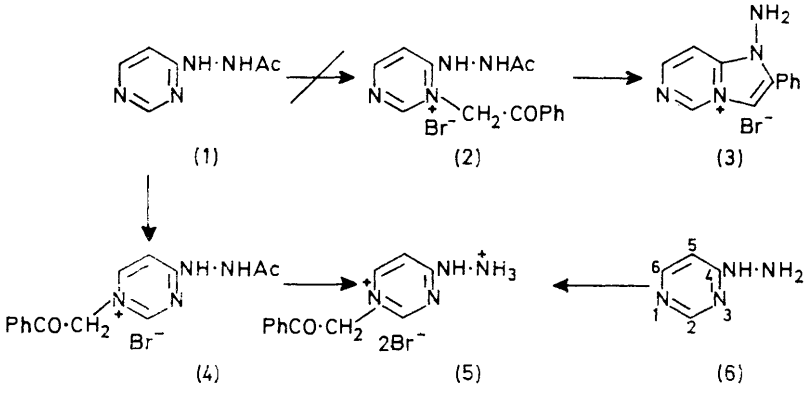
2-Aminopyrrolo[1,2-*a*]- and 3-Aminopyrrolo[1,2-*c*]-pyrimidines

By **David G. Doughty, Edward E. Glover,*** and (in part) **Kenneth D. Vaughan,** Department of Chemistry, Teeside Polytechnic, Middlesbrough, Cleveland TS1 3BA

Treatment of 4-amino-6-methylpyrimidine with phenacyl bromide followed by base gives 3-amino-6-phenylpyrrolo[1,2-*c*]pyrimidine and not 7-methyl-2-phenylimidazo[1,2-*c*]pyrimidine as reported previously. Similar treatment of 4-amino-2-methyl- and 4-amino-2,6-dimethyl-pyrimidine yields 2-amino-7-phenyl- and 2-amino-4-methyl-7-phenyl-pyrrolo[1,2-*a*]pyrimidine, respectively.

We were interested in the preparation of 1-aminoimidazo[1,2-*c*]-pyrimidinium salts such as (3). A route *via* treatment of the acetylated 4-pyrimidylhydrazine (1) with phenacyl bromide and subsequent cyclization of the intermediate quaternary salt (2) with aqueous acid in a manner analogous to that previously described [1] for the formation of 1-amino-2-phenylimidazo[1,2-*a*]pyridinium salts seemed possible. The product of the reaction between (1) and phenacyl bromide was, however, the quaternary salt (4), derived by quaternization at N-1, and



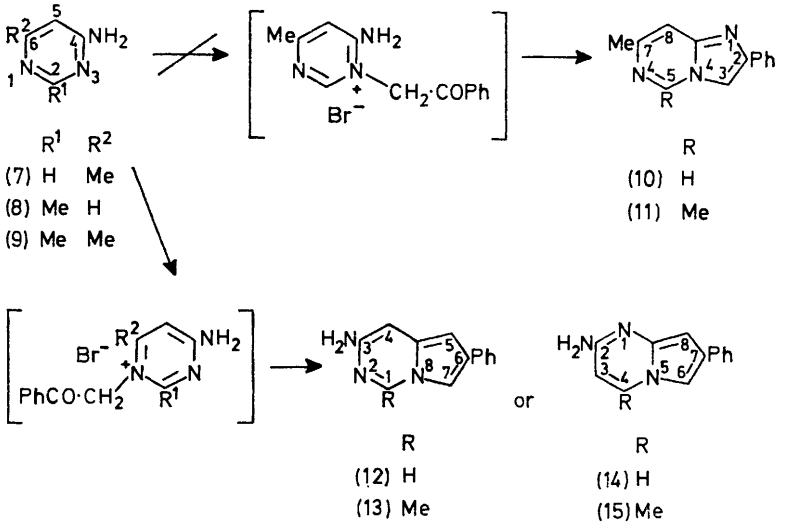
subsequent hydrolysis with hydrobromic acid gave the bromide hydrobromide (5). Compound (5) was also obtained by treatment of 4-pyrimidylhydrazine (6) with phenacyl bromide followed by hydrobromic acid, and its structure followed from elemental analysis and a carbonyl i.r. band at 1 695 cm^{-1} (KBr disc). Thus the quaternization of 4-pyrimidylhydrazine, like that of 4-aminopyrimidine,[2,3] occurs preferentially at N-1.

An alternative route envisaged to the *N*-amino-salt (3) would involve *N*-amination of 2-phenylimidazo[1,2-*c*]pyrimidine with *O*-mesitylsulphonyl- [4] or *O*-*p*-tolylsulphonyl-hydroxylamine.[5]

Despite the preference of 4-aminopyrimidine for quaternization at N-1,[2,3] a 20% yield of a mixture of 2-methyl- and 3-methyl-imidazo[1,2-*c*]pyrimidines has been obtained [6] from treatment of 4-aminopyrimidine with 2-bromopropionaldehyde. The 7-methyl-2-phenyl compound (10) [7,8] and the 5,7-dimethyl-2-phenyl compound (11) [9] have been reported as the products from the action of phenacyl bromide on 4-amino-6-methylpyrimidine, and on 4-amino-2,6-dimethylpyrimidine, respectively, after basification. We treated the more readily accessible 4-amino-2,6-dimethylpyrimidine [10] (9) with phenacyl bromide followed by base and obtained a compound, the i.r. spectrum of which showed strong NH bands in the 3 100—3 500 cm^{-1} region and the ^1H n.m.r. spectrum of which [solvent $(CD_3)_2SO$; in external Me_4Si standard] showed only one methyl signal (δ 2.15). We deduced that our product was either the aminopyrrolo-[1,2-*c*]pyrimidine (13) or the aminopyrrolo[1,2-*a*]pyrimidine (15), and not the reported [9] imidazo[1,2-*c*]pyrimidine (11). In order to distinguish between these possibilities, both 4-amino-6-methylpyrimidine (7) and the 4-amino-2-methyl compound (8) were treated with phenacyl bromide followed by base. In each case the product [(12) and (14), respectively] was characterized by the absence of a methyl signal in the ^1H n.m.r. spectrum and the presence of strong NH i.r. bands in the 3 100—3 500 cm^{-1} region. It was concluded, therefore, that compounds (12) and (14) were, respectively, 3-amino-6-phenylpyrrolo-[1,2-*c*]pyrimidine and 2-amino-7-phenylpyrrolo[1,2-*a*]-pyrimidine. The formation of (12) contrasts with the previously reported [7,8] formation of the imidazopyrimidine (10) from the reaction between 4-amino-6-methylpyrimidine (7) and phenacyl bromide.

[1] E. E. Glover and M. Yorke, *J. Chem. Soc.* (*C*), 1971, 3281.
[2] D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 1955, 4035.
[3] F. H. S. Curd and D. N. Richardson, *J. Chem. Soc.*, 1955, 1853.
[4] Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Letters*, 1972, 4133.
[5] E. E. Glover and K. T. Rowbottom, *J.C.S. Perkin I*, 1976, 367.
[6] P. Guerret, R. Jacquier, and G. Maury, *J. Heterocyclic Chem.*, 1971, **8**, 643.
[7] E. Ochiai and M. Yanai, *J. Pharm. Soc. Japan*, 1939, **59**, 97.
[8] J. G. Fischer and J. M. Straley, B.P. 1,159,691.
[9] N. P. Buu-Hoï, L. Petit, and N. D. Xuong, *Compt. rend.*, 1959, **248**, 1832.
[10] A. R. Ronzio and W. B. Cook, *Org. Synth.*, Coll. Vol. III, 1955, 71.

The u.v. spectrum of the product of the reaction between 4-amino-2,6-dimethylpyrimidine (9) and phenacyl bromide was almost identical with that of (14) and different from that of (12), establishing this substance as the pyrrolo[1,2-*a*]pyrimidine (15), as distinct from the pyrrolo[1,2-*c*] pyrimidine (13).



Reactants	Product	Yield (%)	M.p. (°C)	Cryst. solvent	Found (%) C	H	N	Rqd. (%) C	H	N
4-Pyrimidylhydrazine [11] (0.55 g) in dry pyridine (2 ml) + Ac_2O (0.51 g) [a]	(1)	55	154	MeCN	47.2	5.4	37.1	47.4	5.3	36.8
(1) (0.3 g) + $PhCO{\cdot}CH_2Br$ (0.4 g) in dry MeCN (5 ml) [b]	(4)	46	222—223	MeOH–Et_2O	47.5	4.5	15.6	47.9	4.3	16.0
4-Pyrimidylhydrazine [11] (0.22 g) + $PhCO{\cdot}CH_2Br$ (0.4 g) in MeCN [c]	(5)	21	204—206	48% HBr	36.7	3.8	14.1	36.9	3.6	14.4
(4) (0.2 g) in 48% hydrobromic acid (6 ml) [d]	(5)	37	204—206	48% HBr						
(7) [e] (4.4 g) + $PhCO{\cdot}CH_2Br$ (8 g) in EtOH (20 ml) [f]	(12) [g-j]	21	240 [k,l]	PhH [m]	74.6	5.2	20.1	74.6	5.3	20.1
(8) [12] (4.4 g) + $PhCO{\cdot}CH_2Br$ (8 g) in EtOH (20 ml) [f]	(14) [n]	47	205 [k]	PhH [m]	74.3	5.1	20.4	74.6	5.3	20.1
(9) [10] (5 g) + $PhCO{\cdot}CH_2Br$ (8 g) in EtOH (20 ml) [f]	(15) [o,p]	13	174 [k]	PhH [m]	74.9	6.0	19.3	75.3	5.9	18.8

[a] The acetic anhydride was added dropwise to the stirred solution. Ether was then added and the precipitated gummy product triturated until solid. [b] The solution was boiled under reflux for 0.5 h. An oil which separated initially slowly solidified, after which the cooled mixture was filtered and the solid product recrystallized. [c] The solution was heated under reflux on a boiling water-bath for 5 min and then cooled. The solvent was then decanted and the residual oil treated with 48% hydrobromic acid (2 ml), giving the bromide hydrobromide, which was filtered off. [d] The solution was boiled under reflux for 0.5 h and then cooled, and the product was filtered off. [e] Prepared from 4-amino-6-methylpyrimidine-2-thiol by the procedure described [13] for the preparation of 4-aminopyrimidine from 4-aminopyrimidine-2-thiol. [f] The solution was boiled under reflux for 5 h and evaporated. The residue was then boiled with acetone and the residual solid filtered off. The solid was then added to hot aqueous 10% sodium carbonate, and the product separated. [g] ν_{NH} (KBr) 3 440, 3 320, 3 215, and 3 130 cm^{-1}, $\lambda_{max.}$(MeOH) 262, 360sh, and 390sh nm (log ε 4.7, 3.2, and 3.1). [h] The green *benzoyl derivative*, recrystallized from ethanol and then benzene, had m.p. 234° (decomp.) (Found: C, 76.3; H, 4.7. $C_{20}H_{15}N_3O$ requires C, 76.7; H, 4.8%). [i] The *hydrobromide*, recrystallized from ethanol, decomposed at 220 °C (Found: C, 54.1; H, 4.3; N, 14.3. $C_{13}H_{11}N_3$,HBr requires C, 53.8; H, 4.2; N, 14.5%). [j] The *acetyl derivative*, obtained by boiling a solution of the base with an equivalent amount of acetic anhydride in an excess of pyridine followed by evaporation and recrystallization from ethanol, had m.p. 268° (decomp.) (Found: N, 16.4, 16.5 $C_{15}H_{13}N_3O$ requires N, 16.7%). [k] With decomp. [l] The product of this reaction has previously been reported [7,8] as 7-methyl-2-phenylimidazo[1,2-*c*]pyrimidine, m.p. 244°. [m] May also be purified by vacuum sublimation. [n] ν_{NH} (KBr) 3 460, 3 310, 3 280, and 3 120 cm^{-1}, $\lambda_{max.}$(MeOH) 226, 259, 285sh, 302sh, 313sh, and 373 nm (log ε 4.2, 4.63, 4.05, 3.94, 3.86, and 3.38). [o] ν_{NH} (KBr) 3 440, 3 300, 3 280, and 3 140 cm^{-1}, $\lambda_{max.}$(MeOH) 225, 259, 283sh, 298sh, 310sh, and 361 nm (log ε 4.17, 4.66, 4.1, 3.98, 3.9, and 3.49). [p] The product of this reaction has previously been reported [9] as 5,7-dimethyl-2-phenylimidazo[1,2-*c*]pyrimidine, m.p. 170°.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus and n.m.r., i.r., and u.v. spectra on Perkin-Elmer spectrophotometers, models R12A, 237, and 137UV respectively.

We thank Allen and Hanburys for maintenance grants (to D. G. D. and K. D. V.).

[6/722 *Received*, 12*th April*, 1976]

[11] J. H. Chesterfield, J. F. W. McOmie, and E. R. Sayer, *J. Chem. Soc.*, 1955, 3478.
[12] H. R. Henze, W. J. Clegg, and C. W. Smart, *J. Org. Chem.*, 1952, **17**, 1320.
[13] D. J. Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.