Some Stable Derivatives of 7,8-Dihydropurines

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The synthesis of a number of 7,8-dihydropurines is described. The unusual stability of these molecules is due to the presence of an electron withdrawing substituent in the 6-position.

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Reduced forms of purines have been relatively little investigated [1], despite their biological significance in the mechanisms of enzyme-mediated purine interconversions [2]. Purines **1** are described as being difficult to reduce, and the hydrogenated derivatives as unstable toward oxidation and hydrolytic degradation [1,3]. 7,8-Dihydropurines **2** are particularly rare, the only reported examples bearing stabilizing substituents on the 7- and/or 9-N atoms [3,9]. For example, Albert [3] observed that catalytic or borohydride reduction of 9-methyl-8-trifluoromethylpurine gave a 1:2 mixture of the 7,8- and 1,6-dihydro derivatives **3** and **4a** respectively; in the absence of the 9-substituent only the 1,6-dihydro-derivative **4b** was obtained. We here report the synthesis of a novel class of 7,8-dihydropurines **2** unsubstituted in the dihydroimidazole ring, stabilized only by the presence of an electron-withdrawing substituent in the pyrimidine ring.

Results and Discussion.

6-Cyano-, 6-carboxamido-, and several 6-ethoxycarbonylpurines were reduced to the 7,8-dihydro-derivatives with sodium cyanoborohydride in dilute hydrochloric acid. The aromatic ethoxycarbonylpurines were prepared by a modification of the method of Clark [10], in which the 4,5-diaminopyrimidine precursors **5** were cyclized with diethoxymethyl acetate rather than a formic acid/acetic anhydride mixture. The aromatic cyano and carboxamido derivatives were obtained from 6-iodopurine according to Hitchings *et al.* [11]. The dihydro compounds were remarkably stable. The solids may be stored indefinitely with no precaution against atmospheric oxidation; solutions in neutral or dilute acidic aqueous solution, or in ethanol, methanol. dimethylformamide or dimethylsulfoxide were stable even on prolonged exposure to air, often over several days.

Elemental analyses (Table I) and mass spectra (Table II) of the dihydro compounds **2** confirmed the addition of one mole of hydrogen to the aromatic species. The ^{1}H-nmr spectra of the reduced purines (Table II) showed an upfield shift of the 8-CH_2 signal by about 3.5 ppm with respect to that of the 8-CH of the corresponding aromatic compound (Table II). In the 2-substituted derivatives of 6-ethoxycarbonylpurine it was at once clear that reduction had occurred in the imidazole ring, as only reduction at the 7,8-double bond could furnish a methylene group. It was considered important, however, in the case of a 2-unsubstituted derivative to demonstrate that reduction had not occurred at the 1,2-position of the pyrimidine ring, *e.g* **7**, particularly in view of the fact that several 1,2-dihydropurines had been described previously [6,8].

In the ^{13}C-nmr spectrum of 6-cyanopurine, the similarity of the ^{1}H-^{13}C coupling constants at the 2- and 8-positions (152.12 ppm, d, J = 211.3 Hz and 149.29 ppm, d, J = 215.3 Hz) did not permit assignment of these resonances to the 6- or the 5-membered rings with confidence. Thus although the expected upfield shift of one of the carbon resonances was observed in the spectrum of the corresponding dihydro derivative (62.87 ppm, t, J = 156.7 Hz) and the coupling constant of the remaining aromatic proton (147.22 ppm, d, J = 203.8 Hz) fell within a reasonable range for an aromatic pyrimidine ring [12], we felt that further evidence was needed before a 7,8-dihydro structure was unambiguously assigned.

Deuterium labelling of either the 2- or the 8-position in

Table I

Purines

Compound No.	R_2	R_6	Yield (%)	Mp (°C)	Elemental Analyses Found C	H	N	Other	Required C	H	N	Other	Molecular Formula
1a	H	CO_2Et	75	224-225	48.97	4.27	29.1		50.00	4.20	29.16		$C_8H_8N_4O_2$
1b	OEt	CO_2Et	91	160-161 [a]	50.97	5.16	23.61		50.84	5.12	23.72		$C_{10}H_{12}N_4O_3$
1c	SMe	CO_2Et	90	220-222	45.42	4.26	23.41	13.44 (S)	45.37	4.23	23.52	13.44 (S)	$C_9H_{10}N_4O_2S$
1d	NME_2	CO_2Et	83	213-214 [b]	50.92	5.61	29.97		51.05	5.57	28.77		$C_{10}H_{13}N_5O_2$
1e	Cl	CO_2Et	70	235	42.42	3.12	24.62	15.55 (Cl)	42.39	3.11	24.72	15.55 (Cl)	$C_8H_7N_4ClO_2$
1f	H	CN	40	183-185 [c]	49.57	2.12	48.22		49.65	2.08	48.26		$C_6H_3N_5$
1g	H	$CONH_2$	63	315 dec [d]	39.83	3.78	38.64		39.78	3.89	38.66		$C_6H_4N_5O.H_2O$
Dihydropurines													
2a	H	CO_2Et	34	>250 dec	38.51	4.99	22.57		38.59	5.26	22.53		$C_8H_{10}N_4O_2.HCl.H_2O$
2b	OEt	CO_2Et	18	199-201	50.37	5.98	23.44		50.41	5.92	23.52		$C_{10}H_{14}N_4O_3$
2c	SMe	CO_2Et	66	210-213	44.89	5.03	23.23	13.29 (S)	44.98	5.04	23.23	13.34 (S)	$C_9H_{12}N_4O_2S$
2d	NME_2	CO_2Et	53	190 dec	50.40	6.41	29.38		50.62	6.37	29.52		$C_{10}H_{15}N_5O_2$
2e	Cl	CO_2Et	48	218-220	41.94	4.02	24.45	15.60 (Cl)	42.02	3.97	24.51	15.51 (Cl)	$C_8H_9ClN_4O_2$
2f	H	CN	74	232-233	48.85	3.45	47.56		48.97	3.43	47.60		$C_6H_5N_5$
2g	H	$CONH_2$	32	250 dec	43.62	4.30	42.38		43.63	4.27	42.41		$C_6H_7N_5O$

[a] Lit mp (ref 10), 162°. [b] Lit mp (ref 10), 215-217°. [c] Lit mp (ref 11), 177-178°. [d] Lit mp (ref 11), 315° dec.

the aromatic purine would allow a determination of which of the carbon atoms became sp^3 hybridized upon reduction by a comparison of the ^{1}H-nmr spectrum of the labelled and unlabelled dihydro derivatives. Deuterium exchange in the 8-position of purines by heating in deuterium oxide has been described, but may be accompanied by exchange in other positions [13,14]; in the present case, in order to eliminate ambiguity between the 2-and 8-positions, and to avoid degradation of the 6-substituent under the exchange conditions, the relevant 2-deuteriopurine was synthesized unambiguously from 2-chloro-4-amino-5-nitro-6-ethoxycarbonylpyrimidine (**6**, R = Cl). Reduction of the latter over palladium in a deuterium atmosphere gave the 2-deuterio-4,5-diaminopyrimidine (**5**, R = ^{2}H) in 90% isotopic purity. The diamine was cyclized to the purine, and the product reduced to the dihydro derivative as described above. A 2-proton singlet was observed in the nmr spectrum (deuteriomethanol) at δ 5.33 ppm, confirming that reduction had occurred across the 7,8-bond. A small singlet (0.1 proton) was observed downfield (δ 7.57) ppm, representing the residual protium in the 2-position. The corresponding signals in a sample of non-deuterated material occurred at 5.31 and 7.55 ppm respectively (Table II). A similar distribution of signals in the aromatic and reduced species of 6-carboxyamido and 6-cyanopyrine (Table II) supports the assignment of a 7,8-dihydro structure to these derivatives also, although deuterium labelled analogs were not made in these cases.

Conclusion.

Ethoxycarbonyl, carboxamido and cyano substituents in the 6-position are capable of markedly stabilizing the 7,8-dihydro forms of purines. The effects may be due to resonance stabilization *e.g.* **8**↔**9**, with a possible contribution from intramolecular hydrogen bonding, **10**. The latter would seem to be less important in view of the stability of 6-cyano-7,8-dihydropurine in which the linear nitrile group is incapable of forming hydrogen bonds with the adjacent 7-NH group.

EXPERIMENTAL

The ^{1}H-nmr spectra were recorded on Varian XL-300 and FT80A spectrometers. Mass spectra (EI) were determined on a Varian MAT CH5 DF instrument at 70eV. Analyses were performed by Atlantic Microlabs Inc., Atlantic, GA.

Table II
^{1}H NMR and Mass Spectroscopy

Purines

Compound Number	R_2	R_6	Chemical Shift[a]	m/e (%)
1a	H	CO_2Et	1.40 (t, 3H, J = 7 Hz), 4.49 (q, 2H, J = 7 Hz), 8.84 (s, 1H), 9.10 (s, 1H), 13.47 (br s, 1H) [c]	193 ($(M + 1)^+$, 41), 148 (25), 120 (100)
1a'	D	CO_2Et	1.38 (t, 3H, J = 7 Hz), 4.49 (q, 2H, J = 7 Hz), 8.84 (s, 1H), 9.09 (s, 0.1H), 13.40 (br s, 1H) [c]	194 ($(M + 1)^+$, 12), 149 (12), 121 (68), 120 (100)
1b	OEt	CO_2Et	1.37 (t, 3H, J = 7 Hz), 1.38 (t, 3H, J = 7 Hz), 4.41 (q, 2H, J = 7 Hz), 4.47 (q, 2H, J = 7 Hz), 8.64 (s, 1H) [c]	236 (M^+, 26), 221 (25), 207 (33) 192 (38), 164 (41), 162 (21), 136 (51), 135 (100), 108 (16)
1c	SMe	CO_2Et	1.40 (t, 3H, J = 7 Hz), 2.61 (s, 3H), 4.48 (q, 2H, J = 7 Hz), 8.74 (s, 1H) [c]	238 (M^+, 57), 209 (16), 192 (29) 166 (14), 165 (28), 164 (100), 151 (21), 150 (23)
1d	NMe_2	CO_2Et	1.38 (t, 3H, J = 7 Hz), 3.15 (s, 6H), 4.45 (q, 2H, J = 7 Hz), 8.38(s, 1H), 12.70 (br s, 1H) [c]	235 (M^+ , 80), 206 (100), 162 (83), 161 (67), 148 (42)
1e	Cl	CO_2Et	1.47 (t, 3H, J = 7 Hz), 4.59 (q, 2H, J = 7 Hz), 8.78 (s, 1H) [b]	226 (M^+, 6), 182 (26), 154 (100), 119 (45)
1f	H	CN	8.87 (s, 1H), 9.02 (s, 1H) [c]	145 (M^+, 100), 118 (9), 91 (8)
1g	H	$CONH_2$	8.09 (br s, 1H), 8.48 (br s, 1H), 8.73 (s, 1H), 9.04 (s, 1H), 13.25 (v br s, 1H) [c]	163 (M^+, 93), 120 (100), 119 (23), 93 (61)
2a	H	CO_2Et	1.35 (t, 3H, J = 7 Hz), 4.48 (q, 2H, J = 7 Hz), 5.31 (s, 2H), 7.55 (s, 1H) [b]	195 (100) 194 (M^+, 72), 193 (49). 165 (22), 148 (23), 121 (47), 120 (46), 119 (37), 93 (24)
2a'	D	CO_2Et	2.47 (t, 3H, J = 7 Hz), 4.36 (q, 2H, J = 7 Hz), 5.33 (s, 2H), 7.57 (s, 0.1H) [b]	195 (M^+, 33), 194 (73), 165 (16), 149 (10), 148 (32), 147 (11), 122 (17), 121 (47), 120 (100), 93 (70)
2b	OEt	CO_2Et	1.30 (t, 3H, J = 7 Hz), 1.36 (t, 3H, J = 7 Hz), 4.25 (q, 2H, J = 7 Hz), 4.34 (q, 2H, J = 7 Hz), 5.23 (s, 2H) [b]	238 (M^+, 39), 209 (12), 192 (18), 164 (23), 135 (100)
2c	SMe	CO_2Et	1.28 (t,3H, J = 7 Hz), 2.35 (s, 3H), 4.24 (q, 2H, J = 7 Hz), 5.14 (s, 2H, 7.26 (s, 1H), 8.60 (s, 1H) [c]	240 (M^+, 76), 239 (20), 211 (12), 194 (25), 168 (13), 167 (26), 166 (35), 165 (30), 164 (20), 151 (100)
2d	NMe_2	CO_2Et	1.37 (t, 3H, J = 7 Hz), 3.03 (s, 6H), 4.35 (q, 2H, J = 7 Hz), 5.13 (s, 2H) [b]	237 (M^+, 90), 235 (18), 206 (15), 191 (34), 164 (25), 163 (100), 162 (62), 148 (35)

Table II (continued)
^{1}H NMR and Mass Spectrospcopy

Dihydropurines

Compound Number	R_2	R_6	Chemical Shift [a]	m/e (%)
2e	Cl	CO_2Et	1.36 (t, 3H, J = 7 Hz), 4.35 (q, 2H, J = 7 Hz), 5.34 (s, 2H) [b]	228 (M^+, 100), 227 (66), 199 (38), 182 (53), 154 (58), 129 (15), 119 (45)
2f	H	CN	5.18 (d, 2H, J = 7 Hz), 7.54 (s, 1H), 8.11 (br s, 1H), 8.73 (br s, 1H) [c]	147 (M^+, 48), 146 (100), 119 (46), 92 (13), 66 (14)
2g	H	$CONH_2$	5.27 (s, 2H), 7.54 (s, 1H) [b]	165 (M^+, 65), 164 (100), 163 (19), 147 (11), 120 (42), 119 (77)

[a] Chemical shift δ ppm from tetramethylsilane (δ0). [b] Spectrum in deuteriomethanol. [a] Spectrum in deuteriodimethyl sulfoxide.

2-Substituted-6-ethoxycarbonylpurines **1** (R^6 = CO_2Et).

The appropriate 2-substituted-4,5-diamino-6-ethoxycarbonylpyrimidine **5** [10] (0.002 mole) was heated under reflux in diethoxymethyl acetate (5 ml). The reagent was removed by evaporation at 50° and 0.5 mm Hg and the residue crystallized from ethanol to give the purine (individual yields, analytical and spectral data are given in Tables I and II).

7,8-Dihydropurines **2**.

The aromatic purine (0.001 mole) was dissolved in *M*-hydrochloric acid (5 ml) and stirred at room temperature during the portionwise addition of sodium cyanoborohydride (0.2 g, 0.003 mole) over 30 minutes. The solution was stirred for a further 1 hour, when the *p*H of the solution was adjusted to 8 with sodium carbonate [15]. The resulting suspension was chilled and filtered to give the dihydropurine, which was washed with water and dried at 25° and 0.1 mm Hg. Data on individual compounds are given in Tables I and II.

2-Deuterio-4,5-diamino-6-ethoxycarbonylpyrimidine (**5**, R = ^{2}H).

4-Amino-2-chloro-6-ethoxycarbonyl-5-nitropyrimidine (**6**) [10] was shaken overnight in ethanol (50 ml) with 5% palladium charcoal in an atmosphere of deuterium gas at 4 atmospheres. The catalyst was removed by filtration and the filtrate evaporated to dryness at 40° *in vacuo*. The residue, which contained a trace of 2-chloro-4,5-diamino-6-ethoxycarbonylpyrimidine [thin-layer chromatography on silica gel with ethanol-ethyl acetate (1:9) as eluent] was crystallised from ethanol to remove the impurity. The diamine, which showed 90% incorporation of deuterium by ^{1}H nmr spectroscopy, was converted without loss of deuterium into the corresponding dihydropurine in two steps as described above.

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[15] With the exception of the 2-unsubstituted compound **2a**, which crystallized directly from the reaction medium as the hydrochloride.