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1,2,3,4,6-Penta-azaindenes (8-Azapurines). Part VI.[1] Methylation of 8-Azapurine

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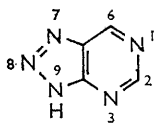
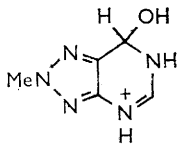
A practicable methylation of 8-azapurine is described which gives 7-, 8-, and 9-methyl-8-azapurine in approximately equal amounts. After solvent extraction (from aqueous acid), which took advantage of the lower basic strength of the 9-isomer, t.l.c. was used to complete the separation of the isomers. Some alternative procedures are discussed.

A PRELIMINARY methylation of 8-azapurine (I), carried out by one of us (W. P.) in 1965, and unpublished, furnished three monomethyl derivatives, m.p. 88°, 133°, and 167°, approximately. Unambiguous syntheses have since established the positions of the methyl group as 9, 8, and 7, respectively.[2-4] We now describe the methylation of 8-azapurine and the separation of these isomers.



(I)



(II)

Dimethyl sulphate in aqueous alkali was found preferable to diazomethane in ether. The relative proportions of the 7-, 8-, and 9-isomers in the *crude* product were 1 : 1 : 1·1 (respectively) at 12—14°, and 1·5 : 1 : 1·1 at 21—23°, as estimated by ^{1}H n.m.r.

Because prior sublimation proved inefficient, advantage was taken of the relatively low basic strength of the 9-isomer (pK_a 0·32) [2] to extract it as the neutral species into dichloromethane. The more basic [3,4] 7- and 8-isomers were extracted, after basification, into dichloromethane and finally separated by t.l.c. on alumina (found preferable to silica). Omission of the acidic extraction necessitated the use of many more plates, which caused more loss of the volatile products. Agreement with the published m.p.s was achieved after one sublimation, or (7-isomer only) recrystallisation from methanol.

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[1] Part V, A. Albert, *J. Chem. Soc.* (*C*), 1969, 152.
[2] A. Albert, *J. Chem. Soc.* (*B*), 1966, 427.
[3] A. Albert, *J. Chem. Soc.* (*C*), 1968, 2076.
[4] A. Albert and K. Tratt, *J. Chem. Soc.* (*C*), 1968, 344.

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Table 2 gives the R_F values of the various compounds on alumina plates and paper. Three minor components were found in addition to those already described. The first was unchanged starting material, which forms a hydrated cation [2] and hence followed the 7-methyl isomer until the final purification. Another was the 1-methyl isomer, which has been independently prepared,[5] the third may be the 3-methyl isomer.

Typical yields from the methylation of 8-azapurine (1·5 g.) at 12—14° are shown in Table 1.

TABLE 1

^{1}H N.m.r. Spectra (60 Mc./sec. in D_2O) and typical yields [from methylation of 8-azapurine (1·5 g.)]

8-Azapurine	Methyl resonance * (τ)	Yield † (g.)	Sublimation temperature (0·01 mm.)	M.p.
7-Methyl-	5·38	0·28 ‡	140°	165—166° (lit.,[4] 166—167°)
8-Methyl-	5·25	0·34	120	131—132 (lit.,[3] 133·5)
9-Methyl-	5·52	0·32	90	87—88 (lit.,[2] 88)

* Relative to sodium trimethylsilylpropanesulphonate (τ 10). † Total yield 56% (range of yields 50—60%). ‡ Larger amounts were, more conveniently, recrystallised from methanol.

TABLE 2

R_F Values for paper and thin-layer chromatography

8-Azapurine	R_F *† (Paper)	R_F *‡ (Alumina)
9-Methyl-	0·74	0·84
8-Methyl-	0·69	0·67
7-Methyl-	0·64	0·05—0·1
1-Methyl-	0·60	
(3?)-Methyl-	0·79	0·4
(Unsubstituted)	0·69	0·0—0·04

* Observed under u.v. light at 254 mm. † Developed with butan-1-ol–5N-acetic acdi (7 : 3). ‡ Developed with ether.

EXPERIMENTAL

For paper chromatography the ascending method was used with butan-1-ol–5N-acetic acid (7 : 3) as developer on Whatman no. 1 paper. For t.l.c. glass plates were coated with Merck alumina (grade $PF_{254+366}$) then dried at 100° for 2 hr. and stored in a sealed box without a desiccant. The R_F values of the 8- and 9-isomers fell below those indicated in Table 2 when thicker plates were used. For estimation of the relative proportions of the main products, the residue, obtained by distilling the solvent from a portion of the dichloromethane extract of the reaction mixture, was dissolved in deuterium oxide. The integrated trace of the methyl ^{1}H n.m.r. resonances (see Table 1) of the solution was measured with a 60 Mc./sec. Perkin-Elmer R10 spectrometer.

Methylation of 8-Azapurine.—To 8-azapurine (1·5 g.) in vigorously stirred aqueous sodium hydroxide (*ca.* 0·4N; 24 ml.), cooled to 12°, dimethyl sulphate (1·5 ml., 1·1 equiv.; freshly distilled) was added dropwise during 15 min. The pH of the mixture was held above 7 by the addition of N-sodium hydroxide. The mixture was stirred at 12° for a total of 2 hr., then the pH was adjusted to 2·0 with 5N-sulphuric acid and the solution was quickly extracted with dichloromethane (5 × 10 ml.). (In preliminary work, the progress of the extraction was checked by t.l.c. on alumina, developed with ether.) The use of higher-boiling solvents led to loss of products because of co-volatilisation of the methyl-8-azapurines. The lower layer (fraction A) contained (*a*) almost all the 9-methyl-8-azapurine, (*b*) the small amount of the suspected 3-isomer, and (*c*) a little of the 7- and 8-methyl-8-azapurines. The aqueous layer, adjusted to pH 7 with 10N-sodium hydroxide, was continuously extracted with dichloromethane for *ca.* 4 hr. The extract (fraction B) contained most of the 7- and 8-methyl-8-azapurines and a little 9-methyl-8-azapurine (20 mg.). Fractions A and B were each applied to the long side of three preparative t.l.c. plates (40 × 20 cm.; covered with 2 mm. of alumina) and developed three times with ether (purest grade). The plates were observed under u.v. light (254 nm.) and each u.v.-absorbing area was removed mechanically from the plates. Corresponding fractions from all plates were pooled; those containing the 8- and the 9-isomer were extracted with ether in a Soxhlet apparatus; that containing the 7-isomer was extracted with water, from which it was back-extracted into dichloromethane. The solvents were then distilled off at atmospheric pressure. On alumina, the 7-isomer slowly decomposed to a yellow substance at 20° in the dark, and more rapidly in daylight.

Dry Column Chromatography.—In an alternative procedure for fractionating the crude methylation mixture, it was extracted (at pH 7) with dichloromethane. The extract, concentrated to a small volume, was added to a dry column (2 cm. diam.) of alumina (60 g. of the grade used for plates) which was then developed and eluted with ether. The following consecutive fractions were obtained, (1) the first 50 ml., no azapurines; (2) 200 ml., 9-methyl-8-azapurine (0·3 g.); (3) 300 ml., mainly 8-methyl-8-azapurine (0·21 g.); (4) 300 ml., mixture of isomers (0·05 g.); (5) 1·2 l., 7-methyl-8-azapurine (0·2 g.). It was found best to dismantle the column as soon as the mixture of 8- and 7-isomers had been eluted, and to extract the alumina with water, which was then back-extracted with dichloromethane. Evaporation of the latter furnished most of the 7-isomer, which was then purified by recrystallisation or t.l.c. This method may be advantageous when the methylation is conducted on a larger scale.

[5] D. Thacker, unpublished work.

[8/1866 *Received, December 18th,* 1968]