690. *Pyrimidine Reactions. Part X.*[1] *The Methylation of Triaminopyrimidines; Conversion of the Resulting Imines into Pteridines*

By D. J. Brown and N. W. Jacobsen

4,5,6- and 2,4,5-Triaminopyrimidine are shown to react with methyl iodide to give strong imino-bases (5,6-diamino-1,4-dihydro-4-imino-1-methylpyrimidine and 4,5-diamino-1,2-dihydro-2-imino-1-methylpyrimidine, respectively). The first of these imines reacts with α-dicarbonyl compounds to give pteridines (*e.g.*, 3,4-dihydro-4-imino-3-methylpteridine) which are not otherwise obtainable. The second imine condenses with ethyl glyoxylate hemiacetal, with an accompanying rearrangement to give 7-hydroxy-2-methylaminopteridine. 5-Amino-1,4-dihydro-4-imino-1-methylpyrimidine also reacts with this hemiacetal but the 3,7-dihydro-3-methyl-7-oxopteridine, formed initially, decomposes *in situ* to yield 3-amino-2-formyl-5-hydroxypyrazine.

5-Amino-4,6-bismethylaminopyrimidine is shown to undergo an unusual extranuclear *N*-methylation with methyl iodide, giving 4,5,6-trismethylaminopyrimidine. 5-Formamido-4,6-bismethylaminopyrimidine however gives two purinium iodides of yet unconfirmed structure.

Ionisation constants and spectra of the compounds were determined and are discussed.

Many pteridines are best made by condensing a 4,5-diaminopyrimidine with an α-dicarbonyl compound. We have now extended this synthesis to use aminoiminopyrimidines, particularly those hitherto unknown examples derived from triaminopyrimidines by methylation.

4,5-Diaminopyrimidine and methyl iodide have been shown[2] to yield 5-amino-1,4-dihydro-4-imino-1-methylpyrimidine (I; R = NH, R′ = H). This imine, treated in alkaline solution with ethyl glyoxylate hemiacetal, gave directly 3-amino-2-formyl-5-hydroxypyrazine (II; R = R′ = H), which was clearly a degradation product of 3,7-dihydro-3-methyl-7-oxopteridine initially formed in the condensation. This imine, moreover, did not condense satisfactorily with either glyoxal or diacetyl.

4,5,6-Triaminopyrimidine (pK_a 5·78[3]) reacted with methyl iodide to give 5,6-diamino-1,4-dihydro-4-imino-1-methylpyrimidine (I; R = NH, R′ = NH_2), a strong base (pK_a

[1] Part IX, D. J. Brown and J. M. Lyall, *Austral. J. Chem.*, 1965, **18**, in the press.
[2] D. J. Brown and N. W. Jacobsen, *J.*, 1962, 3172.
[3] S. F. Mason, *J.*, 1954, 2071.

12·1) of unambiguous structure. With the above hemiacetal under mildly alkaline conditions, it furnished a pteridine (pK_a 1·7). Of the seven possible pteridine products it was shown to be 4-amino-1,7-dihydro-1-methyl-7-oxopteridine (III; R = NH_2, R′ = H) as follows. Four of the possible products could be formed directly: the pteridine (III; R = NH_2, R′ = H), its 3-methyl isomer, the imine (IV; R = OH, R′ = H), and its 1-methyl isomer. Dimroth rearrangement [4] of the second and third of these could give, respectively, 7- and 6-hydroxy-4-methylaminopteridine, and similar rearrangement of the pyrimidine intermediate prior to condensation could eventually yield, in addition to the last two mentioned, 4-amino-7,8-dihydro-8-methyl-7-oxopteridine. All except the two of these, which have an *N*-1-methyl group, are eliminated by the alkaline degradation of the pteridine to 2-carbamoyl-5-hydroxy-3-methylaminopyrazine (II; R = NH_2, R′ = Me) of known structure (see below). Since one of these, 1,4-dihydro-6-hydroxy-4-imino-1-methylpteridine, cannot exist in an amino-oxo-form, it would necessarily be a strong base and is thereby eliminated; the pteridine has therefore the structure (III; R = NH_2, R′ = H).

The above pyrazine was synthesised by condensing 5,6-diamino-1,4-dihydro-1-methyl-4-oxopyrimidine [5] (I; R = O, R′ = NH_2) with ethyl glyoxalate hemiacetal in alkaline solution to give 1,4(1,7)-dihydro-7(4)-hydroxy-1-methyl-4(7)-oxopteridine (III; R = OH, R′ = H), and then degrading the pteridine. The remote possibility that the hydroxy-oxopteridine might be either 1,4-dihydro-6-hydroxy-1-methyl-4-oxopteridine or (4(7)-hydroxy-7,8(4,8)-dihydro-8-methyl-7(4)-oxopteridine (formed by Dimroth rearrangement of the pyrimidine intermediate prior to condensation) was eliminted by the close similarity of the ultraviolet spectrum of the derived pyrazine anion to that of 5-amino-2-carbamoyl-3-methylaminopyrazine as neutral molecule.[5] The pyrazine in question has therefore the structure (II; R = NH_2, R′ = Me) based on the R. Norman Jones rule; [6] the pyrazines derived from the other postulated pteridines would certainly differ from it in their anionic spectra.

With ethyl pyruvate, the imine (I; R = NH, R′ = NH_2) gave 4-amino-1,7-dihydro-1,6-dimethyl-7-oxopteridine (III; R = NH_2, R′ = Me), a structural assignment based on analogy with the previous reaction and the spectral similarity of the two pteridines (see Table).

Although the same imine did not condense cleanly with glyoxal in alkali, it did so in ethanolic hydriodic acid to give 3,4-dihydro-4-imino-3-methylpteridine (IV; R = R′ = H), isomeric with the 1-methyl derivative obtained by direct methylation of 4-aminopteridine.[7] In alkali this iminopteridine was not degraded to a pyrazine, but rapidly ($t_{\frac{1}{2}} < 1$ min. at pH 14·0 and 20°) underwent Dimroth rearrangement [4] to the known [7] 4-methylaminopteridine. The similarly formed homologue, 3,4-dihydro-4-imino-3,6,7-trimethylpteridine (IV; R = R′ = Me), was identified by analysis, its spectrum, and its difference from the known [7] 1,6,7-trimethyl isomer.

Unlike 4,5,6-triaminopyrimidine, 5-amino-4,6-bismethylaminopyrimidine [7] (V; R = NH_2, R′ = NHMe) reacted with methyl iodide to give 4,5,6-trismethylaminopyrimidine (V; R = R′ = NHMe), a relatively weak base of pK_a 6·0. Excluding examples in which a Dimroth rearrangement had occurred (*e.g.*, during the methylation of 4,6-diamino-5-nitropyrimidine [7]) this appears to be the first reported methylation of a 2- or 4-aminopyrimidine not yielding a strong imino- or quaternary base, and suggests that steric factors may be involved. This is independently supported by the failure of 5-bromo-2-dimethylamino-4-methylaminopyrimidine and related compounds to undergo methylation.[8] The product was identified as follows: methylation on N-1 or N-3 was excluded by the ionisation constant and by the n.m.r. spectrum which showed symmetry in the molecule by the

[4] D. J. Brown and J. S. Harper, *J.*, 1963, 1276.
[5] D. J. Brown and N. W. Jacobsen, *J.*, 1965, 1175.
[6] R. N. Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127.
[7] D. J. Brown and N. W. Jacobsen, *J.*, 1960, 1978.
[8] D. J. Brown and T. Teitei, *J.*, 1965, 755.

equivalence of the methyl proton signals from the 4- and 6-methylamino-groups ($\tau = 7{\cdot}00$). There remained but three possible structures for the methylated pyrimidine; one of these, 5-amino-2-methyl-4,6-bismethylaminopyrimidine (pK_a 6·92), was excluded by its preparation from 4,6-dichloro-2-methyl-5-nitropyrimidine[9,10] by full methylamination to 2-methyl-4,6-bismethylamino-5-nitropyrimidine and subsequent hydrogenation of the nitro-group. The second possibility, 5-amino-4-dimethylamino-6-methylaminopyrimidine[11] (V; R = NH_2, R′ = NMe_2) of pK_a 5·35, was also made unambiguously, from 4-chloro-6-methylamino-5-nitropyrimidine[12] (V; R = NO_2, R′ = Cl) by dimethylamination to (V; R = NO_2, R′ = NMe_2) followed by reduction. Thus, by elimination, the methylation product was 4,5,6-trismethylaminopyrimidine. Our first attempt at its unambiguous synthesis, by formylating the triamine (V; R = NH_2, R′ = NHMe) to the formamidopyrimidine (V; R = NHCHO, R′ = NHMe) and subsequent reduction

Ionisation constants and ultraviolet spectra

Compound	pK_a *	$\lambda_{max.}$ (mμ)	log ε †	pH
Pteridine derivatives				
4-Amino-1,7-dihydro-1,6-dimethyl-7-oxo-		231, 248, *251*, *326*, 336, 350	4·28, 4·30, *4·29*, *4·15*, 4·21, 4·08	5·0
cation	1·97 ± 0·02	219, 242, *248*, 290, *317*, 325, *335*	4·09, 4·21, *4·15*, 3·86, *4·06*, 4·10, *4·06*	−0·20
anion	13·82 ± 0·05			
4-Amino-1,7-dihydro-1-methyl-7-oxo-		231, 252, *257*, *329*, 338, 351	4·27, 4·30, *4·29*, *4·08*, 4·13, 4·00	7·0
cation	1·70 ± 0·04	220, 242, *251*, 289; *316*, 326, 338	4·17, 4·19, *4·04*, 3·73, *3·98*, 4·08, 4·05	−0·5
anion	13·24 ± 0·04			
1,4(1,7)-Dihydro-7(4)-hydroxy-1-methyl-4(7)oxo-		230, *239*, 295, 325	4·28, *4·25*, 3·88, 3·97	1·3
anion	3·54 ± 0·03(1·01) ‡	226, 244, *250*, 280, *324*, 333, 346	4·35, 4·30, *4·25*, 3·56, *4·05*, 4·11, 3·98	5·7
3,4-Dihydro-4-imino-3-methyl-				14·0 §
cation	9·5 **	236, *311*, 320, *330*	4·03, *3·78*, 3·79, *3·62*	7·0
3,4-Dihydro-4-imino-3,6,7-trimethyl-				14·0 §
cation	10·5 **	237, *313*, 318, *340*	4·12, *3·92*, 3·94, *3·55*	7·0
7-Hydroxy-2-methylamino-		215, 238, 294, 355	4·33, 4·05, 3·71, 4·21	5·0
cation	2·08 ± 0·03	228, 264, *286*, 336	4·16, 3·86, *3·97*, 3·89	−0·2
anion	7·59 ± 0·02	230, 278, 351, *359*	4·58, 3·83, 4·18, *4·15*	10·3
5,6,7,8-Tetrahydro-5,8-dimethyl-4-methylamino-6,7-dioxo-		214, 229, *245*, *310*, 326	4·11, 4·26, *4·10*, *3·91*, 3·93	6·4
cation	1·53 ± 0·05	235, 318	4·22, 4·11	−1·0
Purine derivatives				
1,6-(or 3,6)-Dihydro-1,7,9(or 3,7,9)-trimethyl-6-methylimino-				14·0 §
cation	12 ††	213, 287	4·09, 4·18	7·0
7,9-Dimethyl-6-methylamino-				14·0 §
cation	11 ††	*270*, 280	*4·10*, 4·15	7·0
2-Methylamino-		219, 240, 319	4·42, 3·88, 3·74	7·0
cation	4·01 ± 0·02(0·005) ‡	223, *244*, 327	4·55, *3·81*, 3·57	1·8
anion	10·32 ± 0·06	226, 272, 316	4·37, 3·48, 3·72	12·5
9-Methyl-6-methylamino-		209, 267	4·27, 4·20	6·5
cation	4·12 ± 0·03	209, 264, *271*	4·25, 4·23, *4·17*	1·9
9-Methyl-6-methylamino-2-methylthio-		214, 241, 281	4·12, 4·32, 4·19	5·5
cation	3·02 ± 0·04	211, 253, 274, *282*	4·21, 4·11, 4·15, *4·14*	0·8

[9] J. Baddiley and A. Topham, *J.*, 1944, 678.
[10] A. Albert, D. J. Brown, and H. C. S. Wood, *J.*, 1954, 3832.
[11] D. Söll and W. Pfleiderer, *Chem. Ber.*, 1963, **96**, 2977.
[12] D. J. Brown, *J. Appl. Chem.*, 1957, **7**, 109.

TABLE (*Continued*)

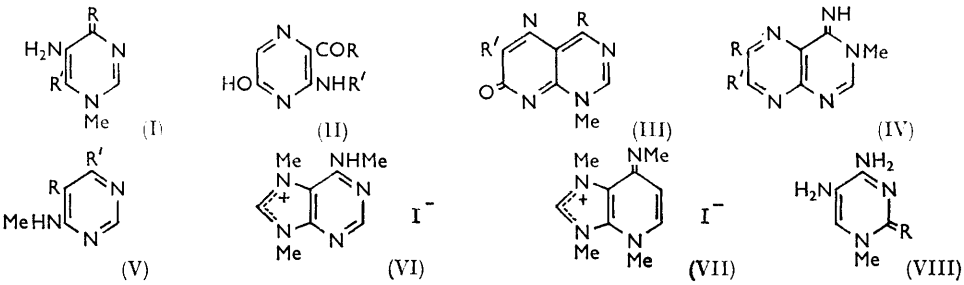
Compound	pK_a *	$\lambda_{max.}$ (mμ) †	log ε †	pH
Pyrazine derivatives				
3-Amino-2-formyl-5-hydroxy- ‡‡				
cation	−1·34 ± 0·05	284, 364	4·05, 4·10	−3·55
2-Carbamoyl-5-hydroxy-3-methylamino-		227, 277, 362	3·54, 4·21, 4·19	5·3
cation	−0·92 ± 0·05	266, 370	4·10, 4·10	−3·1
anion	7·48 ‡‡	211, 277, 355	4·28, 4·19, 4·12	9·7
2-Formyl-5-hydroxy-3-methylamino- ‡‡				
cation	−1·05 ± 0·05	209, 288, 373	4·12, 4·06, 4·09	−3·25
Pyrimidine derivatives				
5-Amino-4-dimethylamino-6-methylamino-		226, 292	4·19, 4·04	7·5
cation	5·35 ± 0·02	235, 312	4·12, 4·14	3·0
4-Amino-5-formamido-2-methylamino-		232, 295	4·13, 3·78	9·0
cation	6·12 ± 0·01(0·01) ‡	216, *276*	4·39, *4·53*	3·0
5-Amino-2-methyl-4,6-bismethylamino-		222, 280	4·33, 3·90	10·3
cation	6·92 ± 0·03(0·01) ‡	225, 285	4·29, 4·08	4·5
4,6-Bismethylamino-2-methylthio-5-nitro-		216, *240*, 300, 360	4·38, *3·86*, 3·73, 4·20	6·0
cation	1·55 ± 0·02	227, 251, 303, 352	4·30, 4·25, 3·91, 4·15	−0·6
4,6-Bismethylamino-5-nitro-		215, *332*, 359	4·51, *3·89*, 4·07	5·0
cation	2·57 ± 0·03	242, 301, 352	4·35, 3·61, 3·87	−0·2
4,5-Diamino-1,2-dihydro-2-imino-1-methyl-		229, 296	4·22, 3·63	¶
cation	13·66 ± 0·05	226, *240*, 297	4·24, *4·07*, 3·72	7·0
5,6-Diamino-1,4-dihydro-4-imino-1-methyl-		222, 278	4·25, 3·87	14·3
cation	12·11 ± 0·05	219, 287	4·37, 3·98	7·0
4,6-Dihydroxy-2-methylthio-		243, 277	3·83, 3·96	2·6
anion	5·09 ± 0·04	207, *221*, 260, *270*	4·35, *4·14*, 3·92, *3·88*	7·4
4,6-Dihydroxy-2-methylthio-5-nitro-		217, 246, 328	4·31, 3·92, 4·01	−0·2
anion	2·00 ± 0·04	*235*, *267*, 337	*4·00*, *3·75*, 3·96	7·0
4-Dimethylamino-6-methylamino-5-nitro-		225, *244*, 368	4·41, *4·10*, 3·94	5·0
cation	2·90 ± 0·03	253, 304, 363	4·37, 3·52, 3·75	−0·2
5-Formamido-4,6-bismethylamino-		228, 264	4·60, 3·78	7·5
cation	5·00 ± 0·02	228, 272	4·43, 4·14	2·6
5-Formamido-4,6-bismethylamino-2-methylthio-		228, 275	4·62, 4·00	7·0
cation	4·17 ± 0·01	225, 245, 281	4·29, 4·43, 4·11	1·9
2-Methyl-4,6-bismethylamino-5-nitro-		214, *232*, 357	4·57, *4·13*, 4·15	6·0
cation	3·43 ± 0·02	244, 299, 350	4·36, 3·65, 3·95	−0·2
4,5,6-Trismethylamino-		227, 275	4·36, 3·98	8·5
cation	6·01 ± 0·03	228, 230, 280	4·12, 4·12, 4·14	3·5

* Constant determined at 20° spectroscopically (ionic buffer strength of 0·01M) except where otherwise indicated. The methods of A. Albert and E. P. Serjeant (" Ionization Constants of Acids and Bases," Methuen, London, 1962) were used. † Inflexions in italics. ‡ Potentiometrically at concentration (M). § Species unstable at this pH. ¶ Extinction coefficient determined by extrapolation. ** Constant estimated by analogy with the *N*-1-methyl isomer (cf. ref. 6). †† Approximate constant only. ‡‡ See ref. 3.

with lithium aluminium hydride, was a failure. However, when a methylthio-group was introduced to increase ether solubility,[13] the resulting 5-formamido-4,6-bismethylamino-2-methylthiopyrimidine was easily reduced and the crude product was desulphurised to give authentic 4,5,6-trismethylaminopyrimidine (V; R = R′ = NHMe). It proved identical with the methylation product above, and condensed with ethyl oxalate to give 5,6,7,8-tetrahydro-5,8-dimethyl-4-methylamino-6,7-dioxopteridine.

[13] B. R. Baker, R. E. Schaub, and J. P. Joseph, *J. Org. Chem.*, 1954, **19**, 638.

In an attempt to avoid the formation of 4,5,6-trismethylaminopyrimidine and in turn force substitution on a nuclear nitrogen atom, 5-amino-4,6-bismethylaminopyrimidine was formylated prior to methylation. However, the formamidopyrimidine (V; R = NHCHO, R′ = NHMe) reacted with methyl iodide to give a mixture of the mono- and di-methyl derivatives of 9-methyl-6-methylaminopurine. The n.m.r. spectrum of the first purine obtained under milder conditions showed three methyl signals (τ = 5·75, 5·85,



6·80) and was assigned the structure 7,9-dimethyl-6-methylaminopurinium iodide (VI) by analogy with the quaternary purines made by Pfleiderer and Sagi; [14] it was also obtained directly (but not unambiguously) by methylating 9-methyl-6-methylaminopurine. The n.m.r. spectrum of the second (dimethylated) product contained four methyl signals (τ = 5·75, 5·82, 6·20, 6·55) and it was therefore 1,6-dihydro-1,7,9-trimethyl-6-methyliminopurinium iodide or its 3,7,9-trimethyl isomer (VII).

2,4,5-Triaminopyrimidine (pK_a 7·63) [4] reacted with methyl iodide to give a strongly basic imine (pK_a 13·6) which must necessarily be its *N*-1- or *N*-3-methyl derivative. It was shown to be 4,5-diamino-1,2-dihydro-2-imino-1-methylpyrimidine (VIII; R = NH) by hydrolysis consequent on boiling the free base in water. Ammonia was lost and the oxopyrimidine (VIII; R = O) was identified with authentic material [15] by comparisons as base, picrate,[2] and the derived 2,3-dihydro-3,6,7-trimethyl-2-oxopteridine.[16]

When the base (VIII; R = NH) was condensed with ethyl glyoxylate hemiacetal in alkali, the pteridine produced underwent Dimroth rearrangement (see below) to give 7-hydroxy-2-methylaminopteridine. Its structure was confirmed by a second synthesis from 4,5-diamino-2-methylaminopyrimidine [17] and the hemiacetal in alkaline solution. The success of this reaction strongly supports the orientation of the hydroxy-group as 7 (not 6) because 7-hydroxypteridines are generally formed in such alkaline condensations whereas their 6-isomers require neutral or even acidic conditions.[11,18] The 7-hydroxy-configuration was independently confirmed (Jones's rule) [6] by the close similarity of the ultraviolet spectrum of the anion to that of the dianion of 2,7-dihydroxypteridine [19] and by its dissimilarity to that of 2,6-dihydroxypteridine [19] at the same pH. Dimroth rearrangement must have occurred after rather than before the original condensation to a pteridine, because the imine (VIII; R = NH) was stable under alkaline conditions similar to those used in that condensation.

Experimental

Analyses were done by Dr. J. E. Fildes and her staff. N.m.r. spectra were recorded on a Varian A60 spectrometer. Samples were dissolved in deuterium oxide and chemical shifts measured with respect to 3-trimethylsilyl-1-propanesulphonic acid sodium salt as internal reference.

[14] W. Pfleiderer and F. Sagi, *Annalen*, 1964, **673**, 78.
[15] D. J. Brown, *J. Appl. Chem.*, 1955, **5**, 358.
[16] D. J. Brown and S. F. Mason, *J.*, 1956, 3443.
[17] F. Bergmann, G. Levin, H. Kwietny-Govrin, and H. Ungar, *Biochim. Biophys. Acta*, 1961, **47**, 1.
[18] A. Albert, D. J. Brown, and G. Cheeseman, *J.*, 1952, 1620.
[19] A. Albert, J. H. Lister, and C. Pedersen, *J.*, 1956, 4621.

3-*Amino*-2-*formyl*-5-*hydroxypyrazine*.—5-Amino-1,4-dihydro-4-imino-1-methylpyrimidine hydriodide [2] (2·52 g.) and ethyl glyoxylate hemiacetal (2·2 g.) were refluxed in 2N-sodium carbonate (15 ml.) for 30 min. The solution, chilled and acidified to pH 1—2, gave the formylpyrazine (0·47 g.), decomp. *ca.* 222° (from water), identified with authentic material [3] by mixed m. p., chromatography, and infrared spectroscopy.

5,6-*Diamino*-1,4-*dihydro*-4-*imino*-1-*methylpyrimidine* (*or Tautomer*).—4,5,6-Triaminopyrimidine [20] (0·8 g.), methanol (28 ml.), and methyl iodide (10 ml.) were refluxed for 3 hr. Refrigeration gave the *imine hydriodide* (0·66 g.) and evaporation gave a further quantity (0·92 g.). Recrystallised from water and then 50% aqueous ethanol, the hydriodide had m. p. 260° (Found: C, 22·5; H, 3·55; N, 26·2. $C_5H_{10}IN_5$ requires C, 22·5; H, 3·75; N, 26·2%).

4-*Amino*-1,7-*dihydro*-1-*methyl*-7-*oxopteridine*.—When the above iminopyrimidine hydriodide (2·67 g.) and ethyl glyoxylate hemiacetal (2·2 g.) were shaken in 2N-sodium carbonate (15 ml.) at room temperature, the intermediate ethoxycarbonylmethyleneamino-derivative precipitated. The mixture was heated on a steam-bath for 1 hr. and then chilled. Recrystallisation of the solid from water gave the *oxopteridine* (1·3 g.), m. p. 345—350° (decomp.) (Found: C, 47·6; H, 4·1; N, 39·5. $C_7H_7N_5O$ requires C, 47·45; H, 4·0; N, 39·55%).

2-*Carbamoyl*-5-*hydroxy*-3-*methylaminopyrazine*.—The above oxopteridine (0·1 g.) was refluxed for 1 hr. in N-sodium hydroxide (1 ml.). Cooled and acidified to pH 2·5, the solution deposited the *pyrazine* (0·06 g.), decomposing at *ca.* 300° after recrystallising from water (Found: C, 42·6; H, 5·05; N, 33·6. $C_6H_8N_4O_2$ requires C, 42·85; H, 4·8; N, 33·35%).

1,4(1,7)-*Dihydro*-7(4)-*hydroxy*-1-*methyl*-4(7)-*oxopteridine*.—5,6-Diamino-1,4-dihydro-1-methyl-4-oxopyrimidine (2·65 g.)[5] and ethyl glyoxylate hemiacetal (4 g.) were shaken in a buffer of 5N-acetic acid (4·7 ml.), sodium acetate (4·7 g.), and water (20 ml.) at room temperature for 5 min. The yellow carbethoxymethyleneamino-derivative (3·3 g., m. p. 174—175°, from ethanol) was collected, washed with water and ethanol, and heated on the steam-bath with N-sodium hydroxide (30 ml.) for 30 min. Chilled and adjusted to pH 5·5, the solution deposited 2-carbamoyl-5-hydroxy-3-methylaminopyrazine (0·42 g.) identical with the specimen above. The filtrate was evaporated to dryness *in vacuo* and the residue was triturated with N-hydrochloric acid. The remaining *oxopteridine* (1·2 g.) had m. p. 275—280° (decomp.) after recrystallising from water (Found: C, 47·35; H, 3·45; N, 31·55. $C_7H_6N_4O_2$ requires C, 47·2; H, 3·4; N, 31·45%).

4-*Amino*-1,7-*dihydro*-1,6-*dimethyl*-7-*oxopteridine*.—5,6-Diamino-1,4-dihydro-4-imino-1-methylpyrimidine hydriodide (0·27 g.), ethyl pyruvate (0·14 g.), and 2N-sodium carbonate (1·5 ml.) were heated on a steam-bath for 15 min. Refrigeration gave the *amino-oxopteridine* (0·1 g.), m. p. *ca.* 330° (decomp.) (from water) (Found: C, 50·15; H, 4·8; N, 36·7. $C_8H_9N_5O$ requires C, 50·25; H, 4·75; N, 36·6%).

3,4-*Dihydro*-4-*imino*-3-*methylpteridine*.—The same iminopyrimidine hydriodide (0·6 g.), glyoxal monohydrate (0·26 g.), and ethanolic 0·1N-hydriodic acid (15 ml.) were refluxed for 10 min. under nitrogen. Chilling gave the yellow-green *iminopteridine hydriodide* (0·42 g.). m. p. 210° (decomp.) (from ethanol) (Found: C, 29·15; H, 2·8; N, 24·45. $C_7H_8IN_5$ requires C, 29·1; H, 2·8; N, 24·25%). Dissolved in warm N-sodium hydroxide (1·5 ml.), the hydriodide (0·15 g.) rearranged rapidly to deposit 4-methylaminopteridine (0·08 g.), m. p. 250—251° (from water), undepressed on admixture with authentic material.[6]

3,4-*Dihydro*-4-*imino*-3,6,7-*trimethylpteridine*.—The iminopyrimidine hydriodide (0·6 g.) and diacetyl (0·3 g.) reacted as above to give the homologous *iminopteridine hydriodide* (0·48 g.). Recrystallised from ethanol (with concentration) it had m. p. 224—225° (decomp.) (cf. 1,6,7-trimethyl isomer, m. p. 247°) [6] (Found: C, 33·75; H, 4·0; N, 21·85. $C_9H_{12}IN_5$ requires C, 34·1; H, 3·8; N, 22·1%).

5-*Formamido*-4,6-*bismethylaminopyrimidine*.—5-Amino-4,6-bismethylaminopyrimidine (2·5 g.) was heated on a steam-bath with 90% formic acid (25 ml.) for 1 hr. The residue from evaporation *in vacuo* was dissolved in water (5 ml.). Adjusted to pH 6 with ammonia, it gave the *formamidopyrimidine* (2·8 g.) which recrystallised from ethyl acetate on concentration and had m. p. 244—245° (efferves.) (Found: C, 46·3; H, 6·3; N, 38·5. $C_7H_{11}N_5O$ requires C, 46·4; H, 6·1; N, 38·65%).

Methylation of 5-*Formamido*-4,6-*bismethylaminopyrimidine*.—(*a*) The formamidopyrimidine (2·0 g.), methanol (50 ml.), and methyl iodide (25 ml.) were heated at 100° for 2 hr. and then concentrated. Chilling gave 7,9-*dimethyl*-6-*methylaminopurinium iodide* (1·8 g.), m. p. 260—

[20] R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Amer. Chem. Soc.*, 1953, **75**, 263.

261° (from ethanol with concentration) (Found: C, 31·55; H, 3·95; N, 22·7. $C_8H_{12}IN_5$ requires C, 31·5; H, 3·95; N, 22·95%).

(*b*) The formamido-derivative (0·5 g.) was rocked in methyl iodide (6 ml.) at 140° for 3 hr. When triturated with ethanol, the dark oil deposited yellow crystals (0·2 g.) of 1,6(or 3,6)-*dihydro*-6-*methylimino*-1,7,9(or 3,7,9)-*trimethylpurinium iodide*, m. p. 320° (from ethanol with concentration) (Found: C, 34·0; H, 4·55; I, 39·4; N, 21·8. $C_9H_{14}IN_5$ requires C, 33·85; H, 4·4; I, 39·75; N, 21·95%).

9-*Methyl*-6-*methylaminopurine*.—The above formamidopyrimidine (0·5 g.) was heated at 250° until effervescence ceased (5 min.). The purine (0·34 g.) had m. p. 185—186° (m. p. 190—191°, 193·5—195° by other methods [21,22]) (from ethanol) (Found: C, 51·65; H, 5·9; N, 42·9. Calc. for $C_7H_9N_5$: C, 51·5; H, 5·5; N, 42·9%). The purine (0·4 g.) rocked in methyl iodide (6 ml.) at 140° for 1 hr. gave 7,9-dimethyl-6-methylaminopurinium iodide (0·45 g.), m. p. 260°, undepressed on admixture with the product above.

4,5,6-*Trismethylaminopyrimidine*.—(*a*) 5-Amino-4,6-bismethylaminopyrimidine [2,7] (from 10 g. of 4,6-bismethylamino-5-nitropyrimidine) was refluxed for 4 hr. in methanol (80 ml.) and methyl iodide (30 ml.). Evaporation *in vacuo* gave the *trismethylaminopyrimidine hydriodide* (7·8 g.), m. p. 191—192° (from ethanol) (Found: C, 28·1; H, 4·65; N, 23·75. $C_7H_{14}IN_5$ requires C, 28·5; H, 4·8; N, 23·75%). An aqueous solution was adjusted to pH 8. Evaporation, extraction with benzene, and recrystallisation gave the base, m. p. 148—149° (Found: C, 50·4; H, 8·05; N, 41·9. $C_7H_{13}N_5$ requires C, 50·3; H, 7·85; N, 41·9%).

(*b*) 5-Formamido-4,6-bismethylamino-2-methylthiopyrimidine (5·0 g.) in dry pyridine (40 ml.) was added slowly to a refluxing solution of lithium aluminium hydride (5·0 g.) in dry ether (400 ml.). After 2 hr. a further quantity (2·0 g.) of the hydride was added, and refluxing was continued for 1 hr. Ethyl acetate (40 ml.), water (40 ml.), and 5N-sodium hydroxide (75 ml.) were in turn added *cautiously*. The combined organic layer and the ethyl acetate extracts (3 × 50 ml.) of the pasty residue were dried ($MgSO_4$), decolourised (charcoal), and evaporated *in vacuo*. The heavy residual oil could not be crystallised. It was suspended in water (200 ml.) at 80° and Raney nickel (*ca.* 25 g.) was added portionwise with stirring. After 1 hr. the filtrate was evaporated and the residue extracted with boiling benzene (100 ml.) to give (on concentration) 4,5,6-trismethylaminopyrimidine (0·8 g.). After two recrystallisations it had m. p. 148°, undepressed on admixture with the above base.

4,6-*Dihydroxy*-2-*methylthiopyrimidine*.—4,6-Dihydroxy-2-mercaptopyrimidine [23] (28 g.) in 2·5N-potassium hydroxide (160 ml.) was shaken with methyl iodide (14 ml.) for 40 min. Acidified (pH 2—3) and chilled, the solution deposited the methylthiopyrimidine (10·4 g.), m. p. ⩽300° (cf. other methods [24]) (Found: C, 37·7; H, 3·6; N, 17·7. Calc. for $C_5H_6N_2O_2S$: C, 38·0; H, 3·85; N, 17·7%).

4,6-*Dihydroxy*-2-*methylthio*-5-*nitropyrimidine*.—The above methylthiopyrimidine (10 g.) was added over 2 hr. to fuming nitric acid (30 ml., decolourised with urea) at 0°. The red solution poured on to ice gave the *nitropyrimidine* (10 g.) which was purified by precipitation from cold alkaline solution and had m. p. 223—224° (decomp.) (Found: C, 29·55; H, 2·5; S, 15·4. $C_5H_5N_3O_4S$ requires C, 29·55; H, 2·5; S, 15·75%). It hydrolysed rapidly in hot water to give 5-nitrobarbituric acid, m. p. 176°.[25]

4,6-*Dichloro*-2-*methylthio*-5-*nitropyrimidine*.—The dihydroxypyrimidine (5·0 g.), phosphoryl chloride (20 ml.), and diethylaniline (6 ml.) were refluxed for 1 hr. After partial evaporation, the residual liquid was poured on ice, to give a grey solid which was filtered off and dried in ether. Evaporation gave the *dichloropyrimidine* (93%), m. p. 61° (from light petroleum) (Found: C, 24·95; H, 1·3; N, 17·4; S, 13·1. $C_5H_3Cl_2N_3O_2S$ requires C, 25·0; H, 1·25; N, 17·5; S, 13·35%).

4,6-*Bismethylamino*-2-*methylthio*-5-*nitropyrimidine*.—Ethanolic methylamine (20%, 18 ml.) was added slowly at 10° to the above dichloropyrimidine (4·5 g.) in methanol (150 ml.). After the mixture had been stirred for 1 hr., the *bismethylaminopyrimidine* (3·95 g.) was recrystallised from ethanol. It had m. p. 190° (Found: C, 36·55; H, 4·75; N, 30·7. $C_7H_{11}N_5O_2S$ requires C, 36·65; H, 4·85; N, 30·55%).

[21] R. K. Robins and H. H. Lin, *J. Amer. Chem. Soc.*, 1957, **79**, 490.
[22] Von H. Goldner and E. Carstens, *J. prakt. Chem.*, 1961, **12**, 242.
[23] A. Michael, *J. prakt. Chem.*, 1887, **35**, 449.
[24] F. E. King and T. J. King, *J.*, 1947, 726; H. L. Wheeler and G. S. Jamieson, *Amer. Chem. J.*, 1904, **32**, 342.
[25] W. W. Hartman and O. E. Sheppard, *Org. Synth.*, Coll. Vol. II, 1943, p. 440.

5-Formamido-4,6-bismethylamino-2-methylthiopyrimidine.—The above nitro-compound (3·75 g.) was hydrogented at atmospheric pressure in methanol (200 ml.) over Raney nickel. The unstable triamine (2·1 g.) obtained on evaporation was heated at 95° with 90% formic acid (20 ml.) for 1 hr. Evaporation, dissolution in water, and neutralisation to pH 6—7 yielded the *formamidopyrimidine* (1·5 g.), m. p. 221—222° (from water) (Found: C, 42·1; H, 5·9; N, 30·7. $C_8H_{13}N_5OS$ requires C, 42·3; H, 5·75; N, 30·8%).

9-Methyl-6-methylamino-2-methylthiopurine.—The above formamidopyrimidine (1·0 g.) was heated at 250° for 30 min. The cooled melt was extracted with warm ethanol (25 ml.) and the remaining *methylthiopurine* (0·58 g.), recrystallised from 50% aqueous ethanol, had m. p. 239° (Found: C, 45·25; H, 5·45; N, 33·45. $C_8H_{11}N_5S$ requires C, 45·95; H, 5·3; N, 33·5%).

2-Methyl-4,6-bismethylamino-5-nitropyrimidine.—4,6-Dichloro-2-methyl-5-nitropyrimidine [9,10] (10 g.) was methylaminated as for the 2-methylthio-analogue described above. The *bismethylamino-compound* (8·5 g.) had m. p. 200—201° (from water or ethanol) (Found: C, 43·0; H, 6·0; N, 34·6. $C_7H_{11}N_5O_2$ requires C, 42·65; H, 5·6; N, 35·5%).

5-Amino-2-methyl-4,6-bismethylaminopyrimidine.—The nitro-compound (5·0 g.), hydrogenated at atmospheric pressure in methanol (150 ml.) over Raney nickel, gave (on evaporation) the *triamine* (3·45 g.), m. p. 145—146° (from benzene) (Found: C, 50·5; H, 7·75; N, 41·65. $C_7H_{13}N_5$ requires C, 50·3; H, 7·85; N, 41·9%). Its *hydriodide* had m. p. 215—217° (from water) (Found: C, 28·6; H, 4·6; N, 23·65. $C_7H_{14}IN_5$ requires C, 28·5; H, 4·8; N, 23·75%).

4-Dimethylamino-6-methylamino-5-nitropyrimidine.—Ethanolic dimethylamine (30%; 6·5 ml.) was added at 20—30° to a suspension of 4-chloro-6-methylamino-5-nitropyrimidine [12] (2·74 g.) in ethanol (25 ml.) and the mixture was refluxed for 30 min. Recrystallised from water, the diamine (2·0 g.) had m. p. 96—97° (cf. m. p. 96—97° for material made by another method [11]) (Found: C, 42·55; H, 5·7; N, 35·6. Calc. for $C_7H_{11}N_5O_2$: C, 42·65; H, 5·6; N, 35·5%).

4,5-Diamino-1,2-dihydro-2-imino-1-methylpyrimidine (or Tautomer).—2,4,5-Triaminopyrimidine [12] (5·0 g.), methanol (25 ml.), and methyl iodide (25 ml.) were refluxed for 4 hr. Evaporation and trituration of the residue with ethanol gave the *imine hydriodide* (3·0 g.), m. p. 263—264° (from 50% aqueous ethanol) (Found: C, 22·5; H, 3·6; N, 26·3. $C_5H_{10}N_5I$ requires C, 22·5; H, 3·75; N, 26·2%). The hydriodide (0·5 g.) was shaken in 10N-sodium hydroxide at 40° for 5 min. The precipitated imino-base, washed with cold ethanol and heated in water (5 ml.) at 100° for 1 hr., gave, on refrigeration and recrystallisation from ethanol (with concentration), 4,5-diamino-1,2-dihydro-1-methyl-2-oxopyrimidine (0·18 g.). It was identified with authentic material [15] by m. p. and mixed m. p. [*ca.* 245° (decomp.)], chromatography in four solvents, preparation of its picrate [2] [m. p. 238—239° (decomp.)] and by conversion into the known [16] 2,3-dihydro-3,6,7-trimethyl-2-oxopteridine (m. p. *ca.* 250—260° with softening at 190—200°).

4,5-Diamino-2-methylaminopyrimidine.—The crude base [26] gave a *picrate*, m. p. 215—216° (decomp.) (from ethanol) (Found: C, 36·0; H, 3·4. $C_{11}H_{12}N_8O_7$ requires C, 35·9; H, 3·3%).

4-Amino-5-formamido-2-methylaminopyrimidine.—The above crude triamine (1·0 g.) was heated with 98% formic acid (3 ml.) on a steam-bath for 20 min. The solid from evaporation *in vacuo* was dissolved in water (5 ml.) and adjustment to pH 9 gave the *formamidopyrimidine* (0·9 g.), m. p. 202° (from ethanol) (Found: C, 43·4; H, 5·35; N, 41·5. $C_6H_9N_5O$ requires C, 43·1; H, 5·4; N, 41·9%). When the solution above was adjusted to pH 6 instead of pH 9, the *formate* of the formamidopyrimidine crystallised. It had m. p. 195° (decomp.) (Found: C, 39·4; H, 5·1; N, 32·8. $C_6H_9N_5O,CH_2O_2$ requires C, 39·4; H, 5·2; N, 32·85%).

2-Methylaminopurine.—The above formamidopyrimidine (0·9 g.) was plunged into a bath at 215°. After a few minutes the mass resolidified, and recrystallisation from water gave the purine (0·5 g.), m. p. 276° (lit.,[17] 278—280°) (Found: N, 47·0. Calc. for $C_6H_7N_5$: N, 47·0%).

7-Hydroxy-2-methylaminopteridine.—(*a*) 4,5-Diamino-2-methylaminopyrimidine (0·35 g.) and ethyl glyoxylate hemiacetal (0·55 g.) were shaken in water (5 ml.) until the ethoxycarbonylmethyleneamino-intermediate had precipitated (5 min.). The suspension was added to M-sodium hydrogen carbonate solution (25 ml.) and refluxed 45 min. Acidified to pH 5 and refrigerated, the solution deposited the buff-coloured *pteridine* (0·06 g.) which, from water, had m. p. $<340°$ after some sublimation (Found: C, 47·5; H, 4·4; N, 39·3. $C_7H_7N_5O$ requires C, 47·45; H, 4·0; N, 39·55%).

[26] A. Albert, D. J. Brown, and G. Cheeseman, *J.*, 1952, 4219.

(*b*) 4,5-Diamino-1,2-dihydro-2-imino-1-methylpyrimidine hydriodide (0·27 g.) and ethyl glyoxylate hemiacetal (0·22 g.) were shaken in sodium hydroxide (2 ml.) at room temperature for 5 min. and then heated at 100° for 5 min. Isolated as before, the rearranged pteridine (0·09 g.) was indistinguishable from the above.

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