Purine Studies. Part 24.[1] Preparation of 1,6- and 7,8-Dihydro-derivatives of 8-Trifluoromethylpurines by Reduction

By **Adrien Albert**, Research School of Chemistry, Australian National University, Canberra, A.C.T. 2600, Australia

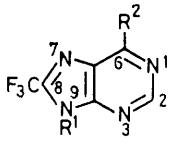
8-Trifluoromethylpurine (1a) was converted by catalytic hydrogenation entirely to the 1,6-dihydro-derivative (3a), whereas 9-methyl-8-trifluoromethypurine (1b) produced a 2 : 1 mixture of the 1,6- (3b) and 7,8- (5) dihydro-derivatives. The new hydrogenated purines are characterised by unusual stability. Physical properties are discussed and compared with those of analogues from several other heterocyclic series.

BECAUSE purines have been found to undergo chemical reduction reluctantly, little is known about the hydropurines, a full account of which occupies only ten pages of the 655-page purine monograph.[2] In particular, this literature presents dihydropurines as difficult to produce and isolate, and unstable to oxygen and cold, dilute acids. In contrast, 8-azapurines (*v*-triazolo[4,5-*d*]pyrimidines) are easily reduced to stable 1,6-dihydro-derivatives.[3] This suggests that purines, if substituted by an electron-attracting group in the 8-position, may provide a fertile source of stable dihydropurines.

RESULTS AND DISCUSSION

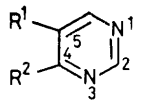
Accordingly, 8-trifluoromethylpurine (1a)[4] was prepared from 4,5-diaminopyrimidine (2a) by an improved method, namely by heating with trifluoroacetic anhydride in an autoclave. This purine (1a), although resistant to palladium-catalysed hydrogenation at atmospheric pressure, was converted quantitatively to the 1,6-dihydro-derivative (3a) at 4 atm. The cation of the purine (1a) was more susceptible, giving the same result at atmospheric pressure, whereas the anion was destroyed under these conditions.

The constitution of (3a) was determined as follows. The ^{1}H n.m.r. spectrum of the starting material (1a) (Table) resembled that of 9-methyl-8-methylsulphonyl-purine [τ 0.79 (1 H, 6-CH) and 0.91 (1 H, 2-CH)];[5] the 6-CH was judged the more deshielded position as is usual in fused pyrimidines. For the hydrogenated product (3a), the signal for CH has moved further upfield, but is much below the CH_2 signal (τ 5.32), which has to be assigned to the pyrimidine ring because hydrogenation of the imidazole ring cannot furnish a methylene group. That this is in the 6- rather than the 2-position is suggested by comparison with the spectrum of 3,4-dihydroquinazoline (4), in which the position of the methylene group was carefully established by synthesis.[6] The signals for compound (4) were found[3a] at τ 2.89 (1 H, 2-CH) and 5.48 (2 H, 4-CH_2), very close to those of the dihydropurine (3a). Further confirmation is provided by the position of the methylene signal in 1,6-dihydro-8-azapurine (τ 5.18),[3a] and in 9-benzyl-1,6-dihydro-8-azapurine (τ 5.10)[7] where the orientation was established by synthesis from a 5-aminomethyl-1,2,3-triazole. More-



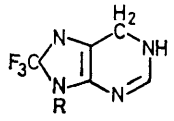
(1)

a; $R^1 = R^2 = H$
b; $R^1 = Me$, $R^2 = H$
c; $R^1 = H$, $R^2 = SMe$
d; $R^1 = H$, $R^2 = NH_2$



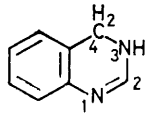
(2)

a; $R^1 = R^2 = NH_2$
b; $R^1 = NH_2$, $R^2 = NHMe$
c; $R^1 = NHCOCF_3$, $R^2 = NHMe$

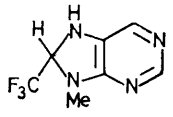


(3)

a; R = H
b; R = Me



(4)



(5)

^{1}H N.m.r. spectra of 8-trifluoromethylpurines

Compound	τ values [a]
(1a) [b]	0.54 (1 H, s, 6-CH), 0.82 (1 H, s, 2-CH)
(1b)	0.65 (1 H, s, 6-CH), 0.90 (1 H, s, 2-CH), 6.04 (3 H, s, Me)
(1c)	1.14 (1 H, s, 2-CH), 7.31 (3 H, s, Me)
(3a)	2.89 (1 H, s, 2-CH), 5.32 [c] (2 H, d, *J* 4 Hz, 6-CH_2)
(3b) [c]	2.28br [d] (NH), 2.97 [e] (1 H, d, *J* 4 Hz, 2-CH), 5.38 (2 H, s, 6-CH_2), 6.49 (3 H, s, Me)
(5)	2.01 (1 H, s, 6-CH), 2.65 (1 H, s, 2-CH), 2.86 [d] (1 H, d, *J* 8 Hz, NH), 4.16 [f] (1 H, quint, *J* 8 Hz, 8-CH), 6.98 (3 H, s, Me)

[a] At 30 °C in $(CD_3)_2SO$. [b] Known substance,[4] but n.m.r. is new. [c] The phthalate had a similar spectrum plus a signal for the ring protons of phthalic acid (τ 2.41, 4 H, AA'BB' multiplet). [d] Signal vanished after addition of D_2O. [e] Doublet, due to coupling with NH, became singlet after addition of D_2O. [f] Quintet, due to coupling to both NH and F_3C, became quartet after D_2O was added.

over, the incremental differences, for the chemical shifts of 2-CH and 6-CH, observed in passing from 9-benzyl-8-azapurine to its 1,6-dihydro derivative,[7] are similar to those found here for the transitions (1a)→(3a) and (1b)→(3b). Finally, hydrolysis of compound (3a) with cold 1N-hydrochloric acid slowly furnished a diazotizable primary aromatic amine.

A homologue of the purine (1a), 9-methyl-8-trifluoromethylpurine (1b), was made similarly from 5-amino-4-methylaminopyrimidine (2b). Attempted synthesis at a lower temperature gave much 4-methylamino-5-trifluoroacetamidopyrimidine (2c) which also arose from cold alkaline hydrolysis of the product (1b). Compound (1b) took up two atoms of hydrogen over palladium at 4 atm. [Attempted hydrogenation of the anion and cation of (1b), even at atmospheric pressure, was destructive.] The product, obtained quantitatively, was a mixture of two dihydro-derivatives in the ratio 1 : 2 (fluorescent : non-fluorescent) as revealed by ^{1}H n.m.r. The isomers were best separated by precipitation of their phthalates; the non-fluorescent 1,6-isomer came down at a slightly higher pH and was less soluble in cold water. The constitution of this isomer (3b) was rapidly established from the similarity of its n.m.r. spectrum to that of the lower homologue (3a) (Table).

The constitution of the fluorescent isomer was assigned as 7,8-dihydro-9-methyl-8-trifluoromethylpurine (5) from the mass spectrum (M^+ 204) and the ^{1}H n.m.r. spectrum. The latter showed a characteristic quintet, which collapsed to a quartet after deuteriation, interpreted as derived from 8-CH coupled to both 7-NH and the fluorine atoms. Signals for 2-CH and 6-CH were considerably downfield from this quintet. The action of sodium borohydride on the purine (1b) produced the same two isomers, and in the same proportion.

This occurrence of hydrogenation in the 7,8-positions breaks new ground because only 1,6-dihydrogenation has been recorded for purines so far.[2,8]

6-Methylthio-8-trifluoromethylpurine (1c) was prepared from 4,5-diamino-6-methylthiopyrimidine [9] and trifluoroacetic anhydride. Neither this purine nor 6-amino-8-trifluoromethylpurine [4] could be hydrogenated under the conditions successful for the purine (1a).

Compounds (1b), (3b), and (5), lacking the hydrogen-bonding NH group of compounds (1a) and (3a), are highly lipophilic and volatile. However, the isomers (3b) and (5) could not be separated by fractional sublimation. The 1,6-dihydropurines are weak bases (pK_a *ca.* 3.5), only slowly attacked by cold 0.1N acid or alkali, and stable in air at 110 °C.

Ultraviolet Spectra.—The u.v. spectra, observed in 96% ethanol, showed only one main peak, reported here as: ($\lambda_{max.}$/nm, followed by log ε). That of the purine (1b) occurred at (270, 3.90) similar to that [4] reported for the purine (1a) in water (264, 3.89). The two 1,6-dihydro-compounds (3a and b) absorb at longer wavelengths, namely (297, 3.73) and (303, 3.83), respectively. Such bathochromy after dihydrogenation is common in hetero-aromatic chemistry, *e.g.* quinoline (312, 3.53) becomes (343, 3.35) after 1,2-dihydrogenation.[10] Another example, 9-benzyl-8-azapurine (263, 3.88), became (293, 3.85) after 1,6-dihydrogenation.[7] The 7,8-dihydro-isomer (5) absorbed at (299, 3.90).

These results call into question the nature of the so-called 1,6-dihydropurine obtained by hydrogenating the cation of purine, said to have no selective absorption in the u.v. (however, no elemental analysis was offered).[11] Butula,[8] who later published a valid microanalysis for the hydrochloride, did not comment on the u.v. spectrum. Thus some mystery surrounds this compound, particularly as n.m.r. and mass spectral data are lacking.

The u.v. spectra of compounds (3a) and (3b) refute the statement that the strong absorption of purines is due entirely to the C(4)=C(5)–C(6)=N(1)– chromophore.[12] It is much more likely that the longer wavelength absorption in purines represents a polarized electronic transition across an axis of the molecule, named the 'L absorption' by Platt (for all aromatic systems) [13] and the '*x* absorption' by Mason (for purines).[14]

Biological Aspects.—Because 1,6-dihydro-8-azapurines have shown a high chemotherapeutic index in mammary and colonic cancer (xenografts) in mice (U.S. National Cancer Institute), it seems desirable to test these dihydropurines similarly.

EXPERIMENTAL

The u.v. spectra were recorded on a Cary Model 16 spectrophotometer. ^{1}H N.m.r. spectra were routinely obtained on a 100 MHz Jeol Minimar instrument, but the data reported in the Table for compound (5) were furnished by a Varian HA-100 instrument, both at 30 °C. Tetramethylsilane was used as the internal standard. The i.r. spectrum was recorded on a Perkin-Elmer spectrometer, model 257. The mass spectra were obtained from an AEI MS 902 instrument. All substances were examined by ascending paper chromatography, after application in aqueous pyridine (constant boiling mixture) to two Whatman No. 1 papers, and developed in (*a*) 3% aqueous NH_4Cl, and (*b*) butanol–5N-acetic acid (7 : 3 v/v).

8-*Trifluoromethylpurine* (1a) (*improved preparation and new data*).—4,5-Diaminopyramidine [15] (0.66 g, 0.006 mol), trifluoroacetic acid (2.1 ml), and trifluoroacetic anhydride (6.6 ml) were placed in a chilled, Teflon-lined autoclave (23 ml capacity; Uniseal Decomposition Vessels, Ltd, Haifa, Israel) and heated at 110 °C (oven temperature) for 24 h. After the vessel cooled, the contents were taken to dryness at (eventually) 60 °C. The residue was cooled, and diluted with water (3 ml) and 4M-sodium formate (0.6 ml). (A). The solution was placed in a bath at 10 °C and adjusted to pH 3.0 with 10N-sodium hydroxide (*ca.* 1 ml). Refrigeration yielded crystals of the desired compound which were set aside. The filtrate, re-adjusted to pH 3.0, was taken to dryness (eventually 60 °C). The residue was rubbed with chloroform (2 × 7 ml), filtered, and the filtrate (dried with $MgSO_4$) was evaporated to give, altogether, an 80% yield of 8-trifluoromethylpurine, m.p. 190 °C (lit.,[4] 192 °C). Recrystallization from 7 parts of ethanol or 120 parts of benzene (2 crops taken in each case) gave material of m.p.

193 °C. The pH chosen for isolation was derived from the published [4] pK_a values (1.0, basic and 5.12, acidic).

9-Methyl-8-trifluoromethylpurine.—5-Amino-4-methylaminopyrimidine [16] (0.744 g, 0.006 mol) was treated as the lower homologue down to (A). The solution was placed in a bath at 10 °C and adjusted to pH 3.5—4.0 with 10N sodium hydroxide (*ca.* 1.8 ml). It was shaken out with chloroform (30 + 15 ml), dried (K_2CO_3), and recovered (at 40 °C eventually) giving *9-methyl-8-trifluoromethylpurine* (90%), m.p. 88 °C, recrystallized from 12 parts of cyclohexane (2 crops). One batch that had hydrolysed slightly was freed from the by-product (2c) by dissolution in cold benzene (8 parts) in which the pyrimidine is insoluble [Found (for material dried by sublimation at 70 °C and 0.01 mmHg): C, 41.8; H, 2.6; N, 28.0; F, 28.1. $C_7H_5F_3N_4$ requires C, 41.6; H, 2.5; N, 27.7; F, 28.2%]. 2N-Ammonia at 20 °C converted it quantitatively to 5-amino-4-methylaminopyrimidine (2b) in 3 days.

4-Methylamino-5-trifluoroacetamidopyrimidine (2c).—This *by-product*, recrystallized from ethanol–benzene (1 : 2) (17 parts), had m.p. 196 °C (Found: C, 38.2; H, 3.1; N, 25.2; F, 25.9. $C_7H_7F_3N_4O$ requires C, 38.2; H, 3.2; N, 25.45; F, 25.9%); $\nu_{max.}$ (Nujol mull) 3 360m (NH), 1 620s (amide I), 1 575s, br (amide II), 1 270 (F sym. bend.), and 1 180 + 1 130 m (d, F asym. bend) cm^{-1}, insoluble in cold 1N-acetic acid (absence of Dimroth retrogression).

6-Methylthio-8-trifluoromethylpurine (1c).—4,5-Diamino-6-methylthiopyrimidine [9] (0.468 g, 0.003 mol), treated as 8-trifluoromethylpurine in the foregoing, gave the title *compound* (86%), m.p. 238 °C (from 45 parts of benzene), insoluble in cold 0.1N-hydrochloric acid [Found (for material dried in air at 110 °C): C, 35.7; H, 2.4; N, 23.8. $C_7H_5F_3N_4S$ requires C, 35.9; H, 2.2; N, 23.9%).

1,6-Dihydro-8-trifluoromethylpurine.—8-Trifluoromethylpurine (0.564 g, 0.003 mol) was added to a pre-reduced suspension of 10% palladium–carbon (0.3 g) in trifluoroacetic acid (21 ml), and hydrogenated at 25 °C and 1 atm until saturated (*ca.* 5 h). The suspension was taken to dryness (eventually at 40 °C), and water (7.5 ml) and Kieselguhr (0.3 g) were added to the cooled residue. The suspension was filtered, and the filtrate was stirred in an ice bath with 0.5M-sodium triphosphate (1 ml), then 10N-sodium hydroxide was added to pH 7 (*ca.* 1.2 ml). The suspension was then refrigerated to give *8-trifluoromethyl-1,6-dihydropurine* (88%), m.p. 194 °C from dimethylformamide–water (3 : 1) (16 parts) [when recrystallization from ethanol was effected, this solvent was retained (even at 100 °C and 0.01 mmHg) as a clathrate] [Found (for material dried at 100 °C and 0.01 mmHg): C, 38.2; H, 2.9; N, 29.2; F, 29.5. $C_6H_5F_3N_4$ requires C, 37.9; H, 2.7; N, 29.5; F, 30.0%]; *m/e* 190 (M^+), 189, 169, 142, 115, 85, and 69 (CF_3). Lead tetra-acetate in acetic acid at 70 °C converted it quantitatively to the starting material.

Hydrogenation of 9-Methyl-8-trifluoromethylpurine.—Pre-reduced 10% palladium–carbon (0.1 g), 8-trifluoromethyl-9-methylpurine (0.202 g, 0.001 mol), and ethanol (50 ml) were hydrogenated at 4 atm and 70 °C for 5 h. Kieselguhr (0.1 g) was added to the cooled suspension which was filtered cold and washed with cold ethanol. The filtrate was taken to dryness (eventually at 60 °C) giving a mixture of the dihydropurines (3b) and (5) (*ca.* 95%), m.p. 98—111 °C. This was stirred with a solution of potassium hydrogenphthalate (0.408 g, 0.002 mol) in water (4 ml), cooled at 20 °C. The pH (4.7) was adjusted to 5.0 with a little 10N-sodium hydroxide. The suspension was chilled for 2 h, and filtered (B) to give *1,6-dihydro-9-methyl-8-trifluoromethylpurine hydrogenphthalate* (60%), m.p. 173 °C from 90 parts of acetonitrile [Found (for material dried at 110 °C in air): C, 48.65; H, 3.7; N, 15.0; F, 15.0. $C_{15}H_{13}F_3N_4O_4$ requires C, 48.65; H, 3.5; N, 15.1; F, 15.4%). The filtrate at (B) was adjusted to pH 6.5 with ammonia, and extracted with chloroform (25 + 15 ml) which was then dried ($MgSO_4$) and recovered. The residue was stirred at 20 °C with potassium hydrogenphthalate (0.13 g) in water (1.3 ml) and the solution was refrigerated overnight, yielding *7,8-dihydro-9-methyl-8-trifluoromethylpurine hydrogenphthalate* (16%), m.p. 157 °C from 25 parts of acetonitrile (Found: C, 48.8; H, 3.4; N, 15.0; F, 15.6%).

Liberation of Bases.—Each phthalate (0.370 g, 0.001 mol), in 2N-ammonia (4.5 ml) was shaken with chloroform (15 + 10 ml), then dried and recovered (eventually at 40 °C). The *1,6-dihydro-isomer* had m.p. 135 °C from cyclohexane–benzene (2 : 1) (48 parts) [Found (for material dried at 60 °C and 0.01 mmHg): C, 41.2; H, 3.5; N, 27.7. $C_7H_7F_3N_4$ requires C, 41.2; H, 3.5; N, 27.4%]; *m/e* 204 (M^+), 203, 202, 134, 110, and 69 (CF_3). The 7,8-dihydro-isomer, m.p. 135 °C from cyclohexane–benzene (2 : 1) (77 parts) gave a large depression of m.p. with the 1,6-isomer, from which it also differed in being fluorescent; *m/e* 204 (M^+), 135 ($M^+ - CF_3$), 109, and 78.

The *hydrochloride* of 1,6-dihydro-9-methyl-8-trifluoromethylpurine was prepared by neutralizing the base with 0.1N-hydrochloric acid and evaporation of the solution at 60 °C. Recrystallized from 80 parts of acetonitrile, it turned yellow and decomposed at 178 °C [Found (for material dried in air at 75 °C): C, 35.1; H, 3.3; N, 23.2; Cl, 14.85; F, 23.6. $C_7H_8ClF_3N_4$ requires C, 35.0; H, 3.35; N, 23.3; Cl, 14.7; F, 23.7%).

Borohydride Reduction of 8-Trifluoromethyl-9-methylpurine.—This purine (1b) (0.101 g, 0.0005 mol), dissolved in tetrahydrofuran (1.5 ml) and cooled in an ice-bath, was stirred with a suspension of sodium borohydride (0.038 g, 0.001 mol) in tetrahydrofuran (3 ml) for 2 h, then overnight at 20 °C. The solvent was removed (eventually at 40 °C); the residue was cooled and diluted with water (1 ml). The pH (7.0) was adjusted to 9 with 15N-ammonia, and the solution was shaken with chloroform (5 + 5 ml) to give 80% of a mixture identical with that described in the foregoing under ' hydrogenation '.

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