 min. After the solvent had been removed *in vacuo*, the residue was treated with water at 60—70° for 1 hr. When the whole was set aside, a yellow precipitate (1·4 g., 64%) of 6,8-dithiouric acid was deposited. This was purified by dissolution in sodium hydroxide, decolorisation (charcoal), and precipitation with glacial acetic acid. Its ultraviolet spectrum ($\lambda_{max.}$ 271 and 373 mμ at pH 1·0) corresponds to that of the by-product isolated by Elion *et al.*[11] on thiation of uric acid, and to that of the compound obtained as under (b) (see Table 2).

(b) *Condensation of* 4,5-*diamino*-6-*mercaptouracil with thiourea*. A mixture of the diamine [4] (1 g.) and thiourea (1·5 g.) was heated for 1 hr. at 175—180°. From an alkaline solution of the product formed, glacial acetic acid precipitated the *dithiouric acid* (0·6 g., 47%) as yellow prisms, decomp. >300° (Found: N, 28·4. $C_5H_4N_4OS_2$ requires N, 28·0%).

[13] Robins, Dille, Willits, and Christensen, *J. Amer. Chem. Soc.*, 1953, **75**, 263.
[14] Loo, Michael, Garceau, and Reid, *J. Amer. Chem. Soc.*, 1959, **81**, 3039.

TABLE 2.

Physical properties of thiouric acids.

Compound	$\lambda_{max.}$ (mμ) at pH: 1·0	8·0	12·0	R_F (solvent B)	Fluorescence	Ref.
6-Thiouric acid	260, 355	244, 347		0·17	Violet	12, 15
8-Thiouric acid			246, 306	0·14	Violet	15
6,8-Dithiouric acid	271, 373	265, 368		0·23	Violet	12

8-Hydroxy-2-methylpurine.—Condensation of 4,5-diamino-2-methylpyrimidine [12] (0·2 g.) and urea (0·4 g.) was carried out at 160° during 45 min. The *product* (0·13 g., 55%) crystallised from water in colourless rods, decomp. >300° (Found: C, 47·8; H, 3·9; N, 37·0. $C_6H_6N_4O$ requires C, 48·0; H, 4·0; N, 37·3%).

This purine did not undergo thiation, when heated with phosphorus pentasulphide for 2 hr. After prolonged reaction (4—6 hr.), only tars were formed.

Similar results were obtained in attempts to thiate 8-hydroxypurine.

Thiation of 4,5-Diamino-6-hydroxypyrimidine.—The reaction between this diamine [15] (1 g.) and phosphorus pentasulphide (3 g.) was carried out in pyridine during 90 min. The solvent was removed *in vacuo* and the residue decomposed with water (40 ml.) at 80°. After filtration and cooling, 0·8 g. (50%) of 4,5-diamino-6-mercaptopyrimidine was obtained, exhibiting $\lambda_{max.}$ (pH 1) 240 and 305 mμ.[16]

In contrast, 4,5-diamino-6-hydroxy-2-methylpyrimidine [13] was recovered unchanged after 6 hours' interaction with phosphorus pentasulphide in boiling pyridine.

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[15] Albert, Brown, and Cheeseman, *J.*, 1951, 474.
[16] Elion and Hitchings, *J. Amer. Chem. Soc.*, 1954, **76**, 4027.