Action of Nitrous Acid on Some Methylpyrimidines

By **Derek T. Hurst** * and (in part) **Stephen G. Jonas, Jerry Outram,** and Miss **Rosemary A. Patterson,** School of Chemical and Physical Sciences, Kingston Polytechnic, Kingston upon Thames KT1 2EE

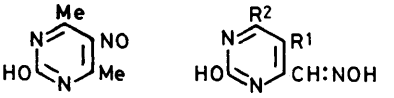
The action of aqueous sodium nitrite in acid solution on simple 2-mercapto-methylpyrimidines gives bipyrimidinyl disulphides. Similar reactions with 2-hydroxy-4-methylpyrimidines result in attack at the methyl groups giving (hydroxyiminomethyl)pyrimidines, whereas 2-amino-4-methylpyrimidines undergo concomitant deamination and methyl attack. Application of this nitrosation procedure to 1,4,5,6-tetramethylpyrimidin-2-one affords 1,4,5-trimethylpyrimidine-2,6-dione; an analogous reaction occurs with the corresponding 2-thione. This represents a novel pyrimidine demethylation reaction.

The bipyrimidinyl disulphides show potential as reagents for the spectroscopic determination of thiol groups and nitrite ion.

NITROSOPYRIMIDINES are usually made by treatment of a pyrimidine with sodium nitrite in aqueous acid, but the presence of at least two electron-releasing groups is required for success and, in all but two cases, ring nitrosation occurs at the 5-position.[1] However, the early claim [2] that 2-hydroxy-4,6-dimethylpyrimidine † reacts with nitrite to give 2-hydroxy-4,6-dimethyl-5-nitrosopyrimidine (1) has since been clarified and the product has been shown [3] to be 2-hydroxy-4-hydroxyiminomethyl-6-methylpyrimidine (2b). A similar reaction with 2-hydroxy-4-methylpyrimidine has been shown [4] to give 2-hydroxy-4-hydroxyiminomethylpyrimidine (2a). However, it has been reported [5] that 4-hydroxy-2-methylpyrimidine reacts with aqueous nitrous acid to give 4-hydroxypyrimidine-2-carboxylic acid, whereas 4,6-dihydroxy-2-methylpyrimidine has been shown [6] to give 4,6-dihydroxy-2-hydroxyiminomethyl-5-nitrosopyrimidine (3), although apparently 2,4-dihydroxy-6-methylpyrimidine does not react with nitrous acid.[7] A few other instances of nitrosation at a 2- or 4-methyl group of a pyrimidine by either inorganic nitrite (for examples see refs. 8—11) or an organic nitrite [12] have been reported.

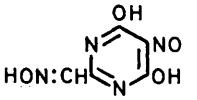
The action of nitrite on substituted pyrimidines can also result in diazotisation of amino-groups and subsequent production of halogenopyrimidines in the presence of excess of halide ion (for examples see refs. 11, 13, and 14) or in deamination (*e.g.* refs. 11 and 15); Trattner and his co-workers [16] have reported that a 4-amino-group is unreactive towards nitrous acid whereas a 2-amino-group is reactive.

It has also been reported that 4-amino-6-mercaptopyrimidine [17] and 2,4-diamino-6-mercaptopyrimidine [18] react with nitrite to give the corresponding bipyrimidinyl disulphide (4a or b); such disulphides are more usually obtained by using iodine in alkaline solution as oxidant. However, 4,6-diamino-2-mercapto- [19] and 4-amino-6-hydroxy-2-mercapto-pyrimidine [20] have been shown to undergo 5-nitrosation under similar conditions, and it is



(1)

(2) a; $R^1 = R^2 = H$
b; $R^1 = H, R^2 = Me$
c; $R^1 = H, R^2 = CH{:}NOH$
d; $R^1 = H, R^2 = Ph$
e; $R^1 = Me, R^2 = CH{:}NOH$
f; $R^1 = R^2 = Me$



(3)

reported [21] that nitrous acid reacts with 2-thiouracil to give uracil.

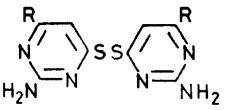
Thus pyrimidines may undergo a variety of reactions with nitrite. This paper described part of a continuing investigation of the reactions of nitrous acid with simple substituted pyrimidines with a view to providing some rationalisation for the products observed. Some of the initial results of a study of some simple substituted methylpyrimidines are reported.

As some 2-hydroxy- and 2-amino-4-methylpyrimidines are known to undergo attack at the methyl group when

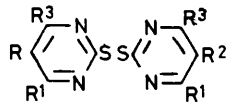
† In this paper, pyrimidones and pyrimidinethiones are represented as hydroxy- and mercapto-pyrimidines irrespective of the true tautomeric forms.

[1] (*a*) D. J. Brown, ' The Pyrimidines,' Wiley–Interscience, New York and London, 1962; (*b*) D. J. Brown, ' The Pyrimidines, Supplement I ' Wiley–Interscience, New York and London, 1970.
[2] R. Majima, *Ber.*, 1908, **41**, 176.
[3] A. J. Boulton, D. T. Hurst, J. F. W. McOmie, and M. S. Tute, *J. Chem. Soc.* (*C*), 1967, 1202.
[4] G. D. Daves, D. E. O'Brien, L. R. Lewis, and C. C. Cheng, *J. Heterocyclic Chem.*, 1964, **1**, 130.
[5] (*a*) A. Behrend, *Annalen*, 1885, **229**, 1; (*b*) W. Huber and H. A. Holscher, *Ber.*, 1938, **71**, 87.
[6] F. E. King and T. J. King, *J. Chem. Soc.*, 1947, 943.
[7] J. C. Davis, H. H. Ballard, and J. W. Jones, *J. Heterocyclic Chem.*, 1970, **7**, 406.
[8] P. Bitterli and H. Erlenmeyer, *Helv. Chim. Acta*, 1951, **34**, 835.
[9] A. Behrend, *Annalen*, 1888, **245**, 213.
[10] F. L. Rose, *J. Chem. Soc.*, 1954, 4116.
[11] D. T. Hurst, *Tetrahedron Letters*, 1970, 979.
[12] H. Bredereck, G. Simchen, and P. Speh, *Annalen*, 1970, **737**, 46.
[13] K. L. Howard, U.S.P. 2,447,409/1949 (*Chem. Abs.*, 1949, **43**, 8105).
[14] M. P. L. Caton, D. T. Hurst, J. F. W. McOmie, and R. R. Hunt, *J. Chem. Soc.* (*C*), 1967, 1204.
[15] J. A. Bee and F. L. Rose, *J. Chem. Soc.* (*C*), 1966, 2031.
[16] R. B. Trattner, G. B. Elion, G. H. Hitchings, and D. M. Sharefkin, *J. Org. Chem.*, 1964, **29**, 2674.
[17] M. Israel, H. K. Protopapa, H. N. Schlein, and E. J. Modest, *J. Medicin. Chem.*, 1964, **7**, 5.
[18] M. Israel, H. K. Protopapa, H. N. Schlein, and E. J. Modest, *J. Medicin. Chem.*, 1964, **7**, 792.
[19] A. Bendich, J. F. Tinker, and G. B. Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3019.
[20] W. Traube, *Annalen*, 1904, **331**, 64.
[21] S. Iida and H. Hayatsu, *Biochem. Biophys. Res. Comm.*, 1971, **43**, 163.

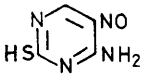
treated with nitrous acid,[3,4,11] the possibility of a similar reaction occurring with 2-mercaptopyrimidines was investigated. However, when 2-mercapto-4-methyl-, 2-mercapto-4,6-dimethyl-, or 2-mercapto-4,5,6-trimethylpyrimidine (as hydrochloride salts) was dissolved in



(4) a; R = H
b; R = NH_2



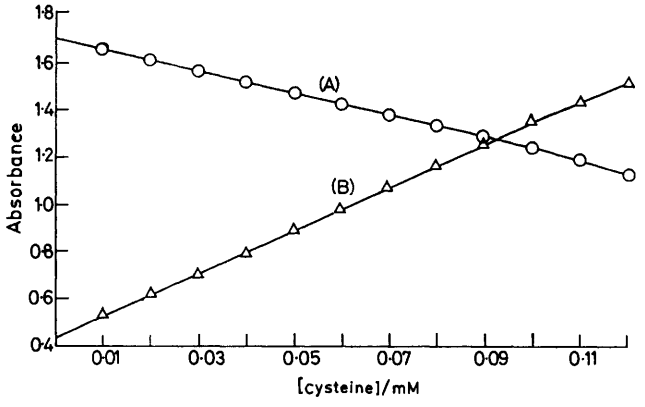
(5) a; R^1 = Me, R^2 = R^3 = H
b; R^1 = R^3 = Me, R^2 = H
c; R^1 = R^2 = R^3 = Me
d; R^1 = R^2 = R^3 = H



(6)

water at room temperature and an aqueous solution of sodium nitrite was added, an immediate precipitate of the bipyrimidinyl disulphide (5a, b, or c) was obtained. A similar disulphide (5d) was obtained by acidification of a solution of 2-mercaptopyrimidine and sodium nitrite in aqueous sodium hydroxide. Yields were high and the reaction seems preferable for the production of such compounds to the method involving iodine in alkaline solution. A similar reaction with 4-amino-6-hydroxy-2-mercaptopyrimidine did, however, yield the 5-nitroso-derivative (6).

Some bipyridinyl disulphides and the bipyrimidinyl disulphide (5d) have been reported [22-24] to be useful



Calibration curve of the disulphide (5b)–cysteine system: (A) absorbance at 236 nm; (B) absorbance at 280 nm

reagents for the determination of thiol groups, with which some such disulphides react according to equation (i).

$$PyS\text{–}SPy + 2RSH \rightleftharpoons RS\text{–}SR + 2PySH \quad (i)$$

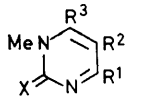
The u.v. spectra of the mercaptopyrimidines and the bipyrimidinyl disulphides are very different (Table), since the 2- and 4-mercaptopyrimidines exist in the thione form. This difference could afford a convenient method for the determination of thiol groups in solution. The bipyrimidinyl disulphides (5a—d) all reacted rapidly with cysteine in aqueous buffer (pH 7.0)–methanol at room temperature. The Figure is a typical calibration graph, showing the range of linearity. Further investigations of this reaction and is applicability are in hand and the usefulness of the mercaptopyrimidine ⟶ bipyrimidinyl disulphide reaction for the spectrophotometric determination of nitrite is also being studied.

Absorption maxima for the bipyrimidinyl disulphides (5a—d) and the corresponding pyrimidinethiones

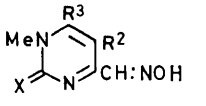
Pyrimidine-2-thione	$\lambda_{max.}$/nm	Disulphide	$\lambda_{max.}$/nm
2-Mercaptopyrimidine	276	(5a)	235
4-Methyl-	280	(5b)	236
4,6-Dimethyl-	281	(5c)	241
4,5,6-Trimethyl-	277	(5d)	239

Whereas the mercapto-methylpyrimidines do not seem to undergo attack at the methyl group when treated with nitrous acid, the 2-amino-methylpyrimidines seem to undergo both deamination and *C*-nitrosation.[11] When 2-amino-4-methylpyrimidine was dissolved in acetic acid at room temperature and aqueous sodium nitrite was added, a mild exothermic reaction occurred and cooling the solution caused deposition of crystalline 2-hydroxy-4-hydroxyiminomethylpyrimidine (2a). A similar reaction with 2-amino-4-methyl-6-phenylpyrimidine gave the analogous product (2d).

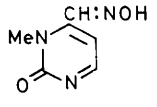
Dissolution of 2-amino- or 2-hydroxy-4,6-dimethylpyrimidine in glacial acetic acid at room temperature followed by addition of sodium nitrite resulted in the bishydroxyiminomethyl derivative (2c) and not the monohydroxyiminomethyl product (2b) formed in aqueous solution. The increased solubility of the compound (2b) in acetic acid relative to water is an important factor in bringing about the second nitrosation. 2-Amino- and 2-hydroxy-4,5,6-trimethylpyrimidine form



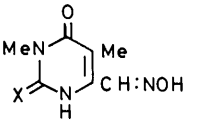
(7) a; R^1 = R^2 = H, R^3 = Me, X = O
b; R^1 = R^3 = Me, R^2 = H, X = O
c; R^1 = R^2 = R^3 = Me, X = O
d; R^1 = R^2 = R^3 = Me, X = S



(8) a; R^2 = H, R^3 = CH:NOH, X = O
b; R^2 = H, R^3 = CH:NOH, X = S



(9)



(10) a; X = O
b; X = S

an analogous product (2e) under similar conditions. However, when either 2-amino-4,6-dimethyl- or 2-amino-4,5,6-trimethylpyrimidine is treated with sodium nitrite in aqueous solution, the product precipitated is a monohydroxyiminomethyl derivative, but n.m.r. and elemental analytical data show that a mixture of de-

[22] R. E. Humphrey, W. Hinze, and W. M. Jenkines, *Analyt. Chem.*, 1971, **43**, 140.

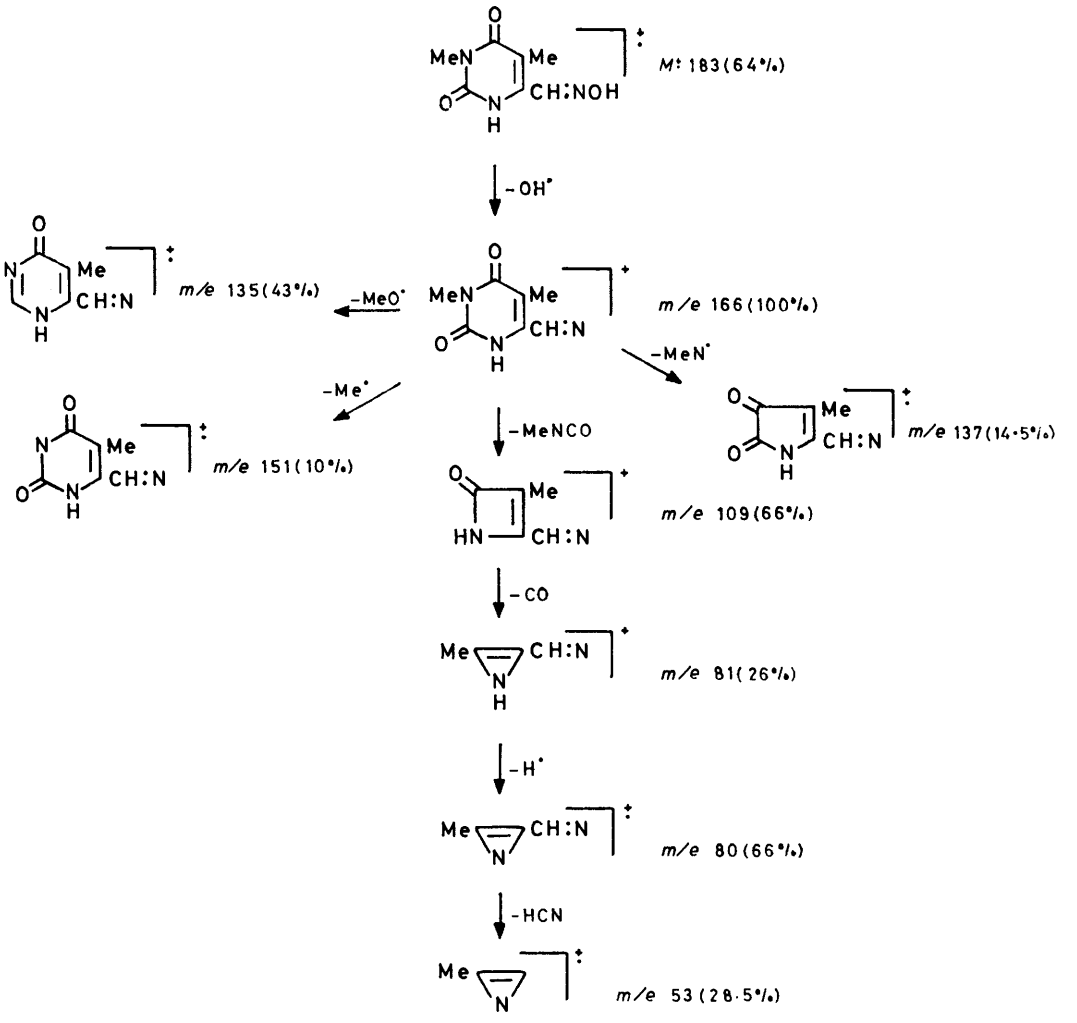
[23] D. R. Grassetti and J. F. Murray, *Analyt. Chim. Acta*, 1969, **46**, 139.

[24] D. R. Grassetti and J. F. Murray, *Arch. Biochem. Biophys.*, 1967, **119**, 41.

aminated and amino-monohydroxyiminomethyl derivatives is present. We have so far been unable to effect a satisfactory separation of these mixtures by t.l.c.

We have also investigated the reactions of sodium nitrite in aqueous acetic acid solution with the *N*-methylpyrimidones and pyrimidinethiones (7a—e). The 5-methyl group is not attacked by nitrous acid, in contrast to the ' activated ' 2-, 4-, and 6-methyl groups, and the

The rates and courses of reactions between nitrous acid and pyrimidines appear to be dependent on the presence and orientation of substituents, the temperature, and the solvent. A variety of different reactions occur with different pyrimidines, and the products may be useful intermediates. For example, dehydration of hydroxyiminomethylpyrimidines provides a convenient route to cyanopyrimidines, exemplified by the conversion



SCHEME Fragmentation of 4-hydroxyiminomethyl-1,5-dimethylpyrimidine-2,6-dione (10a)

N-methyl group was expected to be similarly inactive. Under the conditions so far investigated we have isolated the bishydroxyiminomethyl derivatives (8a and b) and the monohydroxyiminomethyl derivative (9). However, from the reaction of 1,4,5,6-tetramethylpyrimidin-2-one (7c) with sodium nitrite in aqueous acetic acid the only product isolated so far is the dione (10a). The structure has been confirmed by spectroscopic and elemental analysis, the principal mass spectroscopic fragment ions being shown in the Scheme. We have also isolated the product (10b) from a similar reaction with the thione. This reaction represents a novel demethylation.

of (2a) into 2-chloro-4-cyanopyrimidine [4] and our conversion of (2c) into 2-chloro-4,6-dicyanopyrimidine.[25] However, there are may points of interest regarding pyrimidine–nitrous acid reactions that need to be clarified. For example, the 2-methyl substituent in 4-hydroxy-2-methylpyrimidine and the 4-methyl substituent in 2-hydroxy-4-methylpyrimidine seem to react differently, and the methyl groups in 2,4-dihydroxy-6-methyl- and 2,4-dimethyl-6-hydroxypyrimidine do not seem to react. 2-Amino-4-methylpyrimidine undergoes deamination at room temperature whereas 2,4-diamino-

[25] D. T. Hurst, unpublished work.

6-dimethylaminopyrimidine seems to undergo [26] 5-nitrosation without deamination at 80 °C.

EXPERIMENTAL

N.m.r. spectra were recorded with a Perkin-Elmer R10 60 MHz spectrometer, and mass spectra with an A.E.I. MS9 spectrometer. Elemental analyses were carried out by the Butterworth Microanalytical Consultancy.

Bipyrimidin-2-yl Disulphide.—2-Mercaptopyrimidine (1.0 g) was dissolved in 4M-sodium hydroxide (10 ml) and sodium nitrite (0.8 g) in water (5 ml) was added. The mixture was stirred at room temperature while 4M-hydrochloric acid was added dropwise until no further precipitation occurred. The precipitate (*ca.* 100%) crystallized from ether–ethanol as needles, m.p. 138—139° (lit.,[27] 139—140°).

Bis-4-methylpyrimidin-2-yl disulphide was obtained similarly in 100% yield; m.p. 103—105° (from ether–light petroleum) (lit.,[27] 108—109°).

Bis-4,6-dimethylpyrimidin-2-yl Disulphide.—2-Mercapto-4,6-dimethylpyrimidine hydrochloride (1.0 g) was dissolved in water (10 ml) and sodium nitrite (0.8 g) in water (5 ml) was added dropwise with stirring. The white precipitate was collected and recrystallised from ethanol–light petroleum (b.p. 40—60 °C) to give needles (100%), m.p. 162—163° (lit.,[28] 162—163°).

Bis-4,5,6-trimethylpyrimidin-2-yl disulphide was obtained similarly in quantitative yield as crystals, m.p. 196—198° (from ethanol–ether) (Found: C, 54.7; H, 6.0; N, 18.4. $C_{14}H_{18}N_4S_2$ requires C, 54.9; H, 5.9; N, 18.3%).

Determination of Cysteine.—Solutions of the bipyrimidinyl disulphide (0.4mM) were made in phosphate buffer–methanol (pH 7.0) and various amounts of a solution of reagent grade cysteine hydrochloride were added together with the diluent until the final volume was 3.00 ml. The absorbances were measured at the maxima of the disulphide and the mercaptopyrimidine against a solvent blank.

2-Hydroxy-4-hydroxyiminomethylpyrimidine (2a).[4]—*From 2-amino-4-methylpyrimidine.* 2-Amino-4-methylpyrimidine (1.0 g) was dissolved in glacial acetic acid (10 ml) and sodium nitrite (1.4 g) in water (10 ml) was added. A mild exothermic reaction occurred and the mixture was stirred at ambient temperature for 10 min. Water (10 ml) was added and the mixture was cooled in ice overnight. The product (0.4 g, 35%) was obtained as a pale yellow solid which was washed with water and dried; m.p. 200—205° [lit.[4] (for anhydrous product), 226°], τ (CF_3·CO_2H) 1.63 (d, 6-H), 2.25 (s, 4-CH:N), and 3.2 (d, 5-H) (1 : 1 : 1) (Found: C, 38.3; H, 4.3; N, 26.1. Calc. for $C_5H_5N_3O_2,H_2O$; C, 38.2; H, 4.4; N, 26.8%), $M^{+\cdot}$ (anhydrous product) 139.

2-Amino-4-methyl-6-phenylpyrimidine [29] (*Simplified Synthesis*).—Benzoylacetone (8.7) and guanidinium carbonate (8.0 g) were intimately mixed, a few drops of water were added, and the mixture was heated on a water-bath for 6 h. The solid residue was recrystallised from aqueous ethanol to give 30% of product, m.p. 169—172° (lit., 172—173°).

2-Hydroxy-4-hydroxyiminomethyl-6-phenylpyrimidine (2d).[3]—*From 2-amino-4-methyl-6-phenylpyrimidine.* 2-Amino-4-methyl-6-phenylpyrimidine (0.5 g) was dissolved in glacial acetic acid (10 ml) and sodium nitrite (0.35 g) in water (10 ml) was added dropwise with stirring. The pale yellow mixture was warmed on a water-bath for ½ h then cooled and diluted with water to yield a yellow solid (33%). This product was identical with that obtained by a similar reaction from the 2-hydroxy-derivative; m.p. 224—226° (lit.,[3] 236°) (Found: C, 60.9; H, 4.2; N, 19.5. Calc. for $C_{11}H_9N_3O_2$: C, 61.4; H, 4.2; N, 19.5%).

Action of Aqueous Sodium Nitrite on 2-Amino-4,6-dimethylpyrimidine (cf. *Ref.* 3).—The aminopyrimidine (1.0 g) was dissolved in water (20 ml) containing 4M-hydrochloric acid (1 ml) and to this was added sodium nitrite (0.7 g) in water (5 ml). The mixture was heated to 100 °C. The precipitate was collected, washed, and dried (0.25 g); m.p. >200° (decomp.), τ (CF_3·CO_2H) 7.7 (s, 6-Me), 3.4 (s, 5-H in 2-NH_2 compound), 2.95 (s, 5-H in 2-OH compound), and 2.1 (s, 4-CH:N) (6 : 1 : 1 : 2).

Action of Aqueous Sodium Nitrite on 2-Amino-4,5,6-trimethylpyrimidine.—The trimethylpyrimidine was treated as above to yield a pale yellow product [0.6 g; m.p. *ca.* 215° (decomp.)] similar to the above, a mixture of the deaminated and amino-monohydroxyiminomethyl derivatives, τ (CF_3·CO_2H) 8.0 (s, 5-Me) 7.85 (s, 5-Me), 7.65 (s, 4-Me), and 2.15 (s, C-CH:N) (1.6 : 1.4 : 3 : 1) (Found: C, 50.9; H, 6.0; N, 29.1, 29.0. Calc for $C_6H_9N_3O_2$: C, 50.5; H, 6.0; N, 25.3. Calc. for $C_7H_{10}N_4O$: C, 50.6; H, 6.2; N, 33.7%).

2-Hydroxy-4,6-bishydroxyiminomethylpyrimidine (2c).—(a) *From 2-amino-4,6-dimethylpyrimidine.* The amino-compound (5.0 g) was dissolved in glacial acetic acid (40 ml) and sodium nitrite (8.4 g) in water (20 ml) was added in portions with stirring. A mild exothermic reaction occurred and a yellow, crystalline, product separated. The mixture was left for ½ h then the *product* was collected, washed with water, ethanol, then ether, and air-dried; yield 40%, m.p. 245—250° (decomp.), τ (CF_3·CO_2H) 3.4 (s, 5-H) and 2.4 (s, 4- and 6-CH:N) (1 : 2), $M^{+\cdot}$ 182 (Found: C, 39.5; H, 3.9; N, 30.5. $C_6H_6N_4O_3$ requires C, 39.5; H, 3.3; N, 30.7%).

(b) *From 2-hydroxy-4,6-dimethylpyrimidine hydrochloride.* The hydroxy-compound (2.0 g) was dissolved in glacial acetic acid (20 ml) and water (5.0 ml) then sodium nitrite (1.5 g) in water (5.0 ml) was added, with stirring. The yellow product (70%) was identical with that described above.

2-Hydroxy-4,6-bishydroxyiminomethyl-5-methylpyrimidine (2e).—(a) *From 2-amino-4,5,6-trimethylpyrimidine.* The amino-compound (2.0 g) was dissolved in 50% aqueous acetic acid (50 ml) with gentle warming then sodium nitrite (2.0 g) in water (20 ml) was added in portions with stirring. After 1—2 min the mixture darkened, a mild exothermic reaction occurred, and a yellow-brown precipitate formed. The mixture was cooled to 0 °C and the *product* was collected, washed with ethanol followed by ether, and dried in the oven; yield 50%, m.p. 205° (decomp.), τ (CF_3·CO_2H) 1.8 (s, 4- and 6-CH:N) and 7.8 (s, 5-Me) (2 : 3), $M^{+\cdot}$ 196 (Found: C, 43.6; H, 4.5; N, 27.4. $C_7H_8N_4O_3$ requires C, 42.9; H, 4.1; N, 28.5%).

(b) *From 2-hydroxy-4,5,6-trimethylpyrimidine.* An identical product was formed in 60% yield when the hydroxy-derivative was treated as above.

6-Hydroxyiminomethyl-1-methylpyrimidin-2-one (9).—1,6-Dimethylpyrimidin-2-one [30] (1 g) was dissolved in 4M-hydrochloric acid (5.0 ml) and aqueous sodium nitrite (1.0 g in

[26] B. Roth, J. M. Smith, and M. E. Hultquist, *J. Amer. Chem. Soc.*, 1950, **72**, 1914.

[27] D. R. Grassetti, J. F. Murray, M. E. Brokke, and A. D. Gutman, *J Medicin. Chem.*, 1967, **10**, 1170.

[28] F. Angerstein, *Ber.*, 1901, **34**, 3963.

[29] (*a*) P. N. Evans, *J. prakt. Chem.*, 1892, **46**, 352; (*b*) P. B. Russell, *J. Chem. Soc.*, 1954, 2951.

[30] D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc.* (*C*), 1967, 1928.

3.0 ml) was added dropwise with stirring. After ½ h at room temperature the mixture was cooled in ice and the yellow crystalline product was collected, washed with water, and air dried; yield 35%, m.p. 120°, $M^{+\cdot}$ 153, τ [$(CD_3)_2SO$] 1.25 (d, 6-H), 1.35 (s, 4-CH:N), 2.8 (d, 5-H), and 6.3 (s, 1-Me) (1 : 1 : 1 : 3).

4,6-*Bishydroxyiminomethyl*-1-*methylpyrimidin*-2-*one* (8a).—1,4,6-Trimethylpyrimidin-2-one [31] (1.0 g) was dissolved in glacial acetic acid (5 ml) by gentle warming. Aqueous sodium nitrite (1.0 g in 3.0 ml) was added. The yellow crystalline *precipitate* was collected, washed with water and ethanol, and dried; yield 75%, m.p. 226—230°, $M^{+\cdot}$ 196, τ (CF_3·CO_2H) 1.5 (s, 4-CH:N), 1.9 (s, 6-CH:N), 2.4 (s, 5-H), and 6.0 (s, 1-Me) (1 : 1 : 1 : 3) (Found: C, 43.4; H, 4.1; N, 29.0. $C_7H_8N_7O_3$ requires C, 42.9; H, 4.1; N, 28.5%).

4,6-*Bishydroxyimino*-1-*methylpyrimidine*-2-*thione* (8b), m.p. 191—200° (decomp.), was similarly obtained in 35% yield from 1,4,6-trimethylpyrimidine-2-thione.[29]

1,4,5,6-*Tetramethylpyrimidin*-2-*one Hydrochloride* (7).—3-Methylpentane-2,4-dione (11.5 g) was added to a solution of *N*-methylurea (7.0 g) in ethanol (85 ml), and concentrated hydrochloric acid (18 ml) was then added. The mixture was refluxed for 3 h then left to cool to room temperature overnight. The crystalline *product* (81%) had m.p. 263°, τ (CF_3·CO_2H) 6.1 (s, 1-Me), 7.15 (s, 4-Me), 7.2 (s, 6-Me), and 7.6 (s, 5-Me) (1 : 1 : 1 : 1), $\lambda_{max.}$ (AcOH) 320 nm (Found: C, 51.4; H, 6.8; N, 15.1. $C_8H_{13}N_2O$,HCl requires C, 51.0; H, 6.9; N, 14.9%).

4-*Hydroxyiminomethyl*-1,5-*dimethylpyrimidine*-2,6-*dione* (10a).—1,4,5,6-Tetramethylpyrimidin-2-one (1.0 g) was dissolved in glacial acetic acid (5.0 ml) and aqueous sodium nitrite (1.0 g in 3.0 ml) was added, with stirring. The mixture was then left to cool overnight in ice, and the light brown *solid* obtained was washed with water and dried; yield 65%, m.p. 258° (darkening at 216°), $M^{+\cdot}$ 183, $\lambda_{max.}$ (AcOH) 360 and 265 nm, τ (CF_3·CO_2H) 1.75 (s, 4-CH:N), 6.5 (s, 1-Me), and 7.85 (s, 5-Me) (1 : 3 : 3) (Found: C, 45.9; H, 4.9; N, 22.9. $C_7H_9N_2O$ requires C, 45.9; H, 4.9; N, 23.0%).

1,4,5,6-*Tetramethylpyrimidine*-2-*thione Hydrochloride* (7).—To a solution of *N*-methylthiourea (7.0 g) in ethanol (85 ml) were added 3-methylpentane-2,4-dione (10 g) and concentrated hydrochloric acid (18 m.). The mixture was refluxed for 3 h; on cooling a yellow *precipitate* formed which was collected, recrystallised from ethanol, and dried; yield 90%, m.p. >250° (darkens at 237°), τ (CF_3·CO_2H) 5.8 (s, NMe), 7.2 (s, 4-Me), 7.3 (s, 6-Me), and 7.6 (s, 5-Me) (1 : 1 : 1 : 1) (Found: C, 46.8; H, 6.3; N, 14.1. $C_8H_{12}N_2S$,-HCl requires C, 46.8; H, 6.3; N, 13.7%).

4-*Hydroxyimino*-1,5-*dimethylmethyl*-2-*thioxopyrimidin*-6-*one* (10b).—1,4,5,6-Tetramethylpyrimidin-2-thione hydrochloride (1.0 g) was dissolved in glacial acetic acid (10 ml) and aqueous sodium nitrite (1.0 g in 3.0 ml) was added dropwise with stirring. The mixture was then heated on a water-bath for ½ h until the mixture was red. The mixture deposited a red crystalline *product* on cooling overnight. This was collected, washed with water, and dried; yield 50%, m.p. 170° (decomp.), τ (CF_3·CO_2H) 1.65 (s, 4-CH:N), 5.8 (s, NMe), and 7.4 (s, 5-Me) (1 : 3 : 3), $M^{+\cdot}$ 199 (Found: C, 42.6; H, 4.2; N, 21.1. $C_7H_9N_3O_2S$ requires C, 42.4; H, 4.25; N, 21.1%).

[7/149 *Received*, 28*th January*, 1977]

[31] W. J. Hale and A. G. Williams, *J. Amer. Chem. Soc.*, 1915 **37**, 594.