v-Triazolo[4,5-*d*]pyrimidines (8-Azapurines). Part 21.[1] Synthesis of 2-Substituted 8-Azapurin-6-ones from 4-Amino-1,2,3-triazole-5-carboxamides † and Amidines

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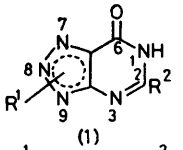
4-Amino-1,2,3-triazole-5-carboxamides (3) (several of them alkylated on a ring-nitrogen atom) were condensed with the acetates of acetamidine, trichloroacetamidine, and benzamidine to give the correspondingly 2-substituted 8-azapurin-6-ones (1). Thus, 4-amino-1-methyl-1,2,3-triazole-5-carboxamide (3b) and acetamidine furnished 2,7-dimethyl-8-azapurin-6-one in excellent yield. The reactions involving trichloroacetamidine halted at an intermediate [*e.g.* at 4-(α-amino-βββ-trichloroethylideneamino)-1,2,3-triazole-5-carboxamide (2d)] which was isolated and cyclized in aqueous alkali. Physical properties (u.v., i.r., *m/e*, pK_a, n.m.r.) of typical products were measured and discussed.

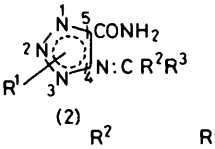
THE medical interest in 8-azapurin-6-one and its derivatives arises from their anti-cancer and anti-allergic properties. Thus unsubstituted 8-azapurin-6-one (azahypoxanthine) was found moderately effective [2] against adenocarcinoma 755, and the 9-ribonucleoside (8-azainisine) prolonged the life of mice with lymphoid leukemia, and also inhibited growth of a solid adenocarcinoma.[3] Further, 8-azapurin-6-ones substituted in the 2-position are anti-allergic and strongly inhibit anaphylaxis in the human lung.[4]

Whereas 8-azapurin-6-ones unsubstituted in the 2-position are readily prepared by heating a 4-amino-1,2,3-triazole-5-carboxamide (3) with formamide, at *ca.* 200°,[5] acetamide and its homologues give only poor yields, and benzamide fails to react. A better approach was suggested by the behaviour of 4-dimethylaminomethyleneamino-1-methyl-1,2,3-triazole-5-carboxamide (2a) which, at its m.p. (168°), evolves dimethylamine



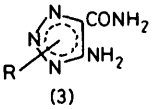
(1)

	R^1	R^2
a;	7-Me	H
b;	7-Me	Me
c;	7-Me	CCl_3
d;	7-Me	Ph
e;	8-Me	Me
f;	8-Me	CCl_3
g;	8-Me	Ph
h;	9-H	Me
i;	9-H	CCl_3
j;	9-CH_2Ph	Me
k;	9-Me	Me



(2)

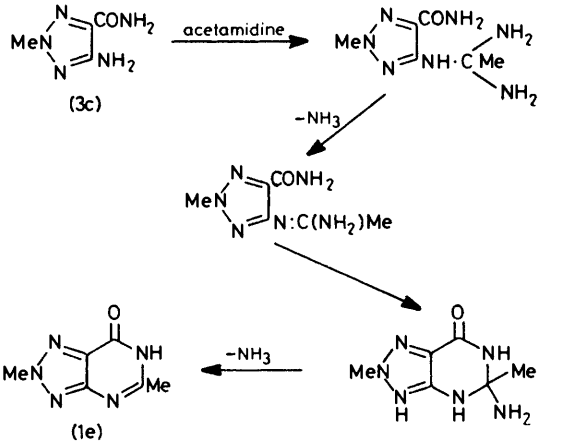
	R^1	R^2	R^3
a;	1-Me	NMe_2	H
b;	1-Me	NH_2	CCl_3
c;	2-Me	NH_2	CCl_3
d;	H	NH_2	CCl_3



(3)

	R
a;	H
b;	1-Me
c;	2-Me
d;	3-Me
e;	3-CH_2Ph

to give 7-methyl-8-azapurin-6-one quantitatively.[6] It was envisioned that the 4-amino-1,2,3-triazole-5-carboxamides (3a—e) would condense with amidines according to the Scheme in which consecutively formed tetrahedral intermediates lose ammonia to give, finally, an



SCHEME

8-azapurin-6-one substituted in the 2-position by the characteristic group of the amidine. This thought was realized by the synthesis, in excellent yields, of the 8-azapurinones (1a—d) named in Table 1, from 4-amino-1-methyl-1,2,3-triazole-5-carboxamide (3b) and formamidine, acetamidine, trichloroacetamidine, and benzamidine, respectively.

The reaction solvents that produced the best yields were normal aliphatic alcohols, followed by ether-alcohols such as methoxyethanol, whereas dimethylformamide proved destructive. Freshly precipitated copper, a possible catalyst, did not improve yields. The amidines were used as acetates, apparently a source of the free base because the hydrochlorides proved unreactive. Acetamidine required a higher temperature (200°) than formamidine, whereas benzamidine and trichloroacetamidine were appreciably more reactive than formamidine.

When the triazole component was varied, the 2-methyl isomer (3c) gave an equally good performance, and so did the *N*-demethylated analogue (3a), although

† In this series, the amino-group of triazoles is consistently numbered 4 to facilitate comparisons.

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this substance (which is an acid [5c] of pK_a 7.8) behaves atypically in some other reactions. Surprisingly poor reactivity was shown by the 3-methyl and 3-benzyl derivatives (3d and e), to be discussed later.

The reactions using trichloroacetamidine did not go to completion but built up the azomethine intermediate: 4-(α-amino-βββ-trichloroethylideneamino)-1,2,3-triazole-5-carboxamide (2d) and its 1- and 2-methyl derivatives (2b and c) respectively (see Table 1, under Intermediate).

It is evident (see Scheme) that the electron-withdrawing nature of the substituent in trichloroacetamidine must greatly favour the nucleophilic addition of the 4-amino group of the triazole to the positively-charged carbon atom in the amidine. Thus facilitated, production of the first tetrahedral intermediate would lead (by restoration of the conjugation) to the ethylideneamino intermediates (2). Normally the latter would react, similarly to the amidine, with the nucleophilic amide group of the triazole; the retardation of this reaction must be attributed to steric hindrance exerted by the three chlorine atoms. However, the ring of the intermediates (2b and c) could be closed by stirring with cold 0.5N-potassium hydroxide, although the nor-analogue (2d), by becoming an anion, offered coulombic repulsion. Alternatively, ring closure of the intermediates (2b and c) could be effected by boiling with acetic acid or octanol but the products were not so clean. Tin(IV) chloride in dichloromethane was ineffective.

Table 1 lists the conditions, yields, purification methods, and m.p.s for the condensations. It is not clear why the reaction should be disfavoured by 3-alkyl substituents in the triazoles (3d and e), particularly as formamide produces 8-azapurin-6-ones equally readily [5a-d] from all five starting materials (5a—e). The larger positive charge on the reactive carbon atom in formamide, compared to that in acetamidine, may overcome the difficulty of splitting off a proton imposed on the 4-amino group of the triazole by proximity to the electron-releasing 3-alkyl group.

In a variant of the main reaction, ethyl acetimidate acetate was substituted (for acetamidinium acetate) for combination with the triazole (3b) to give the azapurinone (1b). The best conditions proved to be 24 h in boiling hexanol; the product was much harder to purify, and the yield lower (50%). In another variant, from a current patent,[6] the triazole (3a) was fused with benzamidine hydrochloride in sodium acetate at 190° for 24 h to give 2-phenyl-8-azapurin-6-one in 13% yield.

Physical Properties.—The i.r. spectra of the 8-azapurinones (Table 2) showed the expected NH stretching bands near 3 200, and strong Amide I, II, and III absorptions near 1 700, 1 600, and 1 300 cm^{-1}, respectively, comparable with results for other 8-azapurin-6-ones.[5] The Amide I band, in the simple amide (2b) occurs at a lower frequency, as is usual in triazole-5-carboxamides.[7] Strong C–Cl stretching bands, near 800 cm^{-1} are evident in the trichloro-derivatives (1c and 2b). Some n.m.r., u.v., and mass spectra are given in the Experimental section. The ^1H n.m.r. signal for a methyl group in the pyrimidine ring is situated much further upfield than that in the triazole ring. The acidic ionization of a typical example (1b) was found to be 9.0 (pK_a), a little weaker (because of the inductive effect of

TABLE 1

Preparation of 8-azapurin-6-ones (1) from 4-amino-1,2,3-triazoles (3) and amidines

8-Azapurin-6-one	Product	Starting materials [a]	Reflux solvent	t/h	Work up [b]	Recrystallization solvent	Parts	M.p. (°C)	Yield (%)
7-Methyl	(1a)	(3b) + F	Butanol	8	C	Ethanol	100	264	82
2,7-Dimethyl	(1b)	(3b) + A	Octanol	4	C	Ethanol	55	281	80
(Intermediate)	(2b)	(3b) + T	Butanol	4	D, E (a)	Ethanol	30	219	67
7-Methyl-2-trichloromethyl	(1c)	(2b) + K			E (a)	H_2O–ethanol (1 : 3 v/v)	50	237	87
7-Methyl-2-phenyl	(1d)	(3b) + B	Butanol	8	D, E (b)	Nitromethane	85	304	81
2,8-Dimethyl	(1e)	(3c) + A	Octanol	4	D, E (c)	Ethanol	90	290	86
(Intermediate)	(2c)	(3c) + T	Ethanol	24	D, E (a)	Ethanol	15	208	65
8-Methyl-2-trichloromethyl	(1f)	(2c) + K			E (a)	Ethanol	42	259	92
8-Methyl-2-phenyl	(1g)	(3c) + B	Butanol	8	C, E (b)	Nitromethane	90	287	86
2-Methyl	(1h)	(3a) + A	Hexanol	4	D, E (b)	Ethanol	30	273	90
(Intermediate)	(2d)	(3a) + T	Ethanol	24	D, E (a)	H_2O–ethanol (1 : 1 v/v)	100	231	82
9-Benzyl-2-methyl	(1j)	(3e) + A	Octanol	8	D, G	Water	200	191	16
2,9-Dimethyl	(1k)	(3d) + A	Octanol	48	D, G	Water	30	258	17

[a] F, Formamidine; A, acetamidine, T, trichloroacetamidine, B, benzamidine (all as acetates); K, 0.5N-KOH. [b] C, Mixture set aside at −10 °C overnight, filtered, and washed with light petroleum; D, solvent distilled from oil-bath, at water-pump vacuum and residue washed with light petroleum; E, after treatment C or D, product was homogenized with water, and the pH adjusted to (a) 2, with H_2SO_4; (b) 3, with formic acid; or (c) 4, with acetic acid; G, residue was rubbed with N-KOH, filtered from starting material, and the filtrate adjusted to pH 4.

TABLE 2

I.r. spectra ($\nu_{max.}$/cm^{-1})

Compound	Spectrum	Medium
(1b)	3 210m, 1 705br,s, 1 595m, 1 380m, 1 265s, and 1 115m	KBr disc
(1e)	3 420, 3 150, 3 015, 2 855 (all m), 1 720m, 1 695s, 1 610s, 1 590m, 1 530m, 1 385m, 1 300m, 1 285s, 865m, and 800m	KBr disc
(1j)	3 440br,m, 3 000br,m 1 685s, 1 600s, 1 555m, 1 525m, 1 375m, 1 280s, and 1 175m	KBr disc
(1c)	3 185m, 3 060br,m, 1 705br,s, 1 595s, 1 420m, 1 300s, and 840s	Nujol
(2b)	3 280br,m, 3 140br,m, 1 680m, 1 645s, 1 605m, 1 570m, 1 415m, 1 325m, 850m, and 785s	Nujol

the second methyl group) than those (8.1—8.8) or 7-, 8-, and 9-methyl-8-azapurin-6-one.[5b-d]

EXPERIMENTAL

^{1}H N.m.r. spectra were obtained with a Varian HFT-80 instrument, at 80 MHz and 33 °C using tetramethylsilane as internal standard, i.r. spectra with a Perkin-Elmer 727 B spectrometer calibrated with polystyrene at 1 603 cm^{-1}, and u.v. spectra with a Cary 16 instrument. Elemental analyses were performed by Galbraith Laboratories, Inc., Tennessee, and by the Australian National University Analytical Services Unit, Canberra, with the results given in Table 3.

The solvents were dried over molecular sieves. Formamidinium and acetamidinium acetates were commercial specimens; benzamidinium acetate, m.p. 243° (decomp.), was made by metathesis from the hydrochloride and silver acetate. These acetates were dried in air at 80° for 15 h. Trichloroacetamidine [8] was simply added with one equivalent of acetic acid to the reaction mixture. The five aminotriazolecarboxamides (3a—e) were made as in refs. 9, 5*b*, 5*c*, 5*d*, and 9 respectively. In the recrystallizations, it was usually profitable to take two crops.

The following preparations illustrate the various methods, delineated by a capital letter, in footnote *b* of Table 1.

2,7-Dimethyl-8-azapurin-6-one (*1,5-Dimethyl-v-triazolo*[4,5-d]*pyrimid-7-one*) (C).—4-Amino-1-methyl-1,2,3-triazole-5-carboxamide (0.141 g, 0.001 mol), acetamidinium acetate (0.35 g, 3 equiv.), and octanol (2 ml) were heated under reflux for 4 h. The mixture was stored at −10° overnight, filtered off, washed with light petroleum (b.p. 60—80°) (2 ml), and recrystallized from ethanol (water was avoided in this work-up because of the unusually high solubility of the product), τ[$(CD_3)_2SO$] 5.81 (7-Me), and 7.77 (2-Me), pK_a (determined potentiometrically [10] as 0.01M-solution in water at 20°) 8.97 ± 0.03.

2,8-Dimethyl-8-azapurin-6-one [D,E(c)].—Using the same quantities and reflux time as in the foregoing, but the 2-methyl isomer (3c) of the triazole, the reaction was worked up by removing the solvent at 135° and 25 mmHg, washing the product with light petroleum (2 ml), and stirring the residue with water (1 ml). The pH of this suspension was lowered to 4 with acetic acid, the product filtered off, dried, and recrystallized from ethanol, τ[$(CD_3)_2SO$] 5.64 (8-Me) and 7.63 (2-Me); *m/e* 165 (M^+), 150, 43, and 42.

9-Benzyl-2-methyl-8-azapurin-6-one (*3-Benzyl-5-methyl-v-triazolo*[4,5-d]*pyrimidin-7-one*) (G).—4-Amino-3-benzyl-1,2,3-triazole-5-carboxamide (0.542 g, 0.002 5 mol), acetamidinium acetate (0.87 g), and octanol (5 ml) were heated under reflux for 8 h. The solvent was taken off at 135° and 25 mmHg, and the residue rubbed with light petroleum (5 ml; discarded) and then with N-KOH (5 ml). Recovered triazole (3e) was filtered off (61%) and the filtrate acidified to pH 4 with acetic acid. The precipitate was filtered off and recrystallized from water, τ($CDCl_3$) — 2.84 (NH), 2.46 (5 H, Ph), and 4.12 (2 H, CH_2); *m/e* 241 (M^+), 212, 184, and 91 (benzyl).

4-(α-Amino-βββ-trichloroethylideneamino)-1-methyl-1,2,3-triazole-5-carboxamide (2b) [D,E(a)].—4-Amino-1-methyl-1,2,3-triazole-5-carboxamide (0.141 g, 0.001 mol), trichloroacetamidine (0.483 g, 0.003 mol), acetic acid (0.18 g, 0.003 mol), and butanol (2 ml) were heated under reflux for 2 h. The solvent was distilled off, the residue washed with light petroleum (2 ml), dried, then triturated with water (1 ml), and the pH lowered to 2, yielding crystals of the title product, recrystallized from ethanol, *m/e* 284 + 286 + (smaller) 288 (M^+), 193 and 136 (both with chlorine) and 113, 85, and 42 (without chlorine), $\lambda_{max.}$ 289 nm (log ε 4.19).

7-Methyl-2-trichloromethyl-8-azapurin-6-one.—This trichloroethylideneamino compound (0.286 g, 0.001 mol) and 0.5N-potassium hydroxide (4 ml) were stirred at 24° for 5 h. Acidification to pH 2 with 5N-H_2SO_4 gave the azapurinone, which was recrystallized, *m/e* 267 + 269 + (smaller) 271 (M^+), 239, and 204 (both with chlorine), $\lambda_{max.}$ 283 nm (log ε 3.93).

TABLE 3

Microanalytical results

Product	Found (%) C	H	N	Cl	Formula	Required (%) C	H	N	Cl
(1a) [a]									
(1b)	43.7	4.1	42.1		$C_6H_7N_5O$	43.6	4.3	42.4	
(1e)	43.85	4.3	42.3		$C_6H_7N_5O$				
(1k)	43.6	4.3	42.4		$C_6H_7N_5O$				
(2b)	25.3	2.5	29.4	37.1	$C_6H_7Cl_3N_6O$	25.2	2.5	29.4	37.3
(2c)	25.2	2.5	29.4	37.3	$C_6H_7Cl_3N_6O$				
(2d)	22.45	2.0	30.9	39.3	$C_5H_5Cl_3N_6O$	22.1	1.9	31.0	38.2
(1c)	27.0	1.5	25.9	39.6	$C_6H_4Cl_3N_5O$	26.8	1.5	26.1	39.6
(1f)	26.9	1.8	26.3	39.9	$C_6H_4Cl_3N_5O$				
(1d)	58.3	4.0	30.9		$C_{11}H_9N_5O$	58.1	4.0	30.8	
(1g)	58.1	3.9	30.7		$C_{11}H_9N_5O$				
(1h) [b]	39.8	3.4	46.2		$C_5H_5N_5O$	39.75	3.3	46.3	
(1j)	59.9	4.7	29.15		$C_{12}H_{11}N_5O$	59.7	4.6	29.0	

[a] Ref. 5*b* [from (3b) and formamide]. [b] D. Acker and J. Castle, *J. Org. Chem.*, 1958, **23**, 2010 (from 4,5-diamino-2-methylpyrimidin-6-one and nitrous acid).

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