v-Triazolo[4,5-*d*]pyrimidines (8-Azapurines).† Part IX.[1] Some Nucleophilic Addition Reactions

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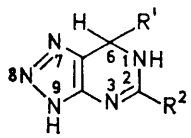
Several *v*-triazolo[4.5-*d*]pyrimidines (8-azapurines) added nucleophilic reagents (shown in parentheses) to give 7-substituted 6,7-dihydro-derivatives (6-substituted 1.6-dihydro-8-azapurines) [shown in square brackets]: *v*-triazolo[4,5-*d*]pyrimidine (potassium hydrogen sulphite. barbituric acid. 2-thiobarbituric acid, benzenethiol, and methanol) [7-sulphonato- (1a). 7-(2.4.6-trioxohexahydropyrimidin-5-yl) (1c), 7-(4.6-dioxo-2-thioxohexahydropyrimidin-5-yl), 7-phenylthio-. and 7-methoxy- (4a) derivatives. respectively]; 5-amino-*v*-triazolo[4.5-*d*]-pyrimidine (2-amino-8-azapurine) (potassium hydrogen sulphite and methanol) [7-sulphonato- (1b) and 7-methoxy-(4d) derivatives]: *v*-triazolo[4.5-*d*]pyrimidine-5(4*H*)-thione (8-azapurine-2-thione) (potassium hydrogen sulphite) [7-sulphonato-derivative (2a: X = S)]; *v*-triazolo[4.5-*d*]pyrimidin-5(4*H*)-one (8-azapurin-2-one) (potassium hydrogen sulphite. methanol, benzenethiol, acetylacetone, ethyl acetoacetate. diethyl malonate. malonamide. and barbituric acid) [7-sulphonato- (2a: X = O). 7-methoxy- (2b). 7-phenylthio-, 7-diacetylmethyl-, 7-(1-ethoxycarbonyl-2-oxopropyl), 7-bis(ethoxycarbonyl)methyl-. 7-dicarbamoylmethyl-, and 7-(2.4.6-trioxohexahydropyrimidin-5-yl) (2d) derivatives]. *v*-Triazolo[4.5-*d*]pyrimidin-5(4*H*)-one was reduced by potassium borohydride to the 6.7-dihydro-derivative (2e) (1.6-dihydro-8-azapurin-2-one).

U.v. and ^{1}H n.m.r. spectra and some ionisation constants are reported and discussed.

MOST 8-azapurines with an unsubstituted 6-position have been shown [2-4] to react with water to give 1,6-dihydro-6-hydroxy-derivatives (1). This covalent hydration is usually prominent mainly in the cation; the only stable neutral species encountered was that of 8-azapurin-2-one. However, many pteridines form stable adducts [5,6] with nucleophiles stronger than water, even under conditions unfavourable for covalent hydration. We now find that 8-azapurines also are capable of forming stable adducts with strong nucleophiles such as hydrogen sulphite ion, and such activated methylene compounds as are used in Michael condensations.[7]

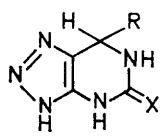
Thus with potassium hydrogen sulphite in aqueous solution, 8-azapurine and its 2-amino-2-oxo- and 2-thioxo-derivatives all formed crystalline 1 : 1 adducts. Because the u.v. spectra of these adducts closely resembled those of the corresponding 1,6-dihydro-compounds and of the 1,6-hydrated species [2] (Table 1), the products were formulated as (1a and b) and (2a). ^{1}H N.m.r. spectroscopy (Table 2) provided the following supporting evidence. Protons in the 6-position gave rise to singlets between τ 4·0 and 4·8 (*cf.* 0·8 for the unsubstituted 8-azapurine [3]). Such a large upfield shift in a fused pyrimidine is characteristic of the conversion of an unsaturated carbon atom into a saturated one by addition across the neighbouring double bond [3] [*cf.* the chemical shift (τ 4·5) of the corresponding C-4 proton in sodium 3,4-dihydro-2-methylthiopteridine-4-sulphonate (3) [6]]. These 8-azapurine adducts were rapidly and completely converted into starting materials by dilute aqueous alkali.

8-Azapurin-2-one, on prolonged refluxing with methanol, formed a 1 : 1 adduct, of which the u.v. spectrum resembled that of the corresponding 1,6-hydrated species,[2] indicating that addition had taken place across the 1,6-bond to give structure (2b). The



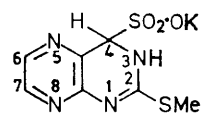
(1)

a; $R^1 = SO_2{\cdot}OK$, $R^2 = H$
b; $R^1 = SO_2{\cdot}OK$, $R^2 = NH_2$
c; $R^1 = -CH{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}CO$

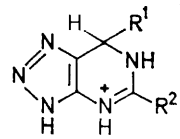


(2)

a; $R = SO_2{\cdot}OK$, X = O or S
b; R = OMe, X = O
c; R = SPh, X = O
d; $R = -CH{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}CO$, X = O
e; R = H, X = O



(3)



(4)

a; R^1 = OMe, R^2 = H
b; R^1 = OMe, $R^2 = NH_2$
c; R^1 = OH, R^2 = H
d; R^1 = OH, $R^2 = NH_2$

n.m.r. spectrum [τ 4·20 (1H, s, H-6)] confirmed this structure (see Tables 1 and 2).

The methanol adducts of 8-azapurine and its 2-amino-derivative were not sufficiently stable for isolation as neutral species, but their cations crystallised as hydrochlorides from anhydrous methanolic hydrogen chloride. The close resemblance between the u.v. spectra of these adducts and those of the corresponding 1,6-hydrated cations [2] indicated that the structures were (4a and b) (see Table 1). A comparison of the n.m.r. spectrum of the methanol adduct (cation) (4a) (H-6 at

† This series was previously entitled '1,2,3,4,6-Penta-azaindenes'.

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TABLE 1

Physical properties of 8-azapurines

8-Azapurine	Ionisation (H_2O; 20°) Charge [a]	pK_a	Spread (±)	Concn. (M)	A.w.l.[b] (λ/nm)	Spectroscopy [c] $\lambda_{max.}$/nm	log ε	pH
Potassium 1,6-dihydro-6-sulphonate	+					261	3·67	1
1,6-Dihydro (for comparison) [d]	+	5·65				262	3·70	3·4
Potassium 2-amino-1,6-dihydro-6-sulphonate [e]	0					241	4·01	5
Potassium 1,2,3,6-tetrahydro-2-thioxo-6-sulphonate	0					269	4·30	5
1,2,3,6-Tetrahydro-2-thioxo (for comparison) [d]	0					265	4·27	5·2
Potassium 1,2,3,6-tetrahydro-2-oxo-6-sulphonate	0					246	3·77	5
1,2,3,6-Tetrahydro-6-hydroxy-2-oxo (for comparison) [d]	0					209, 241	3·73, 3·82	2·5
1,2,3,6-Tetrahydro-6-methoxy-2-oxo	0					240	3·74	*f*
1,6-Dihydro-6-hydroxy (for comparison) [d]	+	2·05				248	3·91	0
1,6-Dihydro-6-methoxy	+					247	3·87	*f*
2-Amino (for comparison) [d]	0					217, *237*, 311 [g]	4·38, *3·68*, 3·84	4·5
2-Amino-1,6-dihydro-6-hydroxy (for comparison) [d]	+	2·50				227, *235*, 326 [g]	3·99, *3·98*, 2·53	0
2-Amino-1,6-dihydro-6-methoxy	+					234	4·07	M [h]
1,2,3,6-Tetrahydro-2-oxo	+	−1·36	0·05	2×10^{-5}	270			
	0					247	3·77	3
	−	8·03	0·05	2×10^{-5}	235	241	3·85	10
	−−	14·48	0·05	2×10^{-5}	260			
6-Bis(ethoxycarbonyl)methyl-1,2,3,6-tetrahydro-2-oxo	+	−1·66	0·05	2×10^{-5}	236			
	0					247	3·76	3
	−	7·73	0·05	2×10^{-5}	235			
6-Dicarbamoylmethyl-1,2,3,6-tetrahydro-2-oxo	0					222, 246	3·82, 3·92	3
	−	7·84	0·03	2×10^{-5}	235			
6-(1-Ethoxycarbonyl-2-oxopropyl)-1,2,3,6-tetrahydro-2-oxo	0					217, 245	3·67, 3·78	M [h]
6-Diacetylmethyl-1,2,3,6-tetrahydro-2-oxo	0					244	3·88	M [h]

[a] Charge refers to the 8-azapurine portion of the molecule; neutral species (0), anion (−), cation (+). [b] Analytical wavelength for spectrometric determinations. [c] Inflections in italics. [d] All values from ref. 2. [e] Potassium disulphite (1 g, 100 ml) added to stabilise the adduct. [f] Methanolic hydrogen chloride (0·001M). [g] A comparison of the cation of 2-amino-8-azapurine (partly hydrated) with that of 2-amino-8-azapurine (anhydrous neutral molecule) shows an increase in the absorption of the inflection in the 235—241 nm area at the expense of that in the 318—326 area. In the methanol and potassium hydrogen sulphite adducts of 2-amino-8-azapurine the single peaks at 234 and 241 nm, respectively, show that addition is complete. [h] M = Methanol.

TABLE 2

^{1}H N.m.r. data (33·3°) for 8-azapurines

8-Azapurine	Chemical shifts (τ) of H-6 τ	Solvent
Potassium 1,6-dihydro-6-sulphonate	4·00	D_2O [a]
Potassium 2-amino-1,6-dihydro-6-sulphonate	4·80	D_2O [b]
Potassium 1,2,3,6-tetrahydro-2-oxo-6-sulphonate	4·31	D_2O
Potassium 1,2,3,6-tetrahydro-2-thioxo-6-sulphonate	4·12	D_2O
1,2,3,6-Tetrahydro-6-methoxy-2-oxo	4·20	$(CD_3)_2SO$ [c]
1,6-Dihydro-6-hydroxy hydrochloride	3·19	HCl–H_2O [d]
1,6-Dihydro-6-methoxy hydrochloride	3·10	D_2O
2-Amino-1,6-dihydro-6-hydroxy hydrochloride	3·51	M-DCl–D_2O [d]
2-Amino-1,6-dihydro-6-methoxy hydrochloride	3·44	D_2O
1,6-Dihydro-6-(2,4,6-trioxohexahydropyrimidin-5-yl)	3·73	$(CD_3)_2SO$
1,6-Dihydro-6-(4,6-dioxo-2-thioxohexahydropyrimidine-5-yl)	3·75	$(CD_3)_2SO$
1,2,3,6-Tetrahydro-2-oxo-6-(2,4,6-trioxohexahydropyrimidin-5-yl)	4·36	$(CD_3)_2SO$
1,2,3,6-Tetrahydro-2-oxo-6-phenylthio	3·59	$(CD_3)_2SO$
1,2,3,6-Tetrahydro-2-oxo	5·42	$(CD_3)_2SO$
6-Diacetylmethyl-1,2,3,6-tetrahydro-2-oxo	4·44	D_2O
6-(1-Ethoxycarbonyl-2-oxopropyl)-1,2,3,6-tetrahydro-2-oxo	4·54	$(CD_3)_2SO$
6-Bis(ethoxycarbonyl)methyl-1,2,3,6-tetrahydro-2-oxo	4·62	$(CD_3)_2SO$
6-Dicarbamoylmethyl-1,2,3,6-tetrahydro-2-oxo	4·65	$(CD_3)_2SO$

[a] For measurements in deuterium oxide, sodium 3-trimethylsilylpropanesulphonate was used as an internal standard. [b] Excess of potassium disulphite (50 mg per ml) added to stabilise the adduct. [c] For $(CD_3)_2SO$ tetramethylsilane was the internal standard: 1 drop of D_2O was added to deuteriate exchangeable protons. [d] Values from ref. 3.

τ 3·10) with that of the corresponding hydrated cation [3] (4c) (H-6 at τ 3·19) confirmed that the methanol adduct was a 1,6-dihydro-derivative. Similarly, the spectrum of the methanol adduct (4b) of the 2-amino-compound (H-6 at τ 3·44) resembled that of the corresponding hydrated cation [3] (4d) (H-6 at τ 3·51).

Benzenethiol (pK_a 6·5) [8] and 8-azapurin-2-one gave the adduct (2c) (H-6 at τ 3·59). A 1 : 1 adduct obtained by the action of benzenethiol on 8-azapurine was unstable in [$^2H_6$]dimethyl sulphoxide; the spectrum obtained was that of an equimolar mixture of starting materials.

8-Azapurine reacted also with potentially carbanionic reagents containing an active methylene group. 1 : 1 Adducts were obtained with barbituric and thiobarbituric acids. When, as here, the adducts had low water solubility, the reactions seemed to proceed more rapidly. The n.m.r. spectra of these compounds (H-6 at τ 3·73 and 3·75 respectively) indicated addition across the 1,6-double bond, as in (1c). It has been established, for similar additions to 2-aminopteridine,[5a] that the reactive carbanion is formed from the active methylene group in position 5 of the major tautomer of these barbituric acids. U.v. spectroscopy was less useful in assignment of structures to these compounds, as the barbituric acid absorption contributed strongly in the region of interest (240—270 nm). 8-Azapurin-2-one formed a similar 1 : 1 adduct with barbituric acid. N.m.r. spectroscopy revealed the 6-proton signal at τ 4·36, confirming 1,6-addition, as in (2d).

The following active methylene compounds also formed 1 : 1 adducts with 8-azapurin-2-one: diethyl malonate, malonamide, ethyl acetoacetate, and acetylacetone. These condensations were carried out in mildly alkaline (potassium hydrogen carbonate) solution (pH *ca.* 8·5), conditions under which the starting heterocycle does not add water.[2] The n.m.r. spectra of these adducts (H-6 at τ 4·4—4·7) indicated saturation of the 1,6-bond. Coupling of the 6-proton with the adjacent active C–H of the reagent and with the pyrimidine 1-NH was observed only as a broadening, probably owing to enhancement of the labile nature of these protons by the high dielectric constant of the solvent. On addition of D_2O to the solution, the signal collapsed to a sharp singlet.

Assignment of structures to these adducts was confirmed by u.v. spectroscopy. As a model compound, 1,6-dihydro-8-azapurin-2-one (2e) was prepared by reduction of 8-azapurin-2-one with potassium borohydride in alkaline solution. The n.m.r. spectrum showed a singlet (2H) at τ 5·42. The u.v. spectrum resembled that of the known 1,6-hydrated neutral species of 8-azapurin-2-one [2] (the latter is unsuitable as a model because the anion is anhydrous). Table 1 shows that the spectra of the adducts of 8-azapurin-2-one with diethyl malonate, malonamide, ethyl acetoacetate, and acetylacetone closely resemble those of the 1,6-dihydro-compound (2e). A comparison of the pK_a values of the latter with those of the adducts sufficiently stable for measurement to be possible, confirmed the structural similarity. For example, the basic pK_a and the first acidic pK_a of compound (2e) (—1·36 and 8·03) are close to those of the diethyl malonate adduct (—1·66 and 7·73).

In undergoing these nucleophilic additions, 8-azapurines apparently resemble the corresponding pteridines. However unsubstituted pteridine was partly hydrated at equilibrium in aqueous solution as the neutral species,[9] whereas no hydration was detectable in the neutral species of 8-azapurine.[2,3] Pteridine readily added methanol under neutral conditions,[10] whereas 8-azapurine did not. 2-Aminopteridine formed neutral 3,4-adducts with a wide range of nucleophiles; [5a] 2-amino-8-azapurine under neutral conditions added only hydrogen sulphite ion, one of the most powerful of nucleophiles. The stronger carbon acids (*e.g.* ethyl cyanoacetate and malononitrile) gave a further reaction which is currently being investigated. The methanol adducts of 8-azapurine and its 2-amino-derivative (4a and b) are probably stabilised by amidinium-ion and guanidinium-ion resonance, respectively.[11] The necessity for the cationic species as substrates in the formation of these covalent methanolates arises from the similar feeble nucleophilicity of primary alcohols and water. The greater range of adducts formed by 8-azapurin-2-one is probably due to stabilisation of the products by urea-type resonance,[11] as in pteridin-2-one monohydrate.

Though 8-azapurines are less reactive than pteridines in forming adducts with nucleophiles, both families are vastly superior to purines, for which no adducts have yet been obtained. The presence of four doubly-bound nitrogen atoms in pteridine creates an almost non-conjugated double bond in the 3,4-position (1·28 Å from *X*-ray diffraction [12]) which vigorously attracts anionic reagents. In purine, the presence of the strongly electron-releasing NH group partly neutralises the electron-attraction of the three doubly-bound nitrogen atoms, so that no isolated double bond is shown in the *X*-ray diffraction pattern [13] [the N(1)–C(6) bond is 1·33 Å; *cf.* pyridine, 1·34 Å], and purines apparently have no tendency to add water covalently.[14] It is logical that the 8-azapurine nucleus, intermediate between those of pteridine and purine in electronic distribution, should have an intermediate affinity; the results show that this does not fall far short of that of pteridine.

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EXPERIMENTAL

Samples for microanalysis were dried at 60° and 20 mmHg unless otherwise stated. Ionisation constants were determined by the methods previously described.[8] U.v. spectra were measured with a Perkin-Elmer model 450 recording spectrophotometer, and the wavelengths and intensity of all maxima were confirmed with an Optica CF4 manual instrument. The ^{1}H n.m.r. spectra were determined with a Perkin-Elmer model R10 instrument operating at 33·3° and 60 MHz.

Condensations with Potassium Hydrogen Sulphite.—Triazolo[4,5-*d*]pyrimidine (8-azapurine) (0·06 g, 0·0005 mol), heated at 90° with a solution of potassium disulphite (0·1 g, 0·00045 mol) in water (0·5 ml) until dissolved (*ca.* 5 min), deposited on cooling *potassium* 6,7-*dihydro*-v-*triazolo*[4,5-d]*pyrimidine*-7-*sulphonate* (1,6-*dihydro*-8-*azapurine*-6-*sulphonate*) (1a) (46%), which, filtered off and washed successively with ice-cold water and ethanol, had m.p. 173° (efferv.) (Found: C, 20·0; H 2·0; N, 29·2. $C_4H_4KN_5O_3S$ requires C, 19·9; H, 1·7; N, 29·0%). Similarly, triazolopyrimidin-5-one (8-azapurin-2-one) gave *potassium* 4,5,6,7-*tetrahydro*-5-*oxo*-v-*triazolo*[4,5-d]*pyrimidine*-7-*sulphonate* (1,2,3,6-*tetrahydro*-2-*oxo*-8-*azapurine*-6-*sulphonate*) (2a; X = O) (42%), which gradually darkened above 250° (Found: C, 17·7; H, 2·0; N, 25·4. $C_4H_4KN_5O_4S,H_2O$ requires C, 17·5; H, 2·2; N, 25·5%). With triazolopyrimidine-5-thione (8-azapurine-2-thione) (0·075 g, 0·0005 mol) and potassium disulphite (0·1 g, 0·00045 mol) in water (0·5 ml) it was necessary to clarify the hot solution by centrifugation to allow deposition of *potassium* 4,5,6,7-*tetrahydro*-5-*thioxo*-v-*triazolo*[4,5-d]*pyrimidine*-7-*sulphonate* (1,2,3,6-*tetrahydro*-2-*thioxo*-8-*azapurine*-6-*sulphonate*) (46%), a pale yellow solid which gradually decomposed above 230° (recrystallised from 5 parts of water) (Found: C, 16·7; H, 2·2; N, 23·6. $C_4H_4KN_5O_3S_2,H_2O$ requires C, 16·5; H, 2·1; N, 24·0%). 5-Aminotriazolo[4,5-*d*]pyrimidine (2-amino-8-azapurine) (0·12 g, 0·0009 mol), shaken with potassium disulphite (0·22 g, 0·001 mol) in water (2 ml) at 25° for 72 h, then heated at 90° until all was dissolved (*ca.* 5 min), deposited, on cooling, *potassium* 5-*amino*-6,7-*dihydro*-v-*triazolo*[4,5-d]*pyrimidine*-7-*sulphonate* (2-*amino*-1,6-*dihydro*-8-*azapurine*-6-*sulphonate*) (1b) (61%), m.p. 282° (decomp.) after being washed once with ice-cold water (Found: C, 18·8; H, 2·4; N, 33·0. $C_4H_5KN_6O_3S$ requires C, 18·8; H, 2·0; N, 33·0%).

Condensations with Methanol.—Triazolo[4,5-*d*]pyrimidin-5-one (8-azapurin-2-one) monohydrate (0·1 g, 0·00065 mol) was heated under reflux with methanol (25 ml) for 4 days. The hot solution, filtered to remove residual starting material and concentrated to 0·5 ml, deposited greenish yellow 6,7-*dihydro*-7-*methoxy*-v-*triazolo*[4,5-d]*pyrimidin*-5(4H)-*one* (1,6-*dihydro*-6-*methoxy*-8-*azapurin*-2-*one*) (2b) (73%), m.p. 247° (from methanol) [Found (material dried at 20° and 0·01 mmHg): C, 35·6; H, 4·3; N, 40·9. $C_5H_7N_5O_2$ requires C, 35·5; H, 4·2; N, 41·4%]. Triazolo-[4,5-*d*]pyrimidine (8-azapurine) (0·1 g, 0·0008 mol) in methanol (1 ml) was stirred at 20° while anhydrous hydrogen chloride was passed in, and stirring was continued until precipitation was complete. The mixture was chilled overnight and filtered. The pale yellow crystals of 6,7-*dihydro*-7-*methoxy*-v-*triazolo*[4,5-d]*pyrimidine* (1,6-*dihydro*-6-*methoxy*-8-*azapurine*) *hydrochloride* (4a) (59%), had m.p. 143° after being washed with ice-cold methanol [Found (material dried at 20° and 0·1 mmHg): C, 31·4; H, 4·3; N, 36·8. $C_5H_8ClN_5O$ requires C, 31·6; H, 4·3; N, 36·95%)]. Similar treatment of 5-aminotriazolopyrimidine (2-amino-8-azapurine) (0·12 g) in methanol (10 ml), followed by concentration to 0·5 ml, gave needles of 5-*amino*-6,7-*dihydro*-7-*methoxy*-v-*triazolo*[4,5-d]*pyrimidine* (2-*amino*-1,6-*dihydro*-6-*methoxy*-8-*azapurine*) *hydrochloride* (4b) (61%), m.p. 198° after being washed with methanol and dried at 20° and 0·1 mmHg (Found: C, 28·8; H, 4·3; N, 41·1. $C_5H_9ClN_6O$ requires C, 29·4; H, 4·4; N, 41·1%).

Condensations with Benzenethiol.—Triazolo[4,5-*d*]pyrimidine (8-azapurine) (0·06 g, 0·0005 mol) was dissolved in water (0·5 ml) and benzenethiol (0·08 g, 0·0007 mol) was added. A precipitate formed immediately. The suspension was shaken at 20° for 5 min; the solid 6,7-*dihydro*-7-*phenylthio*-v-*triazolo*[4,5-d]*pyrimidine* (1,6-*dihydro*-6-*phenylthio*-8-*azapurine*) (52%) was collected and washed with water, ethyl acetate, and ether, m.p. 141° [Found (material dried at 20° and 0·05 mmHg): C, 51·4; H, 4·2; N, 30·2. $C_{10}H_9N_5S$ requires C, 51·9; H, 3·9; N, 30·3%]. A solution of triazolopyrimidin-5-one (8-azapurin-2-one) monohydrate (0·075 g, 0·0005 mol) and potassium hydrogen carbonate (0·1 g) in water (0·25 ml) was clarified by centrifugation, and a suspension of benzenethiol (0·07 g, 0·0006 mol) in a solution of potassium hydrogen carbonate (0·1 g) in water (0·25 ml) was added. The mixture was stirred vigorously at 20° for 2 h. The solid 6,7-*dihydro*-7-*phenylthio*-v-*triazolo*[4,5-d]*pyrimidin*-5-*one* (1,6-*dihydro*-6-*phenylthio*-8-*azapurin*-2-*one*) (2c) (55%) was filtered off and washed with ice-cold water and then ethanol, m.p. 251° (Found: C, 48·5; H, 3·9; N, 28·2. $C_{10}H_9N_5OS$ requires C, 48·6; H, 3·7; N, 28·3%).

Condensations with Barbituric Acids.—To a solution of barbituric acid (0·065 g, 0·0005 mol) in water (5 ml) at 90° was added triazolopyrimidine (0·06 g, 0·0005 mol) in water (0·5 ml), and the mixture was maintained at 90° until crystals began to form (*ca.* 1 min), then refrigerated overnight. The pale yellow 6,7-*dihydro*-7-(2,4,6-*trioxohexahydropyrimidin*-5-*yl*)-v-*triazolo*[4,5-d]*pyrimidine* [1,6-*dihydro*-6-(2,4,6-*trioxohexahydropyrimidin*-5-*yl*)-8-*azapurine*] (1c) (59%) was collected and washed well with water. It gradually darkened above 250° (Found: C, 36·1; H, 3·4; N, 36·3. $C_8H_7N_7O_3,H_3O$ requires C, 36·0; H, 3·4; N, 36·7%). Similar treatment of triazolopyrimidine (0·06 g, 0·0005 mol) with 2-thiobarbituric acid (0·07 g, 0·0005 mol) gave 7-(4,6-*dioxo*-2-*thiohexahydropyrimidin*-5-*yl*)-6,7-*dihydro*-v-*triazolo*[4,5-d]*pyrimidine* [6-(4,6-*dioxo*-2-*thioxohexahydropyrimidin*-5-*yl*)-1,6-*dihydro*-8-*azapurine*] (64%), which gradually darkened above 300° without melting [Found (material dried at 100° and 0·1 mmHg): C, 36·2; H, 2·6; N, 36·5. $C_8H_7N_7O_2S$ requires C, 36·2; H, 2·7; N, 36·95%]. Triazolopyrimidin-5-one monohydrate (0·075 g, 0·0005 mol) and barbituric acid (0·065 g, 0·0005 mol) were suspended in water (10 ml). To the stirred suspension was added 0·5M-potassium carbonate until the solids just dissolved. After 5 min, glacial acetic acid (1 ml) was added. The bright yellow adduct, 6,7-*dihydro*-7-(2,4,6-*trioxohexahydropyrimidin*-5-*yl*)-v-*triazolo*-[4,5-d]*pyrimidin*-5(4H)-*one* [1,6-*dihydro*-6-(2,4,6-*trioxohexahydropyrimidin*-5-*yl*)-8-*azapurin*-2-*one*] (2d) (74%), which was slowly deposited over 48 h, gradually darkened above 290° without melting [Found (material dried at 100° and 0·05 mmHg): C, 35·7; H, 2·6; N, 36·2. $C_8H_8N_7O_4,0·25H_2O$ requires C, 35·6; H, 2·8; N, 36·35%].

Condensations with Aliphatic Michael Reagents.—Ethyl acetoacetate (0·13 g, 0·001 mol) was added to a solution of triazolopyrimidin-5-one monohydrate (0·15 g, 0·001 mol)

and potassium hydrogen carbonate (0·1 g) in water (0·5 ml). The mixture was stirred vigorously until the ester dissolved (*ca.* 5 min). The solution was set aside for 1 h, then adjusted to pH 4 with glacial acetic acid. The crystals of 7-(1-*ethoxycarbonyl*-2-*oxopropyl*)-6,7-*dihydro*-v-*triazolo*[4,5-d]*pyrimidin*-5(4H)-*one* [6-(1-*ethoxycarbonyl*-2-*oxopropyl*)-1,6-*dihydro*-8-*azapurin*-2-*one*] (81·5%), had m.p. 125° after being washed well with water (Found: C, 45·1; H, 5·1; N, 25·4. $C_{10}H_{13}N_5O_4$ requires C, 44·9; H, 4·9; N, 26·2%). Triazolopyrimidin-5-one monohydrate (0·075 g, 0·0005 mol) and diethyl malonate (0·08 g, 0·0005 mol) similarly yielded 7-*bis*(*ethoxycarbonyl*)*methyl*-6,7-*dihydro*-v-*triazolo*[4,5-d]*pyrimidin*-5(4H)-*one* [6-*bis*(*ethoxycarbonyl*)-*methyl*-1,6-*dihydro*-8-*azapurin*-2-*one*] (76%), m.p. 139° after being washed with water and recrystallised from ethyl acetate (*ca.* 10 parts) [Found (material dried at 100° and 20 mmHg): C, 44·5; H, 5·5; N, 23·5. $C_{11}H_{15}N_5O_5$ requires C, 44·4; H, 5·1; N, 23·6%]. A similar reaction with malonamide (0·055 g, 0·00055 mol) gave 7-*dicarbamoylmethyl*-6,7-*dihydro*-v-*triazolo*[4,5-d]*pyrimidin*-5(4H)-*one* (6-*dicarbamoylmethyl*-1,6-*dihydro*-8-*azapurin*-2-*one*) (52%), m.p. 194° after being washed with ice–water (Found: C, 30·8; H, 4·4; N, 35·8. $C_7H_9N_7O_3,2H_2O$ requires C, 30·5; H, 4·8; N, 35·6%). To a solution of triazolopyrimidin-5-one monohydrate (0·075 g, 0·0005 mol) and potassium hydrogen carbonate (0·1 g) in water (0·5 ml) was added acetylacetone (0·1 g, 0·001 mol), then acetic acid (to pH 4). The mixture was evaporated to dryness at 20° under reduced pressure. Extraction of the residue with hot ethyl acetate yielded 7-*diacetylmethyl*-6,7-*dihydro*-v-*triazolo*[4,5-d]*pyrimidin*-5(4H)-*one* (6-*diacetylmethyl*-1,6-*dihydro*-8-*azapurin*-2-*one*) (57%), m.p. 153° (from ethyl acetate) (Found: C, 45·6; H, 4·8. $C_9H_{11}N_5O_3$ requires C, 45·6; H, 4·7%).

Reduction of Triazolo[4,5-d]*pyrimidin*-5-*one* (8-*Azapurin*-2-*one*).—To a stirred solution of triazolopyrimidin-5-one hydrate (0·1 g, 0·00065 mol) in 0·1M-sodium hydroxide (10 ml) was added potassium borohydride (0·2 g). The solution, stirred overnight, acidified to pH 2 with sulphuric acid, and set aside for 2 h, deposited crystals of 6,7-*dihydro*-v-*triazolo*[4,5-d]*pyrimidin*-5(4H)-*one* (1,6-*dihydro*-8-*azapurin*-2-*one*) (2e) (80%) which, after being filtered off and washed with water, gradually darkened above 280° (Found: C, 34·8; H, 3·9; N, 50·0. $C_4H_5N_5O$ requires C, 34·5; H, 3·6; N, 50·35%).

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