Reaction of 9-Substituted Adenines with Chloroacetic Anhydride. Formation of Novel Mesoionic Imidazopyrines

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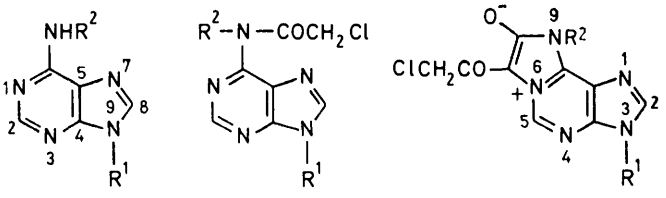
Reaction of the 9-substituted adenines (1) with chloroacetic anhydride in boiling toluene has resulted in the formation of the novel mesoionic imidazopurines (3) in moderate to good yields. The reaction apparently involves an intramolecular alkylation of the initially formed 9-substituted N^6-chloroacetyladenines (2) at N-1, which is in contrast with the exclusive N^7-alkylation in the reaction of 9-substituted N^6-acyladenines with alkyl halides.

RECENT work [1] of ours has demonstrated that 9-substituted N^6-acyl adenines undergo exclusive N^7-alkylation on reaction with alkyl halides. This behaviour is different from that of 9-substituted adenines [2] which, under similar conditions, give N^1 substituted products. This indicates the dominant effect of the N^6-acyl group in directing substitution in 9-substituted adenines. Chheda and Hall [3] have described the intramolecular N^1-alkylation of N^6-chloroacetyl-9-methyladenine, which gave 3-methyl-3*H*-imidazo[2,1-*i*]purin-8(7*H*)-one, and is contrary to expectations based on our previous study.[1]

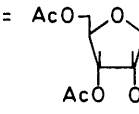
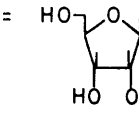
Accordingly, the present work was undertaken to reconfirm the intramolecular alkylation site of 9-substituted N^6-chloroacetyl adenines. We attempted to clarify the structure of the product † obtained from the reaction of 9-substituted adenines with chloroacetic anhydride (2 mol equiv.) and found that the products are the novel mesoionic imidazopurines (3) which can be produced *via* intramolecular N^1-alkylation of the initially formed N^6-chloroacetyl derivatives (2) followed by further chloroacetylation.

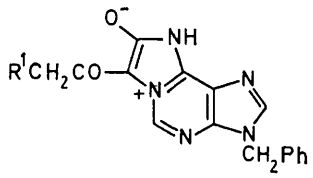
9-Benzyladenine (1a) was allowed to react with chloroacetic anhydride (2 mol equiv.) in toluene under reflux for 1 h and the oily residue thus obtained was triturated with diethyl ether to separate, essentially, a single product. This, when recrystallised from aqueous dimethylformamide (DMF), gave 3-benzyl-7-chloroacetylimidazo[2,1-*i*]purin-6-ylio 8-oxide (3a), m.p. 285—290 °C (decomp.), in 34.1% yield. The structure of compound (3a) was unequivocally established on the basis of following facts.

Microanalytical and mass spectral data confirm the molecular formula as $C_{16}H_{12}ClN_5O_2$. The n.m.r. spectrum [$(CD_3)_2SO$] shows two methylene signals (δ 4.72 and 5.55), two ring proton signals (δ 8.71 and 10.21), and a secondary amine signal (δ 3.70, br, deuterium exchangeable) in addition to the aromatic proton signals. The n.m.r. spectrum of the deuteriated product [2-$^2H_1$] (3a), derived from the C-8 deuteriated 9-benzyladenine [8-$^2H_1$] (1a), shows clearly that the highly deshielded proton signal in the product (δ 10.21) arises from the C-2 proton of the parent 9-benzyladenine (1a). The i.r. spectrum of compound (3a) shows the presence of a secondary amino-group (ν 3 080 cm^{-1}) and a carbonyl group (ν 1 680 cm^{-1}). Reaction of compound (3a) with thiophenol in the presence of triethylamine or morpholine afforded the new compounds (4a) and (4b), respectively, in which the chlorine atom is replaced by the phenylthio- or morpholino-group [^1H n.m.r. in [$(CD_3)_2SO$] (4a), δ 4.40 (2 H, s, CH_2S); (4b), δ 4.05 (2 H, s, CH_2N)]. This reaction shows that the chlorine atom in (3a) is present in the chloroacetyl group. The annelated purine structure (3a) also has the characteristic u.v. spectrum [$\lambda_{max.}$ (MeOH) (ε) 243 (22 000), 279 (23 900), and 335 nm (16 100)].



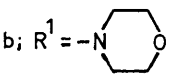
(1) (2) (3)

a; R^1 = CH_2Ph, R^2 = H
b; R^1 = CH_2Ph, R^2 = Me
c; R^1 = R^2 = CH_2Ph
d; R^1 = Me, R^2 = H
e; R^1 = Et, R^2 = H
f; R^1 = Et, R^2 = Me
g; R^1 =  , R^2 = H
h; R^1 =  , R^2 = H



(4)

a; R^1 = SPh

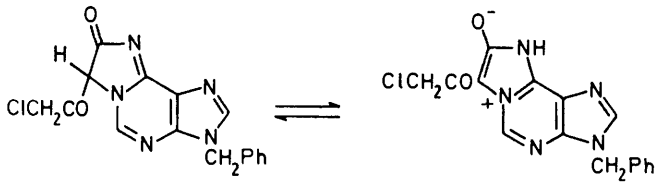
b; R^1 = 

† Chheda and Hall have described the formation of the analogous product without presentation of the gross structure (ref. 3).

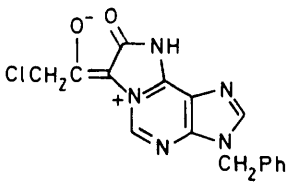
The preparation of fused mesoionic compounds by the reaction of azaheterocycles having an imino-function adjacent to ring nitrogen, *e.g.* 2-monosubstituted aminopyridine [4] and 1-azaphenothiazine,[5] with chloroacetic anhydride and chloroacetic acid is known.

When chloroacetylation of 9-benzyl-N^6-methyladenine (1b) was carried out under conditions similar to the reaction with (1a), the corresponding mesoionic compound (3b), m.p. 190 °C, was obtained in 67.4% yield. The u.v. spectrum of compound (3b) [$\lambda_{max.}$ (MeOH) (ε) 244 (28 900), 268 (21 000), and 335 nm (16 200)] is superimposable on that of (3a). The n.m.r. spectral pattern of compound (3b) is compatible with that of (3a), except for the methyl signal.

This confirms that (3a) exists preferentially in the mesoionic tautomeric form rather than the neutral tautomeric form (A). On the basis of spectral data (*vide supra*), the contribution of an alternative resonance structure (3a') seems to be less significant.



(A) (3a)



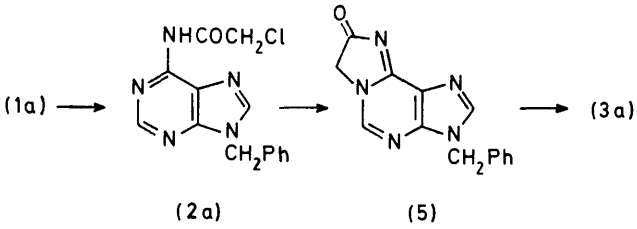
(3a')

Analogously, 2',3',5'-tri-*O*-acetyladenosine (1g) was converted into the corresponding mesoionic compound (3g), m.p. 190—192 °C, in 57.9% yield, and this was deacetylated to give the riboside (3h), m.p. >300 °C (decomp.).

Under analogous conditions, several 9-substituted adenines (1c)—(1f) also afforded the corresponding mesoionic imidazopurines (3c)—(3f) in moderate to good yields.

9-Benzyl-N^6-chloroacetyladenine (2a) was obtained upon treatment of compound (1a) with chloroacetic anhydride in toluene at 70 °C and further reaction of compound (2a) with chloroacetic anhydride resulted in the formation of the mesoionic compound (3a). On the other hand, when compound (2a) was heated in DMF ring closure followed by the loss of hydrogen chloride gave 3-benzyl-3*H*-imidazo[2,1-*i*]purin-8(7*H*)-one (5), m.p. 148—150 °C, which was subsequently converted into the required product (3a) upon treatment with chloroacetic anhydride. Thus, the formation of the mesoionic imidazopurines (3) from the 9-substituted adenines (1) obviously proceeds as shown in the Scheme.

It is concluded that, in sharp contrast with the intermolecular alkylation of 9-substituted N^6-acyladenines at N-7, the intramolecular alkylation of the N^6-chloroacetyladenines (2) occurs at N-1. This may be because the intramolecular alkylation of compounds (2) is thermodynamically controlled.



(1a) (2a) (5) (3a)

SCHEME

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-hot-stage apparatus and are uncorrected. ^{1}H N.m.r. spectra were obtained on a Hitachi R-24B (60 MHz) spectrometer, using $(CD_3)_2SO$ or trifluoroacetic acid as solvent and tetramethylsilane as internal standard. U.v. spectra were recorded with a Hitachi 323 spectrophotometer using MeOH as solvent. Mass spectra were measured at 75 eV with a JEOL-01SG spectrometer.

General Procedure for the 3-Substituted 7-Chloroacetylimidazo[2,1-i]purin-6-ylio 8-Oxides (3).—A mixture of the 9-substituted adenines (1) (1 mmol) and chloroacetic anhydride (2 mmol) in toluene (10 ml) was heated under reflux until compound (1) was removed (by t.l.c.). The reaction mixture was concentrated under reduced pressure to leave an oily residue, which was triturated with diethyl ether, filtered off, and recrystallised from an appropriate solvent to give the *imidazo[2,1-i]purin-6-ylio 8-oxides* (3) (see Tables 1 and 2).

3-Benzyl-7-phenylthioacetylimidazo[2,1-i]purin-6-ylio 8-Oxide (4a).—A mixture of compound (3a) (200 mg; 0.59 mmol), thiophenol (97 mg; 0.88 mmol) and triethylamine (0.5 ml) in DMF (50 ml) was stirred at room temperature for 3 h and then concentrated under reduced pressure. The residue was washed with water and recrystallised from DMF–water to give the *mesoionic compound* (4a) (211 mg; 86.8%) as needles, m.p. 292—296 °C (decomp.) (Found: C, 63.6; H, 3.9; N, 16.85. $C_{22}H_{17}N_5O_2S$ requires C, 63.61; H, 4.13; N, 16.86%); $\lambda_{max.}$ (MeOH) 245, 273, and 336 nm; δ [$(CD_3)_2SO$] 4.40 (2 H, s, CH_2CO), 5.57 (2 H, s, CH_2Ph), 7.0—7.6 (10 H, m, ArH), 8.68 (1 H, s, 2-H), and 10.23 (1 H, s, 5-H).

3-Benzyl-7-morpholinoacetylimidazo[2,1-i]purin-6-ylio 8-Oxide (4b).—A mixture of compound (3a) (200 mg; 0.59 mmol) and morpholine (760 mg; 8.72 mmol) in DMF (50 ml) was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was recrystallised from EtOH to give the *mesoionic compound* (4b) as light brown needles, m.p. 238—240 °C (decomp.) (Found: C, 61.35; H, 5.05; N, 21.6. $C_{20}H_{20}N_6O_3$ requires C, 61.21; H, 5.14; N, 21.42%); $\lambda_{max.}$ (MeOH) 238, 278, and 330 nm; δ [$(CD_3)_2SO$] 2.9—4.0 (8 H, m, morpholinomethylene protons), 4.05 (2 H, s, CH_2CO), 5.58 (2 H, s, CH_2Ph), 7.45 (5 H, s, ArH), 8.63 (1 H, s, 2-H), and 10.18 (1 H, s, 5-H).

7-Chloroacetyl-3-(β-D-ribofuranosyl)imidazo[2,1-i]purin-6-

TABLE 1

Preparative, physicochemical, and u.v. spectral data for the 3-substituted 7-chloroacetylimidazo[2,1-*i*]purin-6-ylio 8-oxides (3a)—(3g)

Compound	Reaction time/h	Solvent	M.p./°C	Yield/ %	$\lambda_{max.}$(MeOH)/nm ($\epsilon \times 10^3$)		
(3a)	1.0	DMF–water	285—290 [a]	34.1	243 (22.0)	279 (23.9)	335 (16.1)
(3b)	1.5	EtOH	190	67.4	244 (28.9)	268 (21.0)	335 (16.2)
(3c)	2.5	EtOH	184—185	72.0	247 (48.1)	264 (33.2)	336 (24.1)
(3d)	2.0	DMF–water	250 [a]	45.5	241 (22.7)	278 (20.4)	334 (15.9)
(3e)	1.5	DMF–water	295 [a]	36.7	240 (17.5)	278 (32.5)	335 (19.2)
(3f)	2.0	EtOH	231—232 [a]	57.9	244 (38.2)	267 (26.0)	335 (20.0)
(3g)	3.0	EtOH	190—192	41.4	241 (19.7)	279 (43.2)	335 (18.9)

[a] Decomposed.

TABLE 2

^{1}H N.m.r. spectral and microanalytical data for the 3-substituted 7-chloroacetylimidazo[2,1-*i*]purin-6-ylio 8-oxides (3a)—(3g)

Compound	^{1}H N.m.r. (δ)		Found (%)			Formula	Requires (%)		
	2-H	5-H	C	H	N		C	H	N
(3a)	8.71	10.21 [a]	56.5	3.6	20.35	$C_{16}H_{12}ClN_5O_2$	56.23	3.54	20.49
(3b)	8.84	10.27 [a]	57.5	4.15	19.85	$C_{17}H_{14}ClN_5O_2$	57.39	3.97	19.69
(3c)	8.91	10.31 [a]	64.1	4.25	16.35	$C_{23}H_{18}ClN_5O_2$	63.96	4.20	16.22
(3d)	9.52	10.77 [b]	45.3	2.95	26.1	$C_{10}H_8ClN_5O_2$	45.21	3.04	26.36
(3e)	9.53	10.79 [b]	47.5	3.55	24.95	$C_{11}H_{10}ClN_5O_2$	47.24	3.60	25.04
(3f)	8.73	10.26 [a]	49.25	4.1	23.65	$C_{12}H_{12}ClN_5O_2$	49.07	4.12	23.85
(3g)	8.78	10.24 [a]	46.85	3.85	13.9	$C_{20}H_{20}ClN_5O_9$	47.12	3.95	13.74

[a] In $(CD_3)_2SO$. [b] In CF_3CO_2H.

ylio 8-Oxide (3h).—A solution of compound (3g) (315 mg; 0.62 mmol) in anhydrous MeOH (100 ml), presaturated with ammonia, was stirred in a refrigerator overnight, and then evaporated to dryness at room temperature under reduced pressure. The resultant residue was recrystallised from MeOH to give the *ribofuranosylimidazo*[2,1-i]*purin-6-ylio 8-oxide* (3h) (106 mg; 44.6%) as light brown prisms, m.p. >300 °C (decomp.); *m/e* 383 (M^+); $\lambda_{max.}$ (MeOH) 241 (ε 17 900), 279 (25 400), and 335 nm (14 400); δ [$(CD_3)_2SO$] 4.76 (2 H, s, CH_2CO), 6.05 (1 H, d, *J* 4.4 Hz, 1′-H), 8.79 (1 H, s, 2-H), and 10.16 (1 H, s, 5-H).

9-Benzyl-N^6-chloroacetyladenine (2a).—A mixture of 9-benzyladenine (1a) (225 mg; 1.0 mmol) and chloroacetic anhydride (171 mg; 1.0 mmol) in toluene (20 ml) was stirred at 70 °C for 30 min and then cooled to room temperature to give a pinkish precipitate which was filtered off and dissolved in $CHCl_3$ (8 ml). The latter solution was diluted with diethyl ether (5 ml) to separate the *chloroacetyladenine* (2a) (108 mg; 35.8%) as needles, m.p. 150 °C (Found: C, 55.8; H, 4.25; N, 23.45. $C_{14}H_{12}ClN_5O$ requires C, 55.73; H, 4.01; N, 23.21%); δ [$(CD_3)_2SO$] 4.61 (2 H, s, CH_2CO), 5.50 (2 H, s, CH_2Ph), 7.32 (5 H, s, ArH), and 8.66 and 8.69 (each 1 H, s, 2- and 8-H).

3-Benzyl-3H-imidazo[2,1-i]*purin-8(7H)-one* (5).—A solution of compound (2a) (301 mg; 1.0 mmol) in DMF (10 ml) was heated at 130 °C for 1 h, to give a reddish brown colour, and was then evaporated to dryness and the resultant residue was recrystallised from EtOH to give the *imidazo*[2,1-i]*purin-8(7H)-one* (5) (50.5 mg; 19.1%) as needles, m.p. 148—150 °C (Found: C, 63.15; H, 4.8; N, 26.25. $C_{14}H_{11}N_5O$ requires C, 63.38; H, 4.18; N, 26.40%); *m/e* 265 (M^+); $\lambda_{max.}$ (MeOH) 271sh, 277, and 305 nm; δ [$(CD_3)_2SO$] 4.59 (2 H, s, CH_2CO), 5.41 (2 H, s, CH_2Ph), 7.26 (5 H, s, ArH), and 8.43 and 8.56 (each 1 H, s, 2- and 5-H).

3-Benzyl-7-chloroacetylimidazo[2,1-i]*purin-6-ylio 8-Oxide* (3a).—(a) *From compound* (2a). A mixture of compound (2a) (301.4 mg; 1.0 mmol) and chloroacetic anhydride (171 mg; 1.0 mmol) in toluene (10 ml) was heated under reflux for 1 h and the resultant precipitate was collected by filtration and recrystallised from DMF–water to give the imidazo[2,1-*i*]purin-6-ylio 8-oxide (3a) (171 mg; 49.7%) which was identical in every respect with the sample prepared directly by the reaction of compound (1a) with chloroacetic anhydride.

(b) *From compound* (5). A mixture of compound (5) (5.3 mg; 0.02 mmol) and chloroacetic anhydride (3.5 mg; 0.02 mmol) in toluene (1 ml) was heated under reflux for 30 min, cooled to room temperature, and the resultant precipitate was collected by filtration and recrystallised from DMF–water to give the imidazo[2,1-*i*]purin-6-ylio 8-oxide (3a) (5.8 mg; 84.9%) which was identical in every respect with the sample described above.

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