v-Triazolo[4,5-*d*]pyrimidines (8-Azapurines). Part 24.[1] The 3-Alkyl Derivatives

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4-Methylamino-1,2,3-triazole-5-carboxamide (2e) and its 3-benzyl derivative (2b) were cyclized with hydrochloric acid and triethyl orthoformate to give 3-methyl-8-azapurin-6(1*H*)-one (1c) and its 9-benzyl derivative (1b). The reaction mechanism is discussed. The 8-azapurinone (1c) was converted by phosphorus pentasulphide into 3-methyl-8-azapurine-6(1*H*)-thione (9) and an extraordinary by-product, 5-amino-1,2,3-thiadiazole-4-*N*-(thioformyl)carbothioamide (10). Hydrogenation of the two 8-azapurinones (1c) and (1b) gave 1,2-dihydro-3-methyl-8-azapurin-6(3*H*)-one (7b) and its 9-benzyl derivative (7a), respectively.

4-Methylamino-1,2,3-triazole-5-carbonitrile (12c) was converted by formamidinium acetate into 6-amino-3-methyl-8-azapurine (13a). Hydrogenation of 3-benzyl-4-methylamino-1,2,3-triazole-5-carbonitrile (12b) produced 5-aminomethyl-3-benzyl-4-methylamino-1,2,3-triazole (14a) which gave formyl (14b) and acetyl, formyl (14c) derivatives when cyclization was attempted. Several Dimroth retrogressions were encountered, in which a methyl group appeared to move from the exocyclic 4-amino-group to a nitrogen atom (N-3) in the ring, in one instance displacing a 3-benzyl group. Two other unusual by-products were the highly fluorescent diacylamine, 3-benzyl-4-methylamino-5-*N*-formylcarboxamide (6) obtained by ring-opening of the 8-azapurinone (1b), and bis-(3-benzyl-4-methylamino-1,2,3-triazol-5-carbonyl)amine (3) from the action of sodium ethoxide on the triazole (2d).

^{1}H N.m.r., i.r., and mass spectra of the products are discussed. The ^{1}H n.m.r. spectra of three triazoles showed several twinned sets of signals due to stable rotamers. There were several unusual features in the i.r. spectrum of 3-methyl-8-azapurin-6(1*H*)-one.

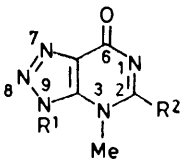
INTEREST in 8-azapurines as potential anti-cancer, anti-viral, and anti-allergenic drugs is sustained by knowledge that they are not incorporated into mammalian DNA, thus lowering the risk of mutagenesis.[2] Following the common practice of *N*-alkylating heterocyclic drugs to obtain a depot effect,[3] many 8-azapurines have been methylated in the 1-, 7-, 8-, and 9-positions. The synthesis of 3-methylated 8-azapurines has proved to be more difficult, and a search of the literature brought to light only the three following examples: 2-amino-3-methyl-8-azapurin-6(3*H*)-one (1a) (an aza-analogue of guanine),[4] 3-methyl-8-azapurine-2,6(1*H*,3*H*)-dione (an aza-analogue of xanthine), and 3-methyl-8-azapurin-2-(3*H*)-one,[5] all made from 1-methylpyrimidinone intermediates.

At the root of this neglect lie two considerations: (*i*) the 3-alkyl series has less stabilizing conjugation than any isomeric *N*-alkyl series; and (*ii*) a transfer of alkyl groups from the 3- to the 9-position could take place if instability led to opening of the pyrimidine ring and then the triazole ring. In the belief that these disadvantages could be avoided, the following project was undertaken to increase the variety of 3-methyl derivatives.

RESULTS AND DISCUSSION

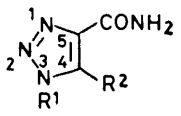
The first attempts were alkylations of available 8-azapurines, similar to recorded methylations (with methyl toluene-4-sulphonate) of purine-6(1*H*)-thione [6] and 6-aminopurine (adenine) [7] to give 3-methyl-6-methylthio-3*H*-purine and 6-amino-3-methyl-3*H*-purine, respectively. Unfortunately 8-azapurine-6(1*H*)-thione and 6-methylthio-8-azapurine were destroyed by this procedure, and 6-amino-8-azapurine furnished only a dimethylated quaternary amine no matter how little methylating agent was used.

Hence it was decided to proceed *via* 1,2,3-triazole intermediates, the flexibility of which has been demonstrated in previous Parts of this series. Accordingly, 4-amino-3-benzyl-1,2,3-triazole-5-carboxamide (2a) † (from cyanoacetamide and benzyl azide [8]) was converted [9] to 3-benzyl-4-methylamino-1,2,3-triazole-5-carboxamide (2b). Unfortunately this did not give the desired 9-benzyl-3-methyl-8-azapurin-6(3*H*)-one (1b) when heated



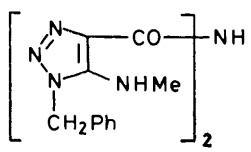
(1)

	R^1	R^2
a;	H	NH_2
b;	CH_2Ph	H
c;	H	H



(2)

	R^1	R^2
a;	CH_2Ph	NH_2
b;	CH_2Ph	NHMe
c;	Me	$NHCH_2Ph$
d;	CH_2Ph	N(CHO)Me
e;	H	NHMe
f;	Me	NH_2
g;	H	N(CHO)Me
h;	H	$N(CH_2OH)Me$



(3)

† In this series, the amino group attached to the triazole ring is consistently numbered 4, to facilitate comparisons.

with the usual reagents for effecting such closures, *e.g.* formamide, formamidinium acetate, formic acid, or triethyl orthoformate (the latter two used alone or with acetic anhydride). Instead, a Dimroth retrogression [10,*] usually took place to give the hitherto unknown 4-benzylamino-3-methyl-1,2,3-triazole-5-carboxamide (2c). This, and similar rearrangements, were confirmed by ^{1}H n.m.r. (see ref. 11, and paragraph on n.m.r. in what follows).

In the expectation of finding a more amenable intermediate, the methylamino-compound (2b) was formylated to 3-benzyl-4-*N*-methylformamido-1,2,3-triazole-5-carboxamide (2d). This compound gave a most unusual ^{1}H n.m.r. spectrum: doublet singlet signals were furnished by each of four substituents (CHO, NH, CH_2, and Me) at 27 °C, as shown in Figure 1 and Table 1.

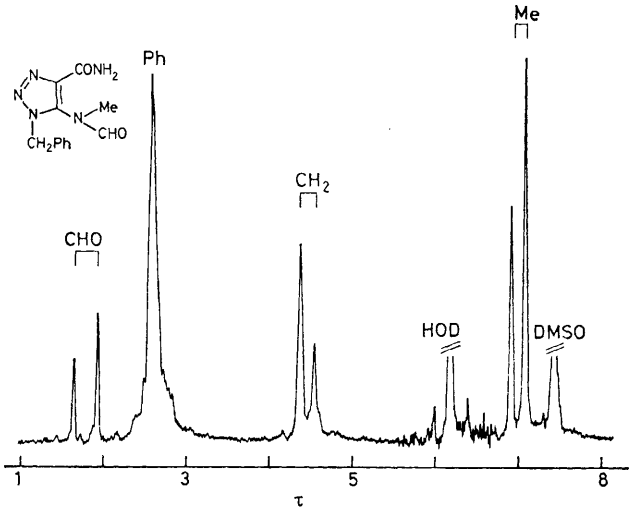


FIGURE 1 ^{1}H N.m.r. spectrum of 3-benzyl-4-*N*-methylformamido-1,2,3-triazole-5-carboxamide [in $(CD_3)_2SO$ + D_2O at 27 °C and 100 MHz]

These coalesced to four single signals at 90 °C, and the twinning reappeared when the solution was cooled to 27 °C. The duplication of signals was not seen in the absence of any one of the groups: CHO, Me, or CH_2Ph. Twinning is attributed to rotational isomerism arising from double-bond character in the link between the ring and the exocyclic nitrogen atom, and a heightened energy barrier to coalescence. Two other examples of multiple twinning of signals arose in the present work.

The formyl compound (2d) was not affected by aqueous sodium hydrogencarbonate, a reagent that converted 4-formamidoimidazole-5-carboxamide to purin-6(1*H*)-one.[12] It was destroyed by heating with formamide, whereas ethanolic sodium ethoxide produced the more complex substance, bis-(3-benzyl-4-methylamino-1,2,3-triazol-5-carbonyl)amine (3). The latter was dissolved without change by 1N-potassium carbonate, but cold 1N-potassium hydroxide quickly hydrolysed it to the amide (2b) and the corresponding acid in equimolar proportions.

* The intramolecular movement of a methyl group from an endo- to an exo-cyclic nitrogen atom occurs in Dimroth rearrangement, whereas a shift in the reverse direction is a retrogression.[10]

TABLE 1

^{1}H N.m.r. spectra of 8-azapurines and 1,2,3-triazoles

Compound	τ Values [a]
(1b)	1.93 (1 H, H-2), 2.50—3.00 (5 H, m, Ph), 4.01 (2 H, CH_2), 6.21 (3 H, Me)
(1c)	1.47 (1 H, H-2), 6.10 (3 H, Me)
(2b) [b]	2.50—3.02 (5 H, m, Ph), 4.20 [c] (1 H, NHMe), 4.42 (2 H, CH_2), 7.12 (3 H, Me)
(2c)	2.74 (6 H, Ph + 4 NH),[d] 5.45 (2 H, d,[e] *J* 6 Hz, CH_2), 6.18 (3 H, Me)
(2d) [f]	1.76 and 2.03 (together 1 H, CHO), 2.10 [c] and 2.84 [c] (2 H, NH), 2.73 (5 H, Ph), 4.46 and 4.63 (2 H, CH_2), 7.01 and 7.18 (3 H, Me)
(2e)	2.8 (br,[c] NH), 3.0 (br,[c] NH), 4.1 (br,[c] 4-NH), 7.19 (centre) (3 H, d,[e] *J* 6 Hz, Me)
(2f) [b]	2.66 (br,[c] NH), 2.95 (br,[c] NH), 6.24 (3 H, Me)
(2g)	1.39 (1 H, CHO), 2.4 [c] (NH), 2.7 [c] (NH), 6.73 (3 H, Me)
(3)	−0.98 [c] (1 H, CONH), 2.6—2.9 (12 H, m, 2 × Ph + 2 NH),[g] 3.4 (br,[c] MeN*H*), 4.40 (4 H, 2 × PhCH_2), 7.05 (6 H, d,[e] *J* 6 Hz, 2 × Me)
(6)	−0.90 (br,[c] CONH), 0.91 (1 H, d,[e] CHO), 2.62—2.71 (5 H, m, Ph), 3.30 (br,[c] 4 NH), 4.46 (2 H, CH_2), 7.03 (3 H, Me)
(7a)	2.37 (br,[c] NH), 2.64—2.85 (5 H, m, Ph), 4.40 (2 H, CH_2Ph), 5.64 (2 H, d,[e] *J* 4 Hz, 2-CH_2), 7.21 (3 H, Me)
(9)	1.47 (1 H, CH), 6.07 (3 H, Me)
(10)	−0.37 [c] (NH), −0.22 (1 H, CHS)
(12a) [h]	1.68 + 1.72 (together 1 H, CHO), 2.65 (5 H, Ph), 4.33 + 4.47 (2 H, CH_2Ph), 6.76 + 6.98 (3 H, Me)
(12b)	2.81 (5 H, Ph), 4.65 (2 H, CH_2), 7.04 (3 H, d,[e] *J* 6 Hz, Me)
(12c)	2.96 [c] (NH), 7.16 (3 H, d,[e] *J* 5 Hz, Me)
(13)	0.99 [c] (NH), 1.30 [c] (NH), 1.63 (1 H, CH), 6.07 (3 H, Me)
AM [b,i]	1.79 (1 H, 2-CH), 1.9 [c] (NH), 5.92 (3 H, Me)
(14a)	2.69 (5 H, m, Ph), 4.65 (2 H, CH_2Ph), 6.23 (2 H, C$H_2$$NH_2$), 7.18 (3 H, d,[e] *J* 6 Hz, Me), 8.2 (br, NH_2)
(14b)	1.7 [c] (NH), 2.09 (1 H, CHO), 2.77 (5 H, Ph), 4.60 [c] (NH), 4.70 (2 H, PhCH_2), 5.70 (2 H, d,[e] *J* 5 Hz, CH_2NH), 7.27 (3 H, d,[e] *J* 6 Hz, Me)
(14c)	1.75br [c] (NH), 1.81 and 2.20 (together 1 H, CHO), 2.71 and 2.83 (5 H, Ph), 4.55 and 4.62 (2 H, CH_2Ph), 5.80 and 5.85 (2 H, CH_2NH), 7.02 and 7.19 (3 H, NMe), 8.26 (3 H, Ac)
(16)	2.07 (1 H, CHO), 2.74 (5 H, Ph), 4.17 [c] (1 H, t, NH coupled to CH_2), 5.72 and 5.90 (each 2 H, 2 × d,[e] each *J* 6 Hz, 2 × CH_2), 6.27 (3 H, Me)

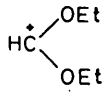
[a] At 30 °C in $(CD_3)_2SO$, $SiMe_4$ as internal standard. [b] Known substance, but n.m.r. is new. [c] Peak vanished when D_2O was added. [d] D_2O converted to 5 H. [e] Doublet, due to coupling within a CHNH group, collapsed to a singlet when D_2O was added. [f] At 27 °C, see Figure 1. [g] D_2O converts to 10 H. [h] Compare with (2d). [i] 6-Amino-9-methyl-8-azapurine.

The desired 9-benzyl-3-methyl-8-azapurin-6(3*H*)-one (1b) was finally produced, in excellent yield, by stirring the unformylated triazole (2b) with triethyl orthoformate and concentrated hydrochloric acid at ambient temperature. For this rather surprising reaction, the following mechanism is suggested. Electrophilic attack by the diethoxycarbenium ion (4), which is known to be stabilized by strong acids during the hydrolysis of this orthoformate,[13] should yield the acetal (5), analogous to the acetals of dimethylformamide used in the preparation of enamines. Loss of two molecules of ethanol would give the isolated product (1b). A previous use of triethyl orthoformate with hydrochloric acid (but to form a *five*-membered ring) was to convert 4,5-diaminopyrimidines to purines.[14]

9-Benzyl-3-methyl-8-azapurin-6-one (1b) lacked the usual stability of the 8-azapurin-6-ones. When boiled

with water for 2 min, it gave, quantitatively, 3-benzyl-4-*N*-methylformamido-1,2,3-triazole-5-carboxamide (2d). When stirred with cold 1N-sodium hydroxide, it produced the deformylated analogue (2b). Cold, dilute acetic acid converted the azapurin-6-one (1b) to an isomer of the amide (2d), namely 3-benzyl-4-methylamino-1,2,3-triazole-5-*N*-formylcarboxamide (6), which was prepared also by the action of phosphoryl chloride and dimethylformamide on the amide (2b). This product (6) displayed the strong fluorescence characteristic of diacylamines.[15]

Attempts to debenzylate the azapurinone (1b) with



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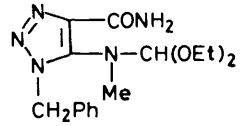

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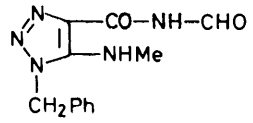

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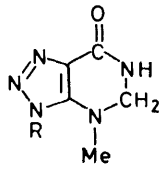


(7)

a; R = CH_2Ph
b; R = H

sodium and ammonia destroyed it, whereas hydrogenation over palladium gave only the dihydro-derivative, 3-benzyl-1,2,3,6-tetrahydro-3-methyl-8-azapurin-6(3*H*)-one (7a).

Access to benzyl-free 3-methyl-8-azapurines was finally obtained *via* 4-methylamino-1,2,3-triazole-5-carboxamide (2e), readily available from debenzylation of the amide (2b).[9] When gently heated, this amide underwent a Dimroth retrogression to the isomeric 4-amino-3-methyl-1,2,3-triazole-5-carboxamide (2f), a tendency that had to be guarded against in planning condensations to yield 3-methyl-8-azapurin-6(3*H*)-one (1c). However, this observation was worthwhile because it provided the first convenient synthesis of 4-amino-3-methyl-1,2,3-triazole-5-carboxamide (2f), the essential intermediate for preparing 9-methyl-8-azapurines;[9] the usual synthesis required the highly toxic, easily detonated reagent methyl azide.[16]

Neither 4-methylamino-1,2,3-triazole-5-carboxamide (2e) nor the formyl derivative, 4-*N*-methylformamido-1,2,3-triazole-5-carboxamide (2g), yielded any 3-methyl-8-azapurin-6(3*H*)-one with the conventional reagents. Fortunately the orthoformate and acid procedure (described earlier) proved to be applicable here, but only if the reaction mixture was heated. 3-Methyl-8-azapurin-6-one, obtained thus, from the triazole (2e), in excellent yield, differed from its 7-,[17] 8-, and 9-,[18] and 1-methyl [19] isomers by giving a *fluorescent* spot on paper chromatography developed in ammonium chloride. Moreover, the NH-stretching band in the i.r. spectrum lies at 3 420 cm^{-1}, a frequency far higher than found in any isomer. This is not an OH-stretching band, as from an enolic tautomer, because very strong amide I, II, and III bands [20] are clearly seen, as in all four isomers. Even more extraordinary features of the spectrum (Figure 2) are the areas of absorption at 2 700—2 400 and

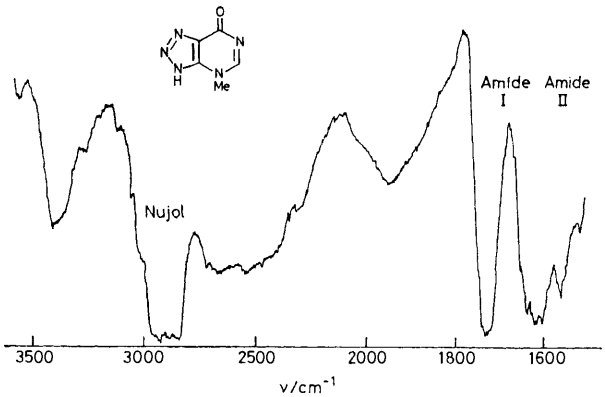
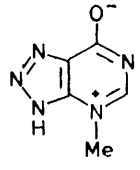


FIGURE 2 I.r. spectrum (Nujol mull) of 3-methyl-8-azapurin-6(1*H*)one

again at 1 950 cm^{-1}, implying a strong dipolar contribution, of type (8) for example, to the reasonance hybrid. The 1-methyl isomer [9] show much less of this i.r. feature, and the other three isomers none. However, the related molecule, 3-methylpurin-6(3*H*)-one (a sample of which was kindly sent by Dr Gertrude Elion) was found to have an i.r. spectrum very similar to that of Figure 2 (see Table 2).

Hydrogenation of 3-methyl-8-azapurin-6-one stopped at the dihydro-derivative, 1,2-dihydro-3-methyl-8-azapurin-6(3*H*)-one (7b) (M^+ 153), which proved hard to



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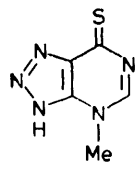


(9)

isolate initially because of its high solubility in water and a tendency to gel in ethanol. Although this base was stable in solution, and to heating in air at 110 °C, the hydrochloride, in moist $(CD_3)_2SO$, gave presumptive evidence (^1H n.m.r.) of reversible ring-opening to 4-*N*-(hydroxymethyl)methylamino-1,2,3-triazole-5-carboxamide (2h). Apart from the expected signals at τ 5.32 (CH_2) and 6.83 (Me) (*cf.* spectrum of neutral species in Table 1), this salt gave strong additional signals at τ 5.75 (CH_2) and 7.24 (Me), the pairs integrating for two and three protons, respectively. It has been noted that hydrogenated pyrimidines have a strong tendency to open in the 2-position.[21] Attempts to deoxygenate

TABLE 2

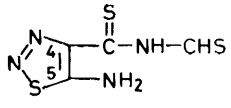
I.r. spectra ($\nu_{max.}$/cm^{-1}) in Nujol

Compound	Spectrum
(1b)	1 650s br (CO str), 1 560s, 1 340m, 1 285m, 1 145m, 1 055m
(1c) [a]	3 420, 3 020 (NH str), 2 700—2 400m, vbr, 1 950w vbr, 1 730s, br (amide I), 1 620s, br (amide II), 1 560m, 1 295m (amide III), 1 140m, 1 045m
MP [b]	3 500, 3 320, 3 100m, 2 700—2 400m vbr, 1 890w, 1 835w, 1 670s vbr, 1 535m, 1 310m, 1 225m, 1 180m, 1 135m, 1 035m
(2d)	3 350, 3 200, 1 660s vbr, 1 610s, 1 590s, 1 330m, 1 295s, 1 280s, 1 245m, 1 115mw
(2e)	3 410, 3 360, 3 315, 3 190 (all m, NH str), 1 655s, br (amide I), 1 585s (amide II), 1 520m, 1 350m, 1 260m, 980m
(3) [c]	3 360m, br (NH), 1 700s, (amide I), 1 605s (amide II), 1 185m, 1 145s, 1 045m, and 835m
(6)	3 320, 3 280m, 1 710s (CO), 1 660s (CO), 1 605s, 1 285m, 1 190s, 1 040m
(7a)	3 180s (NH), 1 655s (amide I), 1 605s, 1 505s (amide II), 1 330m (amide III), 1 285m, 1 230m, 1 210m
(7b)	3 220, 3 120m (NH), 1 670s br (amide I), 1 585s (amide II), 1 340s, 1 215 + 1 195m (tertiary amine doublet), 1 080m, and 965m
(12a)	2 220m (C≡N str), 1 705s (CO str), 1 575s, 1 265m, 1 045m
(12b)	3 300m (NH), 2 215m (C≡N str), 1 610s (C=N str), 1 320m, 1 065m
(12c) [d]	3 350m, 3 270w (NH), 2 240 (C≡N str), 1 700m br, 1 290m, 1 265m, 970m
(13) [e]	3 500w, 3 390w, 3 200—3 000s, br (different types of NH), 1 950w (immonium bend), 1 730s (C=N$^+$ str), 1 635s (C=N str), 1 570s (NH bend), 1 420m, 1 340m, 1 000s, 970s
(14b)	3 360m, 3 290s, 1 640s, 1 590s, 1 535m, 1 430m, 1 250m, 1 230m

[a] Repetition in hexachlorobutadiene furnished an extra signal, 2 950m cm^{-1}. [b] 3-Methylpurin-6-one. [c] Extra signals from hexachlorobutadiene, 3 030w and 1 480s, br cm^{-1}. [d] For spectrum of (12d), see ref. 23. [e] Compare with spectrum (15b) of isomer, 6-amino-9-methyl-8-azapurine, 3 270, 3 090 (NH), 1 690, 1 615, 1 585, 1 330 (all m).

compounds (1c) and (7b), with lithium aluminium hydride or sodium borohydride and an organic acid, led to destruction.

3-Methyl-8-azapurin-6-one was converted to the yellow 3-methyl-8-azapurine-6(3*H*)-thione (9) by phosphorus pentasulphide in pyridine used below its boiling point to avoid destruction of the product. An alkali-insoluble by-product gave microanalytical values for $C_4H_4N_4S_3$ (M^+ 204), had only one unexchangeable ^{1}H n.m.r. signal (τ −0.22), was non-acidic, and evolved



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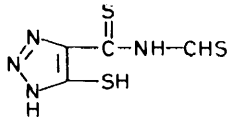
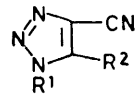


(11)

hydrogen sulphide when boiled with water. It was assigned the structure 5-amino-1,2,3-thiadiazole-4-*N*-(thioformyl)carbothioamide (10), formed apparently by rearrangement of the dibasic acid, 4-mercapto-1,2,3-triazole-5-*N*-(thioformyl)carbothioamide (11) (not isolated). Although the initial opening of the pyrimidine ring of the 8-azapurine is surprising, the ready isomerism of 4-mercapto-1,2,3-triazoles to 5-amino-1,2,3-thiadiazoles is well known.[22]

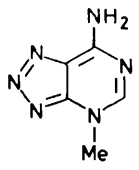
3-Methyl-8-azapurine-6-thione was destroyed during all attempts to de-thiate it with Raney nickel, iodine, nitrous acid, or hydrogen peroxide. Attempts to methylate the sulphur atom led only to the evolution of methanethiol and regeneration of 3-methyl-8-azapurin-6-one (1c). Likewise, 3-methyl-6-methylthiopurine was found [7] to be more prone to decomposition than was any of its *N*-methyl isomers.

In yet another approach to 3-methyl-8-azapurines, 3-benzyl-4-formamido-1,2,3-triazole-5-carbonitrile was prepared, in two steps,[11,23] from 4-amino-3-benzyl-1,2,3-triazole-5-carboxamide (2a), and methylated to 3-benzyl-4-*N*-methylformamido-1,2,3-triazole-5-carbonitrile (12a) (new) which gave a ^{1}H n.m.r. spectrum

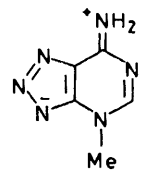


(12)

	R^1	R^2
a;	CH_2Ph	N(CHO)Me
b;	CH_2Ph	NHMe
c;	H	NHMe
d;	Me	NH_2



(13a)



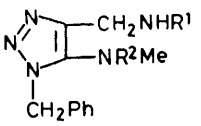
(13b)

indicative of rotational isomerism, similar to that shown in Figure 1. The twinning was dependent on the presence of all three groups, *i.e.* $PhCH_2$, CHO, and Me. Alkaline hydrolysis gave 3-benzyl-4-methylamino-1,2,3-triazole-5-carbonitrile (12b) which was correlated with the foregoing intermediates by conversion to the corresponding amide (2b) with hydrogen peroxide.

The nitrile (12b) was debenzylated with sodium and ammonia to 4-methylamino-1,2,3-triazole-5-carbonitrile (12c), which retrogressed to the known [24] 4-amino-3-methyl-1,2,3-triazole-5-carbonitrile (12d) instantaneously at 180 °C. 6-Amino-3-methyl-8-azapurine (13) was obtained almost quantitatively by heating the nitrile (12c) with formamidinium acetate. Like 6-amino-3-methylpurine,[25] it has much weaker acidic properties than the unmethylated analogue. This indicates that it is not the tautomer with ionizable hydrogen in the 9-position but, rather, the primary amine (13a) mixed or hybridized with the immonium zwitterion (13b), and the i.r. spectrum provides evidence for both these forms. That it was not the isomeric 6-amino-9-methyl-8-azapurine, which could have arisen by retrogression of the

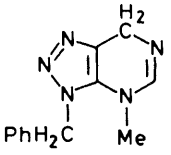
starting material during the preparation, was confirmed by i.r. and chromatographic comparisons with authentic [26] material.

The nitrile (12b) was smoothly hydrogenated to 4-aminomethyl-3-benzyl-5-methylamino-1,2,3-triazole (14a), which failed to give 9-benzyl-3,6-dihydro-3-methyl-8-azapurine (15) when heated with formamidinium acetate, a method which has worked well in this series.[19,27] 3-Benzyl-5-formamidomethyl-4-methylamino-1,2,3-triazole (14b), isolated from these attempts, was more conveniently prepared from the amine (14a) and acetic formic anhydride. When heated to 200 °C, the formyl derivative (14b) underwent retrogression to 4-benzylamino-5-formamidomethyl-3-methyl-1,2,3-triazole (16). Other attempts to cyclize compounds (14a) and (14b),

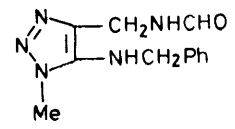


(14)

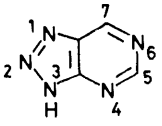
	R^1	R^2
a;	H	H
b;	CHO	H
c;	COMe	CHO



(15)



(16)



(17)

using a range of bases, acids, Lewis acids, and alternative sources of the formyl group, were uniformly unsuccessful. Interestingly, the amine (14a), when heated with triethyl orthoformate and acetic anhydride, furnished 5-acetamidomethyl-3-benzyl-4-*N*-methylformamido-1,2,3-triazole (14c) of which the ^{1}H n.m.r. spectrum showed even more pairs of signals due to rotational isomerism than did compounds (2d) and (12a). The formyl and acetyl groups were assigned with the help of data in ref. 27.

The ^{1}H n.m.r. spectra, summarised in Table 1, present values and assignments compatible with those published in earlier Parts of this series. Intramolecular rearrangements of triazoles were detected with the aid of the following data: a PhCH_2 signal occurs at *ca.* τ 4.4 when the group is attached to a ring-nitrogen atom, but at *ca.* τ 5.6 when the attachment is exocyclic.[11] For a methyl group, the corresponding figures are τ 6.2 and 7.2. In the 8-azapurine series, an *N*-methyl group in the pyrimidine ring, unless this is hydrogenated as in compounds (7a and b), occurs at only slightly higher field than one in the triazole ring (*cf.* Table 1 and refs. 29 and 30). The i.r. spectra, listed in Table 2, are consistent with those reported earlier with the exception of the example shown in Figure 2.

EXPERIMENTAL

^{1}H N.m.r. spectra were routinely obtained on a 100-MHz JEOL Minimar spectrometer at 30 °C with tetramethylsilane as internal standard, but the data used in Figure 1 were furnished by a Varian HA 100 instrument locked on to hexamethyldisiloxane. I.r. spectra (Nujol mulls) were usually recorded on a Perkin-Elmer grating spectrometer model 257 (but model 567 was used for Figure 2), calibrated with polystyrene at 1 601 cm^{-1}. Both routine and precision mass spectra were obtained from the different facilities of an AEI MS 902 instrument. Elemental analyses were performed mainly by the Analytical Chemistry Service of the Australian National University, the others at Galbraith Laboratories, Tennessee. The indentity of specimens was tested by (*i*) mixed m.p.s where practicable; (*ii*) i.r. spectroscopy, and (*iii*) comparative chromatography. All substances were examined by ascending paper chromatography, after application in aqueous pyridine (27 : 40 v/v) to two Whatman No. 1 papers, and developed respectively in (*a*) 3% aqueous NH_4Cl; and (*b*) butanol–5N-acetic acid (7 : 3 v/v). Yields, purification, and microanalytical results are given in Table 3.

4-Benzylamino-3-methyl-1,2,3-triazole-5-carboxamide (2a).—3-Benzyl-4-methylamino-1,2,3-triazole-5-carboxamide [9] (1.15 g, 0.005 mol) and formamide (10 ml) were heated at 190 °C for 1 h. Dilution with water (20 ml) precipitated the title compound, *m/e* 231 (M^+), 214, 185, 106, and 91.

3-Benzyl-4-N-methylformamido-1,2,3-triazole-5-carboxamide (2d).—3-Benzyl-4-methylamino-1,2,3-triazole-5-carboxamide [9] (2b) (1.15 g), acetic anhydride (5 ml), and formic acid (5 ml) were heated in a bath at 110 °C for 30 min. The volatile portion was removed at 105 °C and 25 mmHg. Addition of water (5 ml) to the cooled residue deposited the *title compound*, *m/e* 259 (M^+), 231, 185, 159, 158, 157, 140, and 91. A high-resolution spectrum furnished *m/e* 231.1122 (^{12}C = 12.0000) for the second peak, showing that CO, and not NN, had been lost.

Bis-(3-benzyl-4-methylamino-1,2,3-triazole-5-carbonyl)-amine (3).—3-Benzyl-4-*N*-methylformamido-1,2,3-triazole-5-carboxamide (0.52 g, 0.002 mol) was refluxed for 1 h with sodium ethoxide solution [from sodium (0.092 g) and ethanol (4 ml)]. The volatile part was removed at 60 °C and 25 mmHg. Water (5 ml) was added to the cooled residue, and the *title compound* filtered off and dried at 24 °C, *m/e* (chemical ionization) 445 (M^+). It gave a large depression of m.p. with the other diacylamine (6), whose m.p. is similar.

9-Benzyl-3-methyl-8-azapurin-6(3H)-one (1b) {*3-Benzyl-4-methyl-3H-v-triazolo[4,5-d]pyrimidin-7(4H)-one*}.*—3-Benzyl-4-methylamino-1,2,3-triazole-5-carboxamide (2b) (0.231 g, 0.001 mol), triethyl orthoformate (2 ml), and 10N-hydrochloric acid (0.13 ml) were stirred together for 24 h at 24 °C. The precipitate, a hydrochloride, was filtered off, washed with acetone, then rubbed with 3M-sodium acetate (2 ml). Filtration gave the *title compound*. Shortening the reaction time to 1 h gave a 71% yield. The behaviour on paper chromatography was unusual: a dark (absorption) spot resulted from developer (*a*), but a blue fluorescent spot from the more acidic developer (*b*), which caused hydrolysis to the diacylamine (6).

3-Benzyl-4-methylamino-1,2,3-triazole-5-N-formylcarboxamide (6).—(*a*) *Preferred method.* 9-Benzyl-3-methyl-8-azapurin-6-one (1b) (0.241 g, 0.001 mol) and 1M-acetic acid (4 ml) were stirred at 24 °C for 20 h. The mixture, after

* For this type of numbering, see formula (17).

TABLE 3

Purification and analysis of products

Recrystallization			M.p.	Yield	Found (%)					Requires (%)			
Product	Solvent [a]	Parts	(°C)	(%)	C	H	N	S	Formula	C	H	N	S
(1b)	E	84	187	80	59.8	4.9	28.9		$C_{12}H_{11}N_5O$	59.7	4.6	29.0	
(1c)	E	170	229	86	39.9	3.4	46.2		$C_5H_5N_5O$	39.75	3.3	46.3	
(2c)	E	7	138	25	57.2	5.7	30.2		$C_{11}H_{13}N_5O$	57.1	5.7	30.3	
(2d)	B	27	133	85	55.5	5.1	26.9		$C_{12}H_{13}N_5O_2$	55.6	5.05	27.0	
(2g)	E	85	226 [b]	90	35.6	4.2	41.2		$C_5H_7N_5O_2$	35.5	4.2	41.4	
(3)	E	200	182	15	59.4	5.3	28.6		$C_{22}H_{23}N_9O_2$	59.3	5.2	28.3	
(6)	E	80	178 [c]	80	55.6	5.0	27.0		$C_{12}H_{13}N_5O_2$	55.6	5.1	27.0	
(7a)	E	160	232	75	59.3	5.4	28.9		$C_{12}H_{13}N_5O$	59.2	5.4	28.8	
(7b)	N	100	159 [b]	50	39.0	4.6	45.6		$C_5H_7N_5O$	39.2	4.6	45.7	
(9)	D	17	180 [b]	50	35.9	3.1	41.8	19.1	$C_5H_5N_5S$	35.9	3.0	41.9	19.2
(10)	E	150	185 [b]	25	23.8	2.2	27.7	46.4	$C_4H_4N_4S_3$	23.5	2.0	27.4	47.1
(12a)	B	8	80	80	59.8	4.6	29.0		$C_{12}H_{11}N_5O$	59.7	4.6	29.0	
(12b)	B	7	133	95	62.0	5.3	32.8		$C_{11}H_{11}N_5$	62.0	5.2	32.8	
(12c)	W	8	223	90	39.0	4.1	57.1		$C_4H_5N_5$	39.0	4.1	56.9	
(13)	W	65	*d*	89	40.3	4.0	56.2		$C_5H_6N_6$	40.0	4.0	56.0	
(14a)	BC	24	77	62	60.8	7.0	32.1		$C_{11}H_{15}N_5$	60.8	7.0	32.2	
(14b)	W	12	157	84	58.7	6.0	28.4		$C_{12}H_{15}N_5O$	58.8	6.2	28.6	
(14c)	CB	80	100	50	58.4	6.2	24.5		$C_{14}H_{17}N_5O_2$	58.5	6.0	24.4	
(16)	BC	70	104	67	58.5	6.1	28.3		$C_{12}H_{15}N_5O$	58.8	6.2	28.6	

[a] B, benzene; BC, benzene–cyclohexane (1 : 1 v/v); CB, benzene–cyclohexane (2 : 1 v/v); D, dimethylformamide–water (3 : 1 v/v); E, ethanol; N, nitromethane; W, water. [b] Decomposes. [c] Also 169 °C (see text). [d] Unmelted at 300 °C.

refrigeration, yielded crystals of the *title compound*, m.p. 178 °C from ethanol.

(*b*) Phosphoryl chloride (0.17 ml, 0.002 mol) was added dropwise to 3-benzyl-4-methylamino-1,2,3-triazole-5-carboxamide [9] (0.231 g, 0.001 mol) in dimethylformamide (1 ml) at 0 °C. The mixture was then stirred for 10 min at 24 °C, then at 100 °C for 15 min. The mixture was cooled in an ice-bath while ice–water (5 ml) was added, then refrigerated overnight, yielding crystals of the title compound, m.p. 178 °C from ethanol or 169 °C from 160 parts of benzene. Both forms had a similar i.r. spectrum and identical ^{1}H n.m.r. and mass spectra, *m/e* 259 (M^+), 231 (M^+ − CO), 204, 185, 168, 159, 157, 140, 92, and 91 (benzyl) (scanned to 500 Daltons). The solution in 0.1N-potassium hydroxide quickly deposited the deformylated amide (2b).

9-Benzyl-1,2-dihydro-3-methyl-8-azapurin-6(3H)-one (7a) {*3-Benzyl-5,6-dihydro-4-methyl-3H-v-triazolo*[4,5-d]*pyrimidin-7(4H)-one*}.*—9-Benzyl-3-methyl-8-azapurin-6-one (0.241 g, 0.001 mol), ethanolic 3M-ammonia (50 ml), and pre-reduced 10% palladium–carbon (0.04 g) was hydrogenated at 75 °C and 4 atm for 3 h, then filtered while hot. The residue was boiled with ethanol (20 ml) and filtered. The combined filtrates were taken to dryness, and the residue was triturated with 1M-sodium hydrogencarbonate. The *title compound* was filtered off and formed, after recrystallization, large violet-fluorescing plates almost insoluble in boiling water.

4-Amino-3-methyl-1,2,3-triazole-5-carboxamide (2f).—4-Methylamino-1,2,3-triazole-5-carboxamide (2e) [9] (0.3 g) and pentan-1-ol (2 ml) were refluxed for 1 h. The suspension, cooled to −10 °C and filtered, gave the *title compound* (96%), m.p. 243 °C (from ethanol), R_F 0.29 (contrasting with that of starting material, R_F 0.37) when applied in ethanol to a silica t.l.c. plate and developed with chloroform–ethanol (5 : 1 v/v).

4-N-Methylformamido-1,2,3-triazole-5-carboxamide (2g).—4-Methylamino-1,2,3-triazole-5-carboxamide [9] (2e) (0.282 g, 0.002 mol), formic acid (2 ml), and acetic anhydride (2 ml) were heated in a bath (100 °C) for 1 h. The volatile part was removed at 105 °C and 25 mmHg. Water (2 ml), added to the cooled residue, released the *title substance* which was filtered off. It required 6 days for complete hydrolysis at 20 °C by 1M-NaOH (2 mol equiv.) to give 4-methylamino-1,2,3-triazole-5-carboxamide (2e).

3-Methyl-8-azapurin-6(3H)-one (1c) {*4-Methyl-3H-v-triazolo*[4,5-d]*pyrimidin-7(4H)-one*}.—4-Methylamino-1,2,3-triazole-5-carboxamide [9] (2e) (1.41 g, 0.01 mol), triethyl orthoformate (re-fractionated, 15 ml), and 10M-hydrochloric acid (1.3 ml) were refluxed, with stirring, in an oil bath (100 °C) for 1 h. The volatile components were removed *in vacuo* at, eventually, 90 °C. The residue was ground with water (7 ml) and the pH brought up from 0.5 to 2.5 with 10M-sodium hydroxide. Refrigeration followed by filtration gave the *title compound*, *m/e* 151 (M^+), 68, 53, 123, 124, 97, and 96 (arranged in order of decreasing peak intensity). It was a weak base, soluble in 1N-hydrochloric acid; and also in 210 parts of cold water. It was only slowly decomposed by 1M-hydrochloric acid at 20 °C, whereas 1M-sodium hydroxide hydrolysed it in 1 h at 20 °C to 4-*N*-methylformamido-1,2,3-triazole-5-carboxamide (2g). It was also rapidly hydrolysed by boiling water.

1,2-Dihydro-3-methyl-8-azapurin-6(3H)-one (7b) {*5,6-Dihydro-4-methyl-3H-v-triazolo*[4,5-d]*pyrimidin-7(4H)-one*}.—3-Methyl-8-azapurin-6-one (1c) (0.604 g, 0.004 mol), 1M-sodium carbonate (2 ml), and water (40 ml) were hydrogenated over pre-reduced 10% palladium–carbon (0.3 g) at room temperature and pressure. Kieselguhr (0.6 g) was added and the mixture filtered. The cake was boiled with water (5 ml) and then filtered. The combined filtrates were divided into two equal portions, to which was added 1M-hydrochloric acid (4 and 8 ml, respectively), to prepare the neutral species and the hydrochloride, respectively. Both specimens were taken to dryness *in vacuo* (eventually at 90 °C), refluxed with ethanol (15 ml), and filtered (through Kieselguhr) from sodium chloride. By maintaining the filtrates alternatively at room temperature and −10 °C, their initially colloidal deposits were rendered granular. The neutral species, which has a bright violet fluorescence, was then recrystallized from nitromethane to yield the *title compound*. The *hydrochloride* was purified by recrystalliz-

* For this type of numbering, see formula (17).

ation from ethanol (2 crops taken) (Found: C, 31.85; H, 4.5; N, 37.6; Cl, 18.9. $C_5H_8ClN_5O$ requires C, 31.7; H, 4.3; N, 36.9; Cl, 18.7%).

3-*Methyl*-8-*azapurine*-6(3H)-*thione* (9) {4-*Methyl*-3H-v-*triazolo*[4,5-d]*pyrimidine*-7(4H)-*thione*}.—Phosphorus pentasulphide (Fluka; 1.1 g) and dried (NaOH) pyridine (10 ml) were stirred magnetically in a bath at 85 °C, the hard lumps that formed initially being broken down with a rod until a light suspension was attained. 3-Methyl-8-azapurin-6-one (0.75 g, 0.005 mol) was then added, and stirring was continued at the same temperature for 45 min. The mixture was cooled, diluted with water (8 ml), then taken to dryness on a rotatory evaporator (eventually at 50 °C). Water (7 ml) was added to the cooled residue, then enough 2M-ammonia to give pH 5.3. The suspension was filtered, and the insoluble thiadiazole reserved. The filtrate was taken to pH 2.0 with 2.5M-sulphuric acid and filtered at once. The insoluble material was chromatographically pure *title compound*, insoluble in boiling ethanol, and it evolved hydrogen sulphide on contact with boiling water.

5-*Amino*-1,2,3-*thiadiazole*-4-(N-*thioformyl*)*carbothioamide* (10).—The ammonia-insoluble material from the previous preparation was recrystallized from nitromethane (34 parts), then from ethanol, to give the *title compound*, insoluble in 1M-sodium hydroxide and hydrochloric acid, but slowly decomposed by both reagents (cold) with the evolution of hydrogen sulphide; M^+ (chemical ionization) 204; electron impact gave M^+ 176 (loss of NN) and another prominent peak at *m/e* 143.

3-*Benzyl*-4-N-*methylformamido*-1,2,3-*triazole*-5-*carbonitrile* (12a).—Iodomethane (2.8 g, 2 mol. equiv.) and potassium carbonate (dried over a low flow, 2.1 g, 3 mol. equiv.) were added to a solution of 3-benzyl-4-formamido-1,2,3-triazole-5-carbonitrile [22] (2.27 g, 0.01 mol) in sieve-dried dimethylformamide (20 ml). The suspension was stirred for 24 h at 23 °C, and the volatile components were then removed at 110 °C and 25 mmHg. Ice–water (20 ml) was added to the flask contents, cooled in ice, and the pH was brought down from 10 to 7 with phosphoric acid. The gum which deposited soon solidfied. After drying at 23 °C and recrystallization, it gave the *title compound*.

3-*Benzyl*-4-*methylamino*-1,2,3-*triazole*-5-*carbonitrile* (12b).—Sodium hydroxide (10M, 0.15 ml) was added to 3-benzyl-4-*N*-methylformamido-1,2,3-triazole-5-carbonitrile (12a) (0.241 mol) in boiling ethanol (1 ml). The mixture was refluxed for 5 min, then gradually diluted with water (4 ml), refrigerated, and filtered to give the *title compound* which was poorly soluble in boiling water, but very soluble in boiling ethanol. For conversion to the amide, 2M-sodium hydroxide (1 ml), then hydrogen peroxide (30% w/v; 0.25 ml), 1.1 mol equiv. were added to a stirred solution of the nitrile (12b) (0.213 g, 0.001 mol) in ethanol (2 ml) at 65 °C. After 1 h longer at 65 °C, the mixture was refrigerated and filtered to give 3-benzyl-4-methylamino-1,2,3-triazole-5-carboxamide (2b) [9] (75%), m.p. 158 °C.

4-*Methylamino*-1,2,3-*triazole*-5-*carbonitrile* (12c).—Pieces of sodium were added to 3-benzyl-4-methylamino-1,2,3-triazole-5-carbonitrile (12b) (2.13 g, 0.01 mol) in liquid ammonia (100 ml), while stirring, until a permanent blue colour was seen. Ammonium chloride (1.6 g) was slowly added and the ammonia was allowed to evaporate overnight. The residue was freed from toluene at 60 °C on a rotary evaporator, and ice (10 g) was then added. The pH was lowered from 8 to 4.6 with citric acid solution. The suspension was refrigerated, then filtered, to give long needles of the *title compound*. It was completely soluble in dilute alkali and also gave chromatographic evidence of freedom from the retrogression product, 4-amino-3-methyl-1,2,3-triazole-5-carbonitrile.[23]

6-*Amino*-3-*methyl*-8-*azapurine* (13) {7-*Amino*-4-*methyl*-3H-v-*triazolo*[4,5-d]*pyrimidine*}.—4-Methylamino-1,2,3-triazole-5-carbonitrile (12c) (0.123 g, 0.001 mol), formamidine acetate (dried over $CaCl_2$ at 20 °C) (0.31 g, 0.003 mol), and sieve-dried butanol (2 ml) were refluxed (bath at 125 °C) for 1 h. The volatile components were removed at 95 °C and 25 mmHg. The residue was mixed with water (1 ml). Refrigeration and filtration gave the *title compound* as a slightly hygroscopic solid, soluble in 0.1M-hydrochloric acid and 1M-sodium hydroxide but insoluble in 0.5M-sodium carbonate, and insoluble in boiling ethanol.

5-*Aminomethyl*-3-*benzyl*-4-*methylamino*-1,2,3-*triazole* (14a).—3-Benzyl-4-methylamino-1,2,3-triazole-5-carbonitrile (12b) (0.852 g, 0.004 mol) in ethanolic 6M-ammonia (50 ml) was hydrogenated over Raney nickel (1.6 g, weighed wet) at 70 °C and 4 atm for 5 h, then filtered. The residue was boiled with ethanol (10 ml) and filtered. The combined filtrates were taken to dryness *in vacuo*, and the residue mixed with 1M-sodium hydroxide (5 ml), then shaken out with chloroform (2 × 10 ml). The extract was dried (K_2CO_3), the solvent distilled off, and the residue recrystallized to give the *title compound*.

3-*Benzyl*-5-*formamidomethyl*-4-*methylamino*-1,2,3-*triazole* (14b).—Freshly distilled acetic formic anhydride (0.52 g, 3 mol. equiv.) was added to the aminomethyl compound (14a) (0.434 g, 0.002 mol) dissolved in dried (over NaOH) pyridine (4 ml) and the mixture was set aside overnight at 23 °C. Next day, water (3 ml) was added, and the volatile components removed at 50 °C and 25 mmHg. The residue was stirred with water (2.5 ml), and the mixture refrigerated and filtered to give the *title compound*, soluble in 300 parts of boiling benzene, *m/e* 245 (M^+), 154, 126, 91 (benzyl), and 64.

4-*Benzylamino*-5-*formamidomethyl*-3-*methyl*-1,2,3-*triazole* (16).—3-Benzyl-5-formamidomethyl-4-methylamino-1,2,3-triazole (14b) (0.49 g, 0.002 mol) and octanol (5 ml) were refluxed for 6 h. The octanol was distilled off *in vacuo*, and the residue triturated with cyclohexane (4 ml) until it solidified. This solid, after recrystallization, gave the *title compound*, soluble in 5 parts of boiling water, *m/e* 245 (M^+), 216, 200, 154, and 91.

5-*Acetamidomethyl*-3-*benzyl*-4-N-*methylformamido*-1,2,3-*triazole* (14c).—The amine (14a) (0.434 g, 0.002 mol), triethyl orthoformate (6 ml), and acetic anhydride (3 ml) were refluxed for 4 h. The volatile portion was removed *in vacuo* (eventually at 90 °C). The residue was diluted with water (1 ml) and brought to pH 8.5 with aqueous ammonia. The emulsion was extracted with chloroform (2 × 20 ml). The lower layer, dried (K_2CO_3) and concentrated, yielded the *title compound*, *m/e* 287 (M^+), 259, 200, 126, and 91.

I thank Professors S. Sternhell and L. N. Mander, and Dr. R. Bramley for discussion of the n.m.r. results, also Mrs. L.-E. Hogie for skilled experimental assistance. I also thank Professors A. P. Grollman and F. W. Fowler, and Mrs. C. J. Lin, all at the State University of New York, Stony Brook, where some preliminary studies for this project were carried out.

[1/036 *Received*, 12*th January*, 1981]

REFERENCES

[1] Part 23, A. Albert, *J. Chem. Soc., Perkin Trans. 1*, 1981, 887.

[2] J. Nelson, J. Carpenter, L. Rose, and D. Adamson, *Cancer Res.*, 1975, **35**, 2872.
[3] A. Albert, ' Selective Toxicity,' 6th edn., Chapman and Hall, London, 1979, p. 89; T. Higuchi and V. Stella, ' Pro-Drugs as Novel Drug Delivery Systems,' American Chemical Society, Washington, D.C., 1975.
[4] L. B. Townsend and R. K. Robins, *Synth. Proced. Nucleic Acid Chem.*, 1968, **1**, 18.
[5] H. U. Blank and J. J. Fox, *J. Am. Chem. Soc.*, 1968, **90**, 7175.
[6] L. B. Townsend, A. F. Lewis, J. W. Jones, and R. K. Robins, *Synth. Proced. Nucleic Acid Chem.*, 1968, **1**, 36.
[7] J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, 1962, **84**, 1914.
[8] J. R. E. Hoover and A. R. Day, *J. Am. Chem. Soc.*, 1956, **78**, 5832.
[9] A. Albert, *J. Chem. Soc. C*, 1969, 152.
[10] D. J. Brown in ' Mechanisms of Molecular Migration,' ed. B. S. Thyagarajan, Interscience–Wiley, New York, 1968, Vol. I, p. 209.
[11] A. Albert, *J. Chem. Soc. C*, 1970, 230.
[12] E. Shaw, *J. Biol. Chem.*, 1950, **185**, 439.
[13] M. Ahmad, R. G. Bergstrom, M. J. Cashen, A. J. Kresge, R. A. McClelland, and M. F. Powell, *J. Am. Chem. Soc.*, 1977, **99**, 4827; R. H. De Wolfe, ' Carboxylic Orthoacid Derivatives,' Academic Press, New York, 1970.
[14] C. Temple, C. L. Kussner, and J. A. Montgomery, *J. Med. Chem.*, 1962, **5**, 866.
[15] (*a*) J. B. Polya and T. M. Spotswood, *Recl. Trav. Chim. Pays-Bas*, 1949, **68**, 573; (*b*) A. Albert, *J. Chem. Soc., Perkin Trans. 1*, 1972, 461.
[16] A. Dornow and J. Helberg, *Chem. Ber.*, 1960, **93**, 2001.
[17] A. Albert and K. Tratt, *J. Chem. Soc. C*, 1968, 344.
[18] A. Albert, *J. Chem. Soc. C*, 1968, 2076.
[19] A. Albert, *J. Chem. Soc., Perkin Trans. 1*, 1978, 513.
[20] K. Nakanishi, ' Infrared Absorption Spectroscopy,' Holden-Day, San Francisco, 1962, pp. 39—41 and 45—46.
[21] D. J. Brown, ' The Pyrimidines,' Wiley–Interscience, New York, 1962, and Supplement, 1970 (ch. 12 in both).
[22] T. Kindt-Larsen and C. Pedersen, *Acta Chem. Scand.*, 1962, **16**, 1800; M. Regitz and H. Scherer, *Chem. Ber.*, 1969, **102**, 417.
[23] A. Albert, *J. Chem. Soc., Perkin Trans. 1*, 1975, 345.
[24] A. Albert, *J. Chem. Soc. C*, 1969, 2379.
[25] B. C. Pal and C. A. Horton, *J. Chem. Soc.*, 1964, 400.
[26] R. Weiss, R. K. Robins, and C. W. Noell, *J. Org. Chem.*, 1960, **25**, 765.
[27] A. Albert, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1634.
[28] A. Albert, *J. Chem. Soc., Perkin Trans. 1*, 1976, 291.
[29] A. Albert, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2030.
[30] A. Albert and A. M. Trotter, *J. Chem. Soc., Perkin Trans. 1*, 1979, 922.