665. *Pyrimidine Reactions. Part V.*[1] *Nuclear Methylation of Some 6-Substituted 4-Aminopyrimidines.*

By D. J. Brown and T. Teitei.

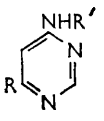
In contrast to its usual behaviour, 4-aminopyrimidine substituted by a methoxy-, methylthio-, or chloro-group at position 6 undergoes methylation at N-3. The structures of the imines formed are proved by their ability to undergo Dimroth rearrangement to 4-methylaminopyrimidines. Of these, the 6-methoxy- and the 6-chloro-derivative are shown to undergo further methylation at N-3, the resulting methylimines giving 1,4-dihydro-1-methyl-6-methylamino-4-oxopyrimidine on hydrolysis. On the other hand, 4-methylamino-6-methylthiopyrimidine is methylated at N-1, the structure of the product being based on spectral evidence. Ionisation constants and ultraviolet spectra are recorded for all compounds.

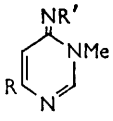
When treated with methyl iodide, 4-aminopyrimidine [2,3] and related di- and tri-amines [1] undergo γ-methylation at N-1. Attachment of a methylthio-,[4] methoxy-,[5] or chloro-group [4] at position 2 does not affect the site of methylation. In contrast, it is now shown that when these groups occupy position 6 α-methylation at N-3 is favoured. The products undergo Dimroth rearrangement [6] to 4-methylaminopyrimidines.

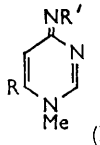
4-Amino-6-methylthiopyrimidine (I; R = SMe, R′ = H) with methyl iodide furnished

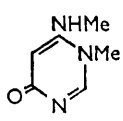
[1] Part IV, Brown and Jacobsen, *J.*, 1962, 3172.
[2] Curd and Richardson, *J.*, 1955, 1853.
[3] Brown, Hoerger, and Mason, *J.*, 1955, 4035.
[4] Curd and Richardson, *J.*, 1955, 1850.
[5] Hilbert, *J. Amer. Chem. Soc.*, 1934, **56**, 190.
[6] Brown and Harper, *J.*, 1963, 1276.

two easily separable, isomeric, and highly basic methyl derivatives (as hydriodides). The first product was shown to be 1,6-dihydro-6-imino-1-methyl-4-methylthiopyrimidine (II; R = SMe, R′ = H) by its rearrangement in alkali at room temperature to 4-methylamino-6-methylthiopyrimidine (I; R = SMe, R′ = Me), in turn identified by unambiguous


(I)


(II)


(III)


(IV)

synthesis of the base and its hydriodide from 4-chloro-6-methylaminopyrimidine. The second product was 1,4-dihydro-4-imino-1-methyl-6-methylthiopyrimidine (III; R = SMe, R′ = H) because desulphurisation with Raney nickel afforded 1,4-dihydro-4-imino-1-methylpyrimidine (III; R = R′ = H), identified as its picrate. Unlike the lower homologue, 4-methylamino-6-methylthiopyrimidine (I; R = SMe, R′ = Me) gave a single strongly basic methyl derivative, probably 1,4-dihydro-1-methyl-4-methylimino-6-methylthiopyrimidine (III; R = SMe, R′ = Me) on the evidence of spectral comparison (see Table) with (II and III; R = SMe, R′ = H).

Methylation of 4-amino-6-methoxypyrimidine gave a single methyl derivative. The ability of this strong base to rearrange in alkali to the known [7] 4-methoxy-6-methylaminopyrimidine showed that it was 1,6-dihydro-6-imino-4-methoxy-1-methylpyrimidine (II; R = OMe, R′ = H). Further methylation of 4-methoxy-6-methylaminopyrimidine (I; R = OMe, R′ = Me) gave two products. One was a weakly basic isomer of the starting material, the other a strongly basic monomethyl derivative. The weak base (pK_a 1·5) was neither 4-dimethylamino-6-hydroxypyrimidine nor 1,6-dihydro-1-methyl-4-methylamino-6-oxopyrimidine, both of which were available for comparison.[8] It was therefore 1,4-dihydro-1-methyl-6-methylamino-4-oxopyrimidine (IV). The strong base yielded this weak base on alkaline hydrolysis, suggesting that it was 1,6-dihydro-4-methoxy-1-methyl-6-methyliminopyrimidine (II; R = OMe, R′ = Me). This was confirmed by the similarity of its spectrum to that of the imine (II; R = OMe, R′ = H). The weak base would arise from it during methylation, not by hydrolysis, but by elimination of methyl iodide as described by Hilbert and Johnson [5,9] for analogous cases.

Methyl iodide and 4-amino-6-chloropyrimidine gave but one product. Its rearrangement in warm ammonia to 4-chloro-6-methylaminopyrimidine showed it to be 4-chloro-1,6-dihydro-6-imino-1-methylpyrimidine (II; R = Cl, R′ = H). In addition, treatment with aqueous sodium hydrogen sulphide both rearranged it and replaced its chloro-substituent, yielding 4-mercapto-6-methylaminopyrimidine. Analogous methylation of 4-chloro-6-methylaminopyrimidine again gave a single base, shown to be 4-chloro-1,6-dihydro-1-methyl-6-methyliminopyrimidine (II; R = Cl, R′ = Me) by its alkaline hydrolysis to 1,4-dihydro-1-methyl-6-methylamino-4-oxopyrimidine (IV).

It seems clear that a localised effect is responsible for the change from γ- to α-methylation when the methoxy-, methylthio-, or chloro-group is detached from position 2 and attached to position 6 of 4-aminopyrimidine. Thus with a 2-substituent any localised effect, be it electronic or steric, should modify N-1 and N-3 approximately equally, but with a 6-substituent, N-1 should suffer more than N-3. If methylation at N-1 was, for example, discouraged by reducing electron density there, it would be reasonable for methylation at N-3 to ensue. Whether the effect acts through a change in relative rates, by favouring one type of reaction at the expense of another or by some other means is unknown, but it may be significant that the groups (OMe, Cl) which have the greater

[7] Brown, *J. Appl. Chem.*, 1955, **5**, 358.
[8] Brown and Harper, *J.*, 1961, 1298.
[9] Hilbert and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 2001.

Ionisation and ultraviolet spectra of substituted pyrimidines.

Pyrimidine derivative	pK_a [a]	$\lambda_{max.}$ (log ε)	pH
4-Amino-6-mercapto [b]		304 (4·29), 238 (4·21)	2·5
	−0·24 ± 0·03 (sp.)	323 (4·20), 280 (3·71), 226 (4·13)	−2·0
	9·25 ± 0·05 (M/200)	287 (4·16), 243 (4·21), 225 (4·24)	12·0
4-Amino-6-methoxy		235 (3·88)	7·0
	4·02 [c]	249 (3·93)	1·8
4-Amino-6-methylthio		274 (3·82), 235 (4·39)	7·0
	3·94 ± 0·05 (M/200)	284 (4·15), 239 (4·28)	1·8
4-Chloro-3,6-dihydro-6-imino-2,3-dimethyl [d]	—	253 (4·15)	7·0
4-Chloro-1,6-dihydro-6-imino-1-methyl [e]	*ca.* 9	256 (4·14)	7·0
4-Chloro-1,6-dihydro-1-methyl-6-methylimino [e]	*ca.* 9	263 (4·09), 222 (3·99)	7·0
1,6-Dihydro-6-imino-4-methoxy-1-methyl [e]	*ca.* 11	253 (4·17)	7·0
1,4-Dihydro-4-imino-1-methyl-6-methylthio [e]	*ca.* 11	285 (4·26), 238 (4·47)	7·0
		282 (4·12), 243 (4·15)	13·4
1,6-Dihydro-6-imino-1-methyl-4-methylthio [e]	*ca.* 11	286 (4·13), 241 (4·28)	7·0
		282 (3·85), 246 (4·28)	13·4
1,6-Dihydro-4-methoxy-1-methyl-6-methylimino [e]	*ca.* 11	263 (4·20)	7·0
1,4-Dihydro-1-methyl-6-methylamino-4-oxo	<2	260 (3·93), 223 (4·44)	7·0
1,6-Dihydro-1-methyl-4-methylamino-6-oxo	<1 [c]	270 (3·83), 237 (4·14)	7·0
1,4-Dihydro-1-methyl-4-methylimino-6-methylthio [e]	*ca.* 11	287 (4·28), 242 (4·43)	7·0
		286 (4·13), 244 (4·20)	13·4
4-Mercapto-6-methylamino		310 (4·32), 252 (4·24)	2·5
	−0·27 ± 0·03 (sp.)	329 (4·08), 268 (4·02), 234 (4·16)	−2·0
	9·64 ± 0·03 (M/200)	293 (4·09), 251 (4·34), 234 (4·28)	12·0
4-Methoxy-6-methylamino	4·23 [c]	254 (4·07)	1·8
		243 (4·05)	7·0
4-Methylamino-6-methylthio	4·42 ± 0·01 (M/200)	286 (4·15), 243 (4·28)	1·8
		280 (3·76), 241 (4·45)	7·0

[a] Measured at 20° potentiometrically (concentration given) or spectrometrically (sp.); cf. Albert and Serjeant, "Ionization of Acids and Bases," Methuen, London, 1962. [b] Prep. in ref. 11. [c] Figures from ref. 8. [d] Prep. in ref. 2. [e] Free base unstable; approximate pK_a obtained potentiometrically at M/100. Spectral data from hydriodide with compensating iodide concentration in reference cell.

effect have also a greater (base-weakening) inductive effect * in the *ortho*-position than has the methylthio-group, which even in position 6 still permits some γ-methylation.

Experimental

Analyses are by Dr. J. E. Fildes and her staff.

4-Amino-6-methylthiopyrimidine.—The base [11] gave a *picrate*, m. p. 213—215° (from ethanol) (Found: C, 35·5; H, 2·5. $C_{11}H_{10}N_6O_7S$ requires C, 35·7; H, 2·7%).

4-Methylamino-6-methylthiopyrimidine.—4-Chloro-6-methylaminopyrimidine [7] (4·2 g.) and thiourea (2·6 g.) were refluxed for 4 hr. in propanol (30 ml.). The residue from evaporation was neutralised with aqueous sodium hydrogen carbonate and again evaporated. The solution of this solid in ammonia was filtered and acidified to pH 6. The resulting *4-mercapto-6-methylaminopyrimidine* (1·0 g.) had m. p. 258—265° (decomp.) (from water) (Found: C, 42·5; H, 5·1; N, 29·7. $C_5H_7N_3S$ requires C, 42·55; H, 5·0; N, 29·8%). This thiol (0·7 g.), methyl iodide (0·8 g.), and N-sodium hydroxide (50 ml.) were shaken at 25° for 1 hr. and then extracted with ether (200 ml.). The residue from evaporation gave the *methylthio-compound* (0·6 g.), m. p. 117—118° (from ethyl acetate) (Found: C, 46·3; H, 5·6; N, 27·2. $C_6H_9N_3S$ requires C, 46·45; H, 5·8; N, 27·1%). Its *picrate* had m. p. 199—201° (Found: C, 37·5; H, 3·0. $C_{12}H_{12}N_6O_7S$ requires C, 37·4; H, 3·1%). The *hydriodide*, prepared as was 2-ethylaminopyrimidine hydriodide,[6] had m. p. 207° (decomp.) (from ethanol) (Found: C, 25·5; H, 3·6; N, 14·8. $C_6H_{10}IN_3S$ requires C, 25·4; H, 3·5; N, 14·8%).

* This is suggested by the pK_a values [10] of the following derivatives of pyridine: 2-OMe, 3·3; 3-OMe, 4·9; 4-OMe, 6·5; 2-Cl, 0·7; 3-Cl, 2·8; 4-Cl, 3·8; 2-SMe, 3·6; 3-SMe, 4·4; 4-SMe, 5·9; unsubstituted, 5·2.

[10] Perrin, *Pure and Appl. Chem.*, 1963, in the press.
[11] Koppel, Springer, Robins, and Cheng, *J. Org. Chem.*, 1961, **26**, 792.

Methylation of 4-*Amino*-6-*methylthiopyrimidine*.—4-Amino-6-methylthiopyrimidine (3·7 g.), methyl iodide (2 ml.), and methanol (15 ml.) were refluxed for 4 hr. After refrigeration, the precipitate was recrystallised from ethanol to give 1,4-*dihydro*-4-*imino*-1-*methyl*-6-*methylthiopyrimidine hydriodide* (2·05 g.), m. p. 234—235° (Found: C, 25·15; H, 3·5; N, 14·9. $C_6H_{10}IN_3S$ requires C, 25·4; H, 3·5; N, 14·8%). An aqueous suspension of silver chloride converted it into the *hydrochloride*, m. p. 250—251° (from ethanol) (Found: C, 37·5; H, 5·1. $C_6H_{10}ClN_3S$ requires C, 37·6; H, 5·2%). The *picrate* had m. p. 241—243° (decomp.) (from methanol) (Found: C, 37·3; H, 3·2. $C_{12}H_{12}N_6O_7S$ requires C, 37·5; H, 3·1%).

Evaporation of the mother-liquors from the reaction mixture, and recrystallisation of the solid from ethanol, gave 1,6-*dihydro*-6-*imino*-1-*methyl*-4-*methylthiopyrimidine hydriodide* (2·0 g.), m. p. 186—187° (Found: C, 25·2; H, 3·5; N, 14·9%).

The hydriodide of the first isomer (0·5 g.) was refluxed with Raney nickel (2·0 g.) in water (10 ml.) for 3 hr. The filtered solution was evaporated to dryness *in vacuo* and the residue moistened with benzene and re-evaporated. The residue in a little ethanol was added to saturated alcoholic picric acid (10 ml.). The resulting picrate had m. p. 175° (from ethyl acetate), undepressed by admixture with that from 1,4-dihydro-4-imino-1-methylpyrimidine [3] (Found: C, 38·9; H, 3·0. Calc. for $C_{11}H_{10}N_6O_7$: C, 39·05; H, 3·0%). 4-*Methylaminopyrimidine picrate*, made from the base [12] for comparison, had m. p. 162—163° (Found: C, 39·2; H, 3·1%).

The hydriodide of the second isomeric methylthio-derivative (0·5 g.) and N-sodium hydroxide (15 ml.) were set aside for 1 day at 25°. Extraction with ether, evaporation, and recrystallisation from ethyl acetate gave 4-methylamino-6-methylthiopyrimidine (0·2 g.), m. p. 117—118° undepressed on admixture with authentic material (see above).

Methylation of 4-*Methylamino*-6-*methylthiopyrimidine*.—The pyrimidine (1·3 g.), methyl iodide (1·3 ml.), and ethanol (15 ml.) were refluxed for 5 hr. The resulting 1,4-*dihydro*-1-*methyl*-4-*methylimino*-6-*methylthiopyrimidine hydriodide* (1·8 g.) had m. p. 200° (decomp.) (from ethanol) (Found: C, 28·2; H, 3·95; N, 14·1. $C_7H_{12}IN_3S$ requires C, 28·3; H, 4·0; N, 14·1%).

Methylation of 4-*Amino*-6-*methoxypyrimidine*.—The amine [8] (1·25 g.), methyl iodide (1·3 ml.), and methanol (10 ml.) were kept at 25° for 2 days. Recrystallisation of the solid from ethanol gave 1,6-*dihydro*-6-*imino*-4-*methoxy*-1-*methylpyrimidine hydriodide* (1·3 g.), m. p. 143—144° (decomp.) (Found: C, 26·9; H, 3·7; N, 15·7. $C_6H_{10}IN_3O$ requires C, 27·0; H, 3·75; N, 15·7%). Some starting material was recovered from the mother-liquors. The above hydriodide (3·4 g.) was left for 2 days at 25° in N-sodium hydroxide (30 ml.). Extraction with ether and recrystallisation from ethyl acetate gave 4-methoxy-6-methylaminopyrimidine (1·1 g.), m. p. 88—89° undepressed on admixture with authentic material [7] (Found: N, 29·9; Calc. for $C_6H_9N_3O$: N, 30·2%).

Methylation of 4-*Methoxy*-6-*methylaminopyrimidine*.—The methoxy-derivative (5·2 g.), methanol (30 ml.), and methyl iodide (5 ml.) were kept for 5 days at 25° (or refluxed for 4 hr.). The solid (3·1 g.) was recrystallised from ethanol to give 1,4-*dihydro*-1-*methyl*-6-*methylamino*-4-*oxopyrimidine*, m. p. 194° (Found: C, 52·2; H, 6·7; N, 30·0. $C_6H_9N_3O$ requires C, 51·8; H, 6·5; N, 30·2%). Concentration of the mother-liquors and recrystallisation gave 1,6-*dihydro*-4-*methoxy*-1-*methyl*-6-*methyliminopyrimidine hydriodide* (1·8 g.), m. p. 215—217° (decomp.) (Found: N, 14·7. $C_7H_{12}IN_3O$ requires N, 14·9%). It yielded an oxo-compound on treatment with N-sodium hydroxide at 100°.

Methylation of 4-*Amino*-6-*chloropyrimidine*.—The chloropyrimidine (7·0 g.), methyl iodide (14 ml.), and ethanol (125 ml.) were refluxed for 12 hr. The solid, recrystallised from ethanol, gave 4-*chloro*-1,6-*dihydro*-6-*imino*-1-*methylpyrimidine hydriodide* (13·0 g.), m. p. 207° (decomp.) (Found: C, 22·2; H, 2·7; N, 15·3. $C_5H_7ClIN_3$ requires C, 22·1; H, 2·6; N, 15·5%). The hydriodide (50 mg.) and 4N-ammonia (2 ml.) were heated at 100° for 2·5 hr. The residue from evaporation was extracted with hot chloroform. Removal of solvent and recrystallisation from water gave 4-chloro-6-methylaminopyrimidine (17 mg.), m. p. *ca.* 137° (lit.,[7] m. p. 135—138°). The same hydriodide (3·0 g.) and sodium hydrogen sulphide (from 25 ml. of 2N-sodium hydroxide) were refluxed for 1·5 hr. and then acidified with acetic acid. The solid on recrystallisation from water afforded 4-mercapto-6-methylaminopyrimidine (1·3 g.), identified with authentic material by mixed m. p. and chromatography (Found: C, 42·3; H, 4·8; N, 29·65. Calc. for $C_5H_7N_3S$: C, 42·55; H, 5·0; N, 29·8%).

[12] Brown and Short, *J.*, 1953, 331.

Methylation of 4-*Chloro*-6-*methylaminopyrimidine.*—Methylation as above gave 4-*chloro*-1,6-*dihydro*-1-*methyl*-6-*methyliminopyrimidine hydriodide* (60%), m. p. 223° (decomp.) (Found: C, 25·3; H, 3·2; N, 14·6. $C_6H_9ClIN_3$ requires C, 25·2; H, 3·15; N, 14·7%). The *hydrochloride* had m. p. 238° (decomp.) (Found: N, 21·7. $C_6H_9ClIN_3$ requires N, 21·65%). The above hydriodide (1·9 g.) was refluxed with 10N-sodium hydroxide in methanol (15 ml.) for 2 hr. and neutralised. The residue from evaporation was dissolved in water and shaken with chloroform. Removal of solvent and recrystallisation from ethyl acetate gave 1,4-dihydro-1-methyl-6-methylamino-4-oxopyrimidine (0·6 g.), m. p. and mixed m. p. 192°.

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