Purine Studies. Part IX.[1] Nucleophilic Addition of Barbituric Acids to Purines

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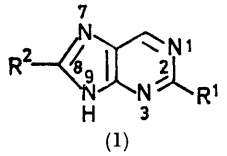
Purine (1a) and its 2-amino- (1b). 2-oxo- (2a). 2-thioxo- (2b). 8-methylsulphonyl- (1c). 2-amino-8-methylsulphonyl- (1d). 8-trifluoromethyl- (1e). 2-amino-8-trifluoromethyl- (1f), and 2-oxo-8-trifluoromethyl- (2c) derivatives underwent addition of 2-thiobarbituric acid across the 1,6-double bond to give the 1,6-dihydro-6-(4,6-dioxo-2-thioxohexahydropyrimidin-5-yl)purines (4a—f) and (5a. b. and e). Purine and its 2-oxo-. 2-thioxo-. and 2-oxo-8-trifluoromethyl derivatives also reacted with barbituric acid. to give the corresponding trioxohexahydropyrimidin-5-yl purines (4g) and (5d and c). respectively. U.v. and ^{1}H n.m.r. spectra are reported and discussed.

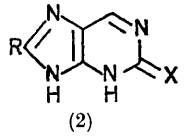
NUCLEOPHILIC addition of water across the 1,6-double bond has been postulated [2] as the initial step in the oxidation of purines to the corresponding purin-6-ones by the enzyme xanthine oxidase. So far no evidence for covalent hydration has been obtained from the ionisation constants and spectra of known purines,[3] though this phenomenon is well established for several other fused pyrimidine systems.[4] However, many pteridines [5,6] and 8-azapurines [7] have been shown to form stable adducts with nucleophiles stronger than water, particularly active methylene reagents, under conditions where the degree of covalent hydration is very low. In view of these results, the reactions of several 6-unsubstituted purines have been examined in order to assess the capability of the nucleus to form adducts, and to determine the factors influencing the stability of the products.

Purine (1a) and its 2-amino-derivative (1b), did not undergo addition of alcohols in anhydrous alcoholic hydrogen chloride; purine and its 2-amino-, 2-oxo- (2a), and 2-thioxo- (2b) derivatives failed to undergo addition of benzenethiol, acetylacetone, ethyl acetoacetate, diethyl malonate, and malonamide in neutral or mildly alkaline aqueous solution, conditions under which the corresponding derivatives of 8-azapurine (3) formed stable, isolable adducts.[7] The reactions were monitored by u.v. and ^{1}H n.m.r. spectroscopy; a hypsochromic shift of the long-wavelength u.v. absorption and an upfield shift of the 6-proton n.m.r. signal are expected on adduct formation.[4,7] In aqueous potassium hydrogen sulphite hypsochromic shifts were observed in the u.v.



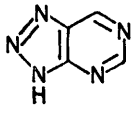
(1)

a; $R^1 = R^2 = H$
b; $R^1 = NH_2$, $R^2 = H$
c; $R^1 = H$, $R^2 = SO_2Me$
d; $R^1 = NH_2$, $R^2 = SO_2Me$
e; $R^1 = H$, $R^2 = CF_3$
f; $R^1 = NH_2$, $R^2 = CF_3$

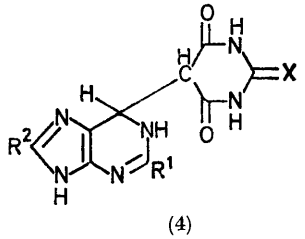


(2)

a; X = O, R = H
b; X = S, R = H
c; X = O, R = CF_3



(3)



(4)

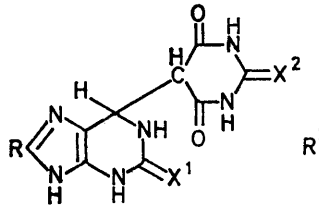
a; $R^1 = R^2 = H$, X = S
b; $R^1 = NH_2$, $R^2 = H$, X = S
c; $R^1 = H$, $R^2 = SO_2Me$, X = S
d; $R^1 = NH_2$, $R^2 = SO_2Me$, X = S
e; $R^1 = NH_2$, $R^2 = CF_3$, X = S
f; $R^1 = H$, $R^2 = CF_3$, X = S
g; $R^1 = R^2 = H$, X = O

spectra, but the solutions were unstable. (These reactions are currently under investigation.) However

[1] Part VIII, R. J. Badger, D. J. Brown, and J. H. Lister, *J.C.S. Perkin I*, 1973, 1906.
[2] F. Bergmann and S. Dikstein, *J. Biol. Chem.*, 1956, **223**, 765.
[3] A. Albert, *J. Chem. Soc.* (*B*), 1966, 438.
[4] (*a*) A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1; (*b*) D. D. Perrin, *ibid.*, p. 43 (reviews).
[5] (*a*) A. Albert and F. Reich, *J. Chem. Soc.*, 1961, 127; (*b*) A. Albert and C. F. Howell, *ibid.*, 1962, 1591; (*c*) A. Albert and J. J. McCormack, *ibid.*, 1965, 6930; (*d*) A. Albert and J. J. McCormack, *J. Chem. Soc.* (*C*), 1966, 1117; (*e*) A. Albert and J. J. McCormack, *ibid.*, 1968, 63.
[6] A. Albert and H. Mizuno, *J. Chem. Soc.* (*B*), 1971, 2423.
[7] A. Albert and W. Pendergast, *J.C.S. Perkin I*, 1972, 457.

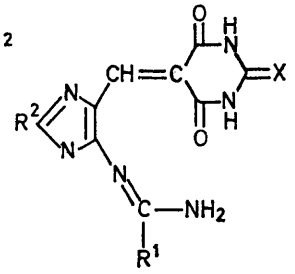
with 2-thiobarbituric acid, and in some cases with barbituric acid, stable 1,6-dihydropurines [(4a, b, and g) and (5a—d)] were isolated in which the pyrimidine system had added across the purine 1,6-double bond.

The structures of these compounds were established by u.v. and n.m.r. spectroscopy. With those purines which had a longest-wavelength $\lambda_{max.}$ value greater than 300 nm, adduct formation resulted in removal of this



(5)

a; R = H, X^1 = O, X^2 = S
b; R = H, X^1 = X^2 = S
c; R = H, X^1 = S, X^2 = O
d; R = H, X^1 = X^2 = O
e; R = CF_3, X^1 = O, X^2 = S



(6)

a; R^1 = R^2 = H, X = S
b; R^1 = OH, R^2 = H, X = S
c; R^1 = OH, R^2 = CF_3, X = S
d; R^1 = R^2 = H, X = O
e; R^1 = OH, R^2 = H, X = O

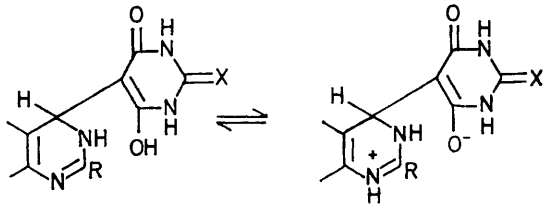
absorption, or at least in considerable diminution of its intensity (Table 1). This is consistent with the observed hypsochromic effect on addition of simple nucleophiles to 8-azapurines [7,8] and pteridines [4-6] where the degree of conjugation is reduced. The spectra of these barbituric acid derivatives are less simple, however, as the new shorter-wavelength absorption of the dihydropurine system cannot be determined accurately owing to a strong overlapping contribution by the pyrimidine unit (in the region 240—290 nm). Thus the foregoing considerations could not be applied to purine itself ($\lambda_{max.}$ 264 nm) but were useful in determining that addition had occurred in its 2-amino-, 2-oxo-, and 2-thioxo-derivatives (Table 1). The u.v. spectra of these adducts in methanol (the only suitable solvent) were often complicated by a slow rearrangement giving rise to an absorption in the visible region around 420—470 nm (Table 1). This was probably due to formation of highly conjugated ring-opened compounds of type (6), similar to those reported [8b] in the reactions of 8-azapurines with ethyl cyanoacetate and malononitrile. There is also some n.m.r. evidence for the formation of one of these compounds (6a) when the adduct (4a) of purine with the thiobarbituric acid is dissolved in hexadeuteriodimethyl sulphoxide (see footnote *g* to Table 2).

In the n.m.r. spectra of purine and its 2-oxo- and 2-thioxo-derivatives, a pronounced upfield shift of the purine 6-proton signal was observed on adduct formation, commensurate with saturation of the 1,6-double bond [*cf.* the corresponding 8-azapurine adducts (Table 2)]. That addition had occurred at the 6-(rather than the 8-)position was demonstrated for the parent purine as follows. Purine deuteriated in the 6-position (50% isotopic purity) was prepared by cyclisation of the corresponding deuteriated 4,5-diaminopyrimidine [9] with formic acid. The n.m.r. spectrum of this compound was similar to that of purine, except that the low-field signal (τ 1·04) was halved in intensity. Formation of the thiobarbituric acid adduct resulted in an upfield shift of this smaller absorption by 2·68 p.p.m.

The tautomeric nature of the pyrimidine portion of these adducts is uncertain. Broadening of the purine 6-proton signal was observed in the n.m.r. spectra, but coupling was never sufficiently well defined to make possible a distinction between tautomers such as (4), (7a), or the zwitterionic structure (7b) proposed for the adduct of pteridine with barbituric acid.[10]

2-Thiobarbituric acid formed adducts with a greater range of purines than did barbituric acid. The lower value of the acidic pK_a of the former [2·3 (ref. 11) as against 3·9 (ref. 12)] provided a greater proportion of the reactive anion at pH 2 (optimum condition for condensation). Thus the thiobarbituric acid adducts were formed rapidly, and their low solubility ensured that they were immediately removed from the reaction medium. The more slowly formed and more soluble barbituric acid derivatives were often not precipitated, but underwent further reactions in solution, probably including ring opening, leading to complex mixtures, especially in the case of the 8-substituted purines described later.

In a search for more reactive purines, the high reactivity of 8-azapurines (unsubstituted in the 6-position)



(7a) (7b)

was recalled. These compounds readily undergo covalent hydration across the 1,6-double bond [8a] and give stable adducts with active methylene compounds, including the barbituric acids.[7] A doubly-bound nitrogen atom in a heteroaromatic system has been compared to an electron-withdrawing substituent at the same position in its capacity to encourage addition reactions; [4a] it thus seemed probable that a purine with an electron-withdrawing substituent in the 8-position might form stable adducts with a wider range of nucleophiles than the corresponding 8-unsubstituted compound. 8-Methylsulphonylpurine (1c) and its 2-amino-derivative (1d), and 8-trifluoromethylpurine (1e) and its 2-amino- (1f) and 2-oxo- (2c) derivatives were examined for addition reactions with methanol, ethanol, benzenethiol, diethyl malonate, acetylacetone, and ethyl acetoacetate

[8] (*a*) A. Albert, *J. Chem. Soc.* (*B*), 1966, 427; (*b*) A. Albert and W. Pendergast, *J.C.S. Perkin I*, 1973, 1620.
[9] S. Matsuura and T. Goto, *J. Chem. Soc.*, 1965, 623.
[10] A. Albert and H. Mizuno, *J.C.S. Perkin I*, 1973, 1974.
[11] Y. Sato, *J. Chem. Soc. Japan*, 1957, **78**, 921.
[12] A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1956, 1294.

under the conditions described for 8-azapurines.[7] No adducts were isolated, nor was there any u.v. or n.m.r. evidence for their formation. However, these purines formed adducts with 2-thiobarbituric acid, which were more stable than their counterparts from 8-unsubstituted purines. Thus an n.m.r. spectrum at 33·3° of the adduct (4a) of purine with 2-thiobarbituric acid in $(CD_3)_2SO$ (at equilibrium), revealed only 12% of the adduct, whereas 50% of the corresponding adduct (4c) of these adducts slightly more than did the trifluoromethyl group; the corresponding adduct of 2-amino-8-trifluoromethylpurine was 80% dissociated in $(CD_3)_2SO$. Similarly the adduct (4f) of 8-trifluoromethylpurine was 70% dissociated; *cf.* 50% for that of 8-methylsulphonylpurine.

The foregoing data show that purines are vastly inferior to pteridines[4,5b-e,6,10,13] in forming adducts. This is reflected in the respective lengths (and hence polarisation) of the pteridine 3,4-bond (1·28 Å by *X*-ray

TABLE 1

U.v. spectroscopy [a]

1,6-Dihydro-6-(4,6-dioxo-2-thioxohexahydropyrimidin-5-yl)purines	Purines [b]	$\lambda_{max.}$/nm	log $\varepsilon_{max.}$	Solvent [d]
Unsubstituted (4a) [e]		288	3·85	M
	Unsubstituted (1a)	263	3·90	5·7
2,3-Dihydro-2-oxo (5a)		*247*, 263, 284	*4·05*, 4·15, 4·15	M
	2,3-Dihydro-2-oxo (2a)	238, 315	3·46, 3·69	6·05
2-Amino (4b)		219, 242, 264, 283	4·46, 4·12, 4·19, 4·21	M
	2-Amino (1b)	*236*, 305	*3·70*, 3·78	7·0
2,3-Dihydro-2-thioxo (5b)		262, 285	4·39, 4·38	M
	2,3-Dihydro-2-thioxo (2b)	241, 286, 348	4·10, 4·25, 3·18	4·98
8-Methylsulphonyl (4c)		287	3·94	M
	8-Methylsulphonyl (1c)	215, 271	4·39, 4·01	2·65
2-Amino-8-methylsulphonyl (4d) [g]		*268*, 284	*4·21*, 4·22	M
	2-Amino-8-methylsulphonyl (1d)	223, 281, 322	4·45, 3·68, 3·90	3·85
8-Trifluoromethyl (4f)		*267*, 288	*4·25*, 4·35	M
	8-Trifluoromethyl (1e)	264	3·89	3·0
2-Amino-8-trifluoromethyl (4e) [h]		260, 286	4·26, 4·27	M
	2-Amino-8-trifluoromethyl (1f)	217, 281, 312	4·40, 3·48, 3·80	4·37
2,3-Dihydro-2-oxo-8-trifluoromethyl (5e) [i]		453	4·50	M
	2,3-Dihydro-2-oxo-8-trifluoromethyl (2c)	213, 281, 316	4·31, 3·77, 3·75	2·0
1,6-Dihydro-6-(2,4,6-trioxohexahydropyrimidin-5-yl)purines				
Unsubstituted (4g) [j]		254	4·06	M
2,3-Dihydro-2-oxo (5a) [k]		257	4·05	M
2,3-Dihydro-2-thioxo (5c)		255. *286*	4·27, *3·96*	M

[a] Inflections in italics. [b] Neutral species; values from S. F. Mason, *J. Chem. Soc.*, 1954, 2071 [for (1a and b) and (2a and b)]; ref. 3 [for (1c, d, and f) and (2c)]; A. Bendich and A. Giner-Sorolla, *J. Amer. Chem. Soc.*, 1958, **80**, 5744 [for (1e)]. [c] Where the solutions were unstable, intensities at the moment of dissolution were obtained by scanning the spectrum at intervals and extrapolating to zero time. [d] Numerals refer to the pH of an aqueous solution; M = methanol. [e] Spectrum gradually changed during 1 h to give an absorption at 466 nm (log ε 3·76). Apparent log ε values for this and subsequent mixtures were calculated on the basis of the original adduct concentration. [f] Spectrum changed smoothly during 3 h to give final spectrum $\lambda_{max.}$ 245 (log ε 3·99), 263 (4·15), 2·80 (4·13), *325* (*3·57*), and 447 nm (2·88), which indicated both dissociation to the purine and ring opening to (6b). [g] Spectrum changed smoothly during 6 h to an equilibrium mixture containing free 2-amino-8-methylsulphonylpurine, $\lambda_{max.}$ 223 (log ε 4·50), 268 (4·24), 284 (4·24), and 320 nm (4·00). [h] Equilibrium spectrum (5 h) indicates presence of the purine, $\lambda_{max.}$ 217 (log ε 4·48), 265 (4·24), *278* (*4·23*), and 310 nm (3·99). [i] Not sufficiently soluble for determination of adduct spectrum. After prolonged shaking with methanol (22 h) spectrum of ring-opened compound (6c) was recorded. [j] Gradually underwent ring opening. Concentration of ring-opened product (6d) reached a maximum after 20 min [$\lambda_{max.}$ 442 nm (4·23) log ε], then decreased to zero as a complex change followed. [k] Equilibrium spectrum (after 17 h): $\lambda_{max.}$ 442 nm (log ε 4·28), 320 (3·57), and 423 nm (3·65); probably represents both ring opening to (6e) and dissociation to give the free purine.

8-methylsulphonylpurine remained undissociated under the same conditions. Similarly the adduct (4b) of 2-aminopurine was fully dissociated in $(CD_3)_2SO$ into the purine and 2-thiobarbituric acid, while the analogous adduct (4d) of 2-amino-8-methylsulphonylpurine was only 70% dissociated. Addition of 10% of D_2O to the solution to exchange the labile protons had the additional effect of shifting the equilibrium in favour of the adduct, which was then only 43% dissociated. Addition of a further 15% of D_2O (to the point of incipient precipitation of the adduct) reduced the dissociation to 34%. The methylsulphonyl group stabilised

[13] A. Albert and K. Ohta, *J. Chem. Soc.* (*C*), 1971, 2357.

[14] T. A. Hamor and J. M. Robertson, *J. Chem. Soc.*, 1956, 3586.

diffraction),[14] and the purine 1,6-bond (1·33 Å; *cf.* pyridine, 1·34 Å).[15] 8-Azapurine, which possesses an extra doubly-bound nitrogen atom would logically fall between the two in affinity for nucleophiles, and this has been shown to be the case.[7]

EXPERIMENTAL

Samples for microanalysis were dried at 20° and 0·1 mmHg. U.v. spectra were obtained with a Perkin-Elmer 450 recording spectrophotometer. ^1H N.m.r. spectra were determined with a Perkin-Elmer R10 spectrometer, at 33·3° and 60 MHz.

Condensation of Purines with Barbituric Acids.—(a) *2-Unsubstituted and 2-aminopurines* (1a—f). The purine (0·0005

[15] G. D. Watson, R. M. Sweet, and R. E. Marsh, *Acta Cryst.*, 1965, **19**, 573.

TABLE 2

^{1}H N.m.r. data (33·3°)

1,6-Dihydro-6-(4,6-dioxo-2-hexahydropyrimidin-5-yl)-purines [a]	Purines [a]	τ Values H-2	H-6	H-8	Others	Solvent [b]
Unsubstituted [c]		2·84 [d]	3·68	2·55 [d]		N-NaOD–D_2O
	Unsubstituted	1·23	1·04	1·58		N-NaOD–D_2O
6-Deuterio [e]		2·94 [c]	3·72 [c,f]	2·70 [c]		N-NaOD–D_2O
Unsubstituted [g]		2·50	3·90	1·64		$(CD_3)_2SO$
	Unsubstituted	0·99	0·77	1·30		$(CD_3)_2SO$
	2-Amino [h]		1·30	1·81		$(CD_3)_2SO$
2,3-Dihydro-2-oxo [i]			4·06	2·87		N-NaOD–D_2O
	2,3-Dihydro-2-oxo		1·61	2·12		N-NaOD–D_2O
2,3-Dihydro-2-thioxo [j]			3·94	2·87		N-NaOD–D_2O
8-Methylsulphonyl [k]		2·10	4·02		6·72 (Me)	$(CD_3)_2SO$
	8-Methylsulphonyl [k]	0·85	0·57		6·49	$(CD_3)_2SO$
2-Amino-8-methylsulphonyl			4·02		6·78	$(CD_3)_2SO$
	2-Amino-8-methylsulphonyl		1·14		6·57	$(CD_3)_2SO$
8-Trifluoromethyl [m]		1·97	3·98			$(CD_3)_2SO$
	8-Trifluoromethyl [m]	0·83	0·57			$(CD_3)_2SO$
2-Amino-8-trifluoromethyl [n]			3·98			$(CD_3)_2SO$
	2-Amino-8-trifluoromethyl [n]		1·16			$(CD_3)_2SO$
1,6-Dihydro-6-(2,4,6-trioxohexahydropyrimidin-5-yl)purines						
Unsubstituted [c]		2·86 [d]	3·79 [e]	2·57 [d]		N-NaOD–D_2O
	Unsubstituted [c]	1·26	1·06	1·54		N-NaOD–D_2O
Unsubstituted		2·10	4·02	1·75		$(CD_3)_2SO$
	Unsubstituted	1·00	0·78	1·31		$(CD_3)_2SO$
2,3-Dihydro-2-thioxo [j]			3·91	2·67		N-NaOD–D_2O
1,6-Dihydro-6-(2,4,6-trioxohexahexahydropyrimidin-5-yl)-8-azapurines (for comparison) [o]						
Unsubstituted			3·73			$(CD_3)_2SO$
2,3-Dihydro-2-oxo			4·36			$(CD_3)_2SO$

[a] Where the spectrum was of an equilibrium mixture of adduct and purine, or where the adduct dissociated completely into the purine, the values for both species were taken from the same solution. [b] For spectra in $(CD_3)_2SO$ tetramethylsilane was used as an internal reference; in D_2O sodium 3-trimethylsilylpropan-1-sulphonate was the reference. [c] Spectrum reverted to that of purine overnight. [d] Assignments uncertain; may be reversed. [e] 50% Deuteriated in the 6-position. [f] Signal reduced in intensity by 50% with respect to the C-2 and C-8 protons. [g] Adduct–purine ratio 12 : 88. Solution also contained 25% ring-opened product (6a) at equilibrium (τ 1·83 and 1·89 p.p.m.; vinyl and imidazole protons, not exchanged by D_2O). [h] Adduct completely dissociated to give the purine immediately after dissolution. [i] Reverted completely to the purine after 5 h. [j] Adduct stable in alkali, but starting purine unstable. [k] C.A.T.-accumulated spectrum (43 scans) on equilibrium mixture; adduct–purine ratio 1 : 1. [l] From equilibrium spectrum. Adduct–purine ratio 30 : 70. Proportion of adduct increased on addition of D_2O (see text). [m] Equilibrium spectrum. Adduct–purine ratio 30 : 70. [n] Equilibrium spectrum. Adduct–purine ratio 20 : 80. [o] Values from ref. 7.

TABLE 3

Products of addition of barbituric acids to purines

1,6-Dihydro-6-(4,6-dioxo-2-thiohexahydropyrimidin-5-yl)-purines	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
Unsubstituted [a]	51	39·1	3·4	30·1	$C_9H_8N_6O_2S,0·75H_2O$	39·0	3·45	30·25
2-Amino [a]	83	37·7	4·1	34·1	$C_9H_9N_7O_2S,0·5H_2O$	37·5	3·5	34·0
2,3-Dihydro-2-oxo [a]	72	37·8	3·3	28·5	$C_9H_8N_6O_3S,0·5H_2O$	37·4	3·1	29·0
2,3-Dihydro-2-thioxo [a]	54	34·3	3·5		$C_9H_8N_6O_2S_2,H_2O$	34·4	3·2	
8-Methylsulphonyl [b]	31	32·8	3·4	22·7	$C_{10}H_{10}N_6O_4S_2,1·5H_2O$	32·5	3·55	22·75
2-Amino-8-methylsulphonyl [b]	52	32·2	3·6	25·7	$C_{10}H_{11}N_7O_4S_2,H_2O$	32·0	3·5	26·1
8-Trifluoromethyl [c]	69	34·1	2·7	23·4	$C_{10}H_7N_6O_2SF_3,H_2O$	34·3	2·6	24·0
2-Amino-8-trifluoromethyl [b]	76	32·0	3·2	25·6	$C_{10}H_8N_7O_2SF_3,1·5H_2O$	32·1	3·0	26·2
2,3-Dihydro-2-oxo-	48	34·2	2·1	9·6 (S)	$C_{10}H_7N_6O_3SF_3$	34·5	2·0	9·2 (S)
1,6-Dihydro-6-(2,4,6-trioxohexahydropyrimidin-5-yl)purines								
Unsubstituted	45	40·2	3·8	31·3	$C_9H_8N_6O_3,H_2O$	40·6	3·8	31·5
2,3-Dihydro-2-oxo	48	37·3	4·0	29·1	$C_9H_{88}N_6O_4,1·5H_2O$	37·1	3·8	28·9
2,3-Dihydro-2-thioxo	38	35·7	3·1	27·5	$C_9H_8N_6O_3S,1·25H_2O$	35·7	3·5	27·8

For preparation of the starting purine see: [a] ref. 16. [b] ref. 3. [c] A. Bendich and A. Giner-Sorolla, *J. Amer. Chem. Soc.*, 1958, **80**, 5744.

mol), dissolved in the minimum volume of water (0·5—2 ml), was added to a supercooled solution of barbituric acid or its 2-thio-analogue (0·0005 mol) in water (5 ml) at 40°. Crystals began to form almost immediately. The suspension was refrigerated overnight and the crystals of the *adduct* were filtered off and washed with cold water.

(b) 2-*Oxo- and* 2-*thioxo-purines* (2a—c). To a stirred suspension of the purine (0·0005 mol) and the barbituric acid (0·0005 mol) in water (10 ml) was added 0·5M-potassium carbonate until the solids just dissolved. Anhydrous acetic acid (1 ml) was then added. The precipitated *adduct* was filtered off and washed with water.

The samples were microanalysed, after drying, without further purification. Crystallisation of the products from water or organic solvents was detrimental to the analyses. Attempts to remove water of crystallisation, present in most cases, by drying at elevated temperatures also resulted in decomposition. Details of analyses and yields are given in Table 3. The compounds did not have sharp m.p.s, but gradually decomposed without melting above 150°.

6-*Deuteriopurine*.— 5,6-Diamino-4-deuteriopyrimidine [9] (50% isotopic purity by n.m.r.) was cyclised with formic acid by the method described for purine.[16] The product (61%), purified by sublimation at 175° and 0·1 mmHg and crystallisation from ethanol (3 parts) showed no sign of deuterium exchange during the reaction (by n.m.r.).

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[16] A. Albert and D. J. Brown, *J. Chem. Soc.*, 1954, 2060.