6-Azapurines. Part 3.[1] Covalent σ-Adducts of the Imidazo[4,5-*e*]-*as*-triazine Ring System[2]

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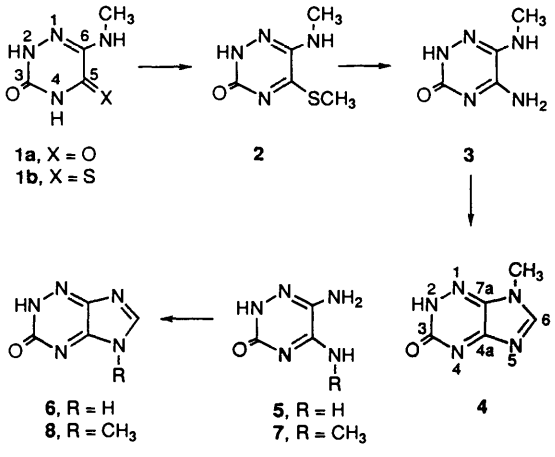
7-Methylimidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one, imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one, and 5-methylimidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one have been synthesized from their respective 5,6-diamino-*as*-triazin-3-ones and selected one-carbon delivering reagents. These 6-azapurines undergo covalent hydration across the azomethine bond located in the imidazole portion of the ring. In water, the σ-adducts ring open to certain *as*-triazin-3-ones whose structures were identified by NMR (^{1}H and ^{13}C) spectroscopy. These *as*-triazin-3-ones provided evidence for the described mode of cleavage.

Recent investigations from our laboratories examined the physical properties of certain imidazo[4,5-*e*]-*as*-triazines† (6-azapurines) and allowed us to define their predominant tautomeric forms in solution[3] and in the solid state.[1] Further study showed that when an oxo group resided on position 3 of this ring system, they became susceptible to covalent hydration. Once formed, the hydrated intermediates immediately underwent ring opening. In an attempt better to understand this process and to determine the site and mode of solvent addition as well as to identify the ring-opened products, 7-methylimidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (**4**), imidazo[4,5-*e*]-*as*-triazine-3(2*H*)-one (**6**), and 5-methylimidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (**8**) (Scheme 1) were prepared and subjected to



Scheme 1

water, methanol and ethanol. We now wish to report our interesting findings on these unique heterocycles.

Results and Discussion

Our synthetic program involving the imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-ones focused on the preparation of **4**, **6** and **8**, from their respective *as*-triazine precursors **3**, **5** and **7**. The synthesis of **4** was pursued first and the route used is illustrated in Scheme 1. 6-Methylamino-3-oxo-3,4-dihydro-*as*-triazine-5(2*H*)-thione (**1b**, Scheme 1), prepared from 6-methylamino-*as*-triazin-3,5(2*H*)-dione (**1a**),[4] was suspended in absolute ethanol and treated with a 1 mol dm^{-3} sodium hydroxide solution at room temperature. The generated sodium salt of **1b** was then mixed with methyl iodide to furnish **2** in good yield. Treatment of **2** with methanolic ammonia at room temperature afforded a near-quantitative yield of 5-amino-6-methylamino-*as*-triazin-3(2*H*)-one. (**3**). The final step involved cyclization of **3** using either triethyl orthoformate (TEOF) or trimethyl orthoformate (TMOF) in the presence of a catalytic amount of concentrated hydrochloric acid. It was during the ring closure of **3** that the sensitivity of **4** to hydroxylic solvents was first noticed.

Owing to the insolubility of the starting 5,6-diamino-*as*-triazin-3-ones (**3**, **5** and **7**) and their respective ring closed 6-azapurines (**4**, **6** and **8**) in TEOF or TMOF, solution was never effected during the entire reaction period. Typically, the suspended solids after being heated in TEOF or TMOF at reflux for 18 h were filtered off and crystallized from either absolute ethanol or anhydrous methanol (Table 1). Examination of the hot crystallization solution (abs. ethanol) of **4** by TLC suggested that cyclization was incomplete. The reaction time was increased to 30 h, but the same result was obtained.

The ^{1}H NMR spectrum [$(CD_3)_2SO$] of crystalline **4** should have only two signals between 0 and 10 ppm; one for the 7-Me resonance (δ 3.61) and the other for the C(6)H proton (δ 8.84, Table 2). Instead, the spectrum of the air-dried, recrystallized (ethanol) material was more complex (see Fig. 1). The expected signals of **4** were only a minor contribution to the total spectrum. The presence of the ethyl spin pattern indicated that ethanol was adding to this 6-azapurine, most likely across the N(5)–C(6) azomethine bond.[4] The singlet at δ 6.14 ppm‡ was assigned to the C(6)H proton of the σ-adduct **9b**. Heating the solid mixture for 24 h under vacuum in an Abderhalen at

† The nomenclature and numbering used throughout this paper is that for the imidazo[4,5-*e*]-*as*-triazine and *as*-triazine ring systems. The numbering for these heterocycles are depicted on structures **1** and **4** (see Scheme 1).

‡ The electronic environment of the C(6)H proton of 6-ethoxy-7-methyl-6,7-dihydro-5*H*-imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (**9b**) appears to be quite similar to that of 7,8-dihydro-9-methyl-8-trifluoromethylpurine since the chemical shift of the C(8)H proton of this dihydropurine is δ 5.84.[5] A Dreiding model of **9b** indicated that when the hydrogen on C(6) resides in an equatorial position, as illustrated in Scheme 2, the N(5)H–C(6)H dihedral angle is approximately 90°. This structural feature may account for the C(6)H signal appearing as a singlet.

Table 1 Synthesis of certain imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-ones[a,e]

Starting material (mmol)	Ring-closing agent	Method	Product (% yield)	M.p./°C slow decomposition	Crystallizing solvent
3 (3.0)	TEOF	A	**4** (89)	218	*b*
3 (3.0)	TMOF	A	**4** (88)	218	*b*
5 (3.0)	TEOF	A	**6** (88)	246	Ethanol
5 (3.94)	TMOF	A	**6** (85)	246	Methanol
5 (0.79)	DEMA	B	**6** (81)	246	Methanol
7 (3.0)	TEOF–TMOF[c]	A	**8** (79)	270	EtOH–MeOH[d]
7 (0.71)	DEMA	B	**8** (56)	270	EtOH–MeOH

[a] Satisfactory analyses (C, H, N; ± 0.4%) were obtained for **4**, **6** and **8**. [b] This heterocycle cannot be recrystallized from hydroxylic solvents and should be dried in an Abderhalen at 100 °C for 6 h. [c] Either reagent gave identical results. [d] Compound **8** was warmed and dissolved in dry methanol and to this solution was added an equal volume of absolute ethanol (MeOH–EtOH *ca.* 1:1). [e] The ultraviolet spectra are as follows: **4**, λ_{max}/nm (pH 1) 289sh (ε/dm^3 mol^{-1} cm^{-1} 4990), 264sh (6050) and 258 (6120); λ_{max}(CH_3CN)/nm 383 (ε/dm^3 mol^{-1} cm^{-1} 3550), 279 (5140) and 227.5 (7710); λ_{max}/nm (pH 11) 357 (ε/dm^3 mol^{-1} cm^{-1} 4230), 283 (4990) and 227 (11 030); **6**, λ_{max}/nm (pH 1) 290sh (ε/dm^3 mol^{-1} cm^{-1} 4940); λ_{max}(MeOH)/nm 347 (ε/dm^3 mol^{-1} cm^{-1} 2440) and 272 (4100); λ_{max}/nm (pH 11) 350 (ε/dm^3 mol^{-1} cm^{-1} 3430), 288 (6350) and 225.5 (7680); **8**, λ_{max}/nm (pH 1) 283 (ε/dm^3 mol^{-1} cm^{-1} 6510); λ_{max}(MeOH)/nm 317 (ε/dm^3 mol^{-1} cm^{-1} 2050) and 278 (4230); λ_{max}/nm (pH 11) 342 (ε/dm^3 mol^{-1} cm^{-1} 5790), 273 (3870), and 228 (10 570).

Table 2 Summary of proton chemical shifts (δ)[a]

Compd.	N(2)H[b]	N*H*CH_3	NCH_3	C(5)NH_2	C(6)NH_2	Other
as-Triazines						
1a	10.93	6.45 (q)	2.64 (d)			11.68 [s, N(4)H]
1b	11.52	6.41 (q)	2.69 (d)			13.31 [br s, N(4)H]
2	11.69	6.10 (q)	2.64 (d)			2.50 [s, SC*H*$_3$]
3	10.89	5.96 (q)	2.66 (d)	7.41 (br s)		
5[c]	10.77			7.00–8.50 (v br s)	5.88 (br s)	
7[c]	10.59	7.62 (q)	2.80 (d)		5.42 (br s)	
10	11.90		2.95 (s)	7.23–8.33[d]		8.19 (s, C*H*O)
	12.04[e]		3.00 (s)[e]	7.60 (br s),[e] 8.11 (br s)[e]		8.24 (s, C*H*O)[e]
11	11.90		3.10 (s)	7.23–8.33[d]		8.11 (s, C*H*O)
	12.04[e]		3.15 (s)[e]	7.52 (br s),[e] 8.01 (br s)[e]		8.17 (s, C*H*O)[e]
12	11.67			8.12 (br s)		8.42 (br s, C*H*O), 9.79 (br s, N*H*CHO)
13	11.63	7.87 (q)	2.79 (d)			8.30 (br s, C*H*O), 9.77 (br s, N*H*CHO)
14[c]	10.80				5.90 (br s)	11.60 [br s, N(4)H]

Compd.	N(2)H[b]	N(5)H[b]	C(6)H	NCH_3	Other
Imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-ones					
4	12.68		8.84 (s)	3.61 (s)	
	12.10[e]		8.91 (s)[e]	3.67 (s)[e]	
6	12.92[f]	12.92[f]	8.61 (s)		
	13.11[f,g]	13.11[f,g]	8.72 (s)[g]		
8	13.02		8.52 (s)	3.51 (s)	
	13.17[g]		8.65 (s)[g]	3.54 (s)[g]	
9a	12.50[h]	10.40[h]	6.20 (s)	2.80 (s)	3.05 (s, OC*H*$_3$)
9b	11.90[h]	10.40[h]	6.14 (s)	2.78 (s)	1.12 (t, OCH$_2$C*H*$_3$) 3.34 (q, OC*H*$_2$CH$_3$)
9c[i]			6.12 (s)	2.80 (s)	

[a] Proton spectra were recorded with a Varian EM-390 spectrometer, unless specified. All samples were dissolved in $(CD_3)_2SO$ containing 1% Me_4Si. Chemical shifts are in parts per million with respect to Me_4Si; s = singlet, d = doublet, t = triplet, q = quartet, v br s = very broad singlet. [b] Broad singlet. [c] Ref. 7. [d] Range for the two broad resonances depicted in Fig. 3. They are the signals for the C(5)-amino groups of **10** and **11** and are deuterium oxide (D_2O) exchangeable. [e] Proton chemical shifts obtained on a Bruker AM-400 spectrometer. For compounds **10** and **11** see ref. 6. [f] This broad singlet (exchangeable in D_2O) integrates for two protons and has been assigned to the N(2)H and N(5)H protons. [g] Proton chemical shifts obtained on a Bruker AM-300 spectrometer. [h] These assignments can be reversed. [i] Spectrum run in $(CD_3)_2SO/D_2O$.

78 °C (refluxing ethanol), and then comparing the ^{1}H NMR spectrum of this 'dried' material with the original one, revealed a decrease in the intensity of the signals at δ 2.78 (7-Me of the σ-adduct) and δ 6.14 as well as the triplet and quartet of the ethyl group. On the other hand, the signals attributed to **4** (δ 3.61 and 8.84) increased in intensity. After 'drying' 48 h at 78 °C, only the signals assigned to **4** and the singlets at δ 2.95, 3.10, 8.11 and 8.19* and the two broad resonances between δ 7.2–8.3 ppm (deuterium oxide exchangeable) remained. The intensity of these latter six signals remained constant throughout the 'drying' process. Subsequent investigation showed that they

* These proton chemical shifts (for **10** and **11**) were obtained with a Varian EM-390 spectrometer. Recently, the population and rotational barriers of the rotamers **10** and **11** have been determined[6] using Bruker AM-300, AM-400 and WH-500 spectrometers. This study provides a more precise measurement of their respective chemical shifts. They are listed in Table 2.

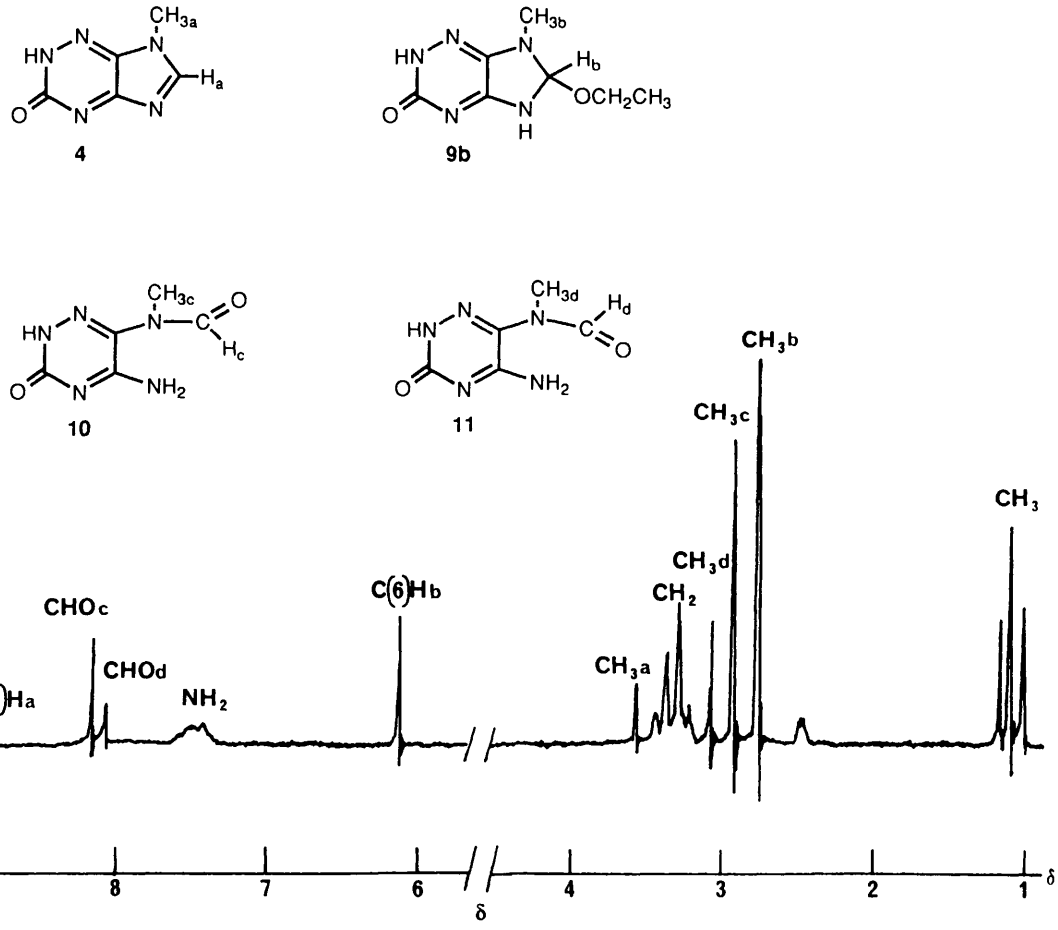
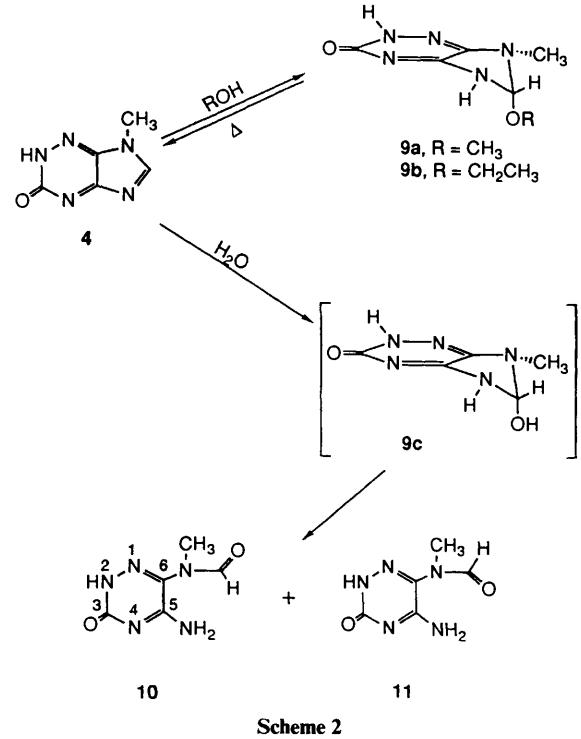


Fig. 1 ^{1}H NMR (90 MHz) spectrum of **4** after recrystallization from absolute ethanol. This spectrum represents the mixture of **4**, **9b**, **10** and **11**. Compounds **10** and **11** (**10**:**11** *ca.* 2.2:1) are formed as a result of the small amount of water found in absolute ethanol. The sample was dissolved in $(CD_3)_2SO$ containing 1% Me_4Si. The chemical shifts are in ppm with respect to Me_4Si.

were derived from **10** and **11** which were produced from **4** by traces of water in the absolute ethanol. It is worth mentioning that raising the drying temperature of the original mixture to 110 °C (toluene at reflux) facilitated the complete elimination of ethanol in less time (16 h). In addition, the regeneration of the N(5)–C(6) azomethine bond (**9b** ⟶ **4**, Scheme 2) could be accomplished by bringing the NMR sample of **9b**, in $(CD_3)_2SO$, rapidly to a boil.

In an effort to verify the formation and existence of the σ-adducts **9a–c**, pure **4** was prepared. This heterocycle could be obtained free of contaminants simply by distilling off the alcohol formed during ring closure of **3**, with either TEOF or TMOF, and collecting **4** by filtration. Methanol, rather than ethanol, was used in the subsequent step as it could be easily obtained free of water. When pure **4** was heated in freshly distilled, anhydrous methanol, **9a** (Scheme 2) was eventually formed, but the reaction never reached completion even under forcing conditions. NMR spectra (^{1}H and ^{13}C) of a sample that was heated in methanol at reflux for 20 h indicated that **4** and **9a** were present in equal amounts. Like the previous mixture containing **9b**, this solid, two-component mixture could be converted back into **4** by thermal elimination of alcohol under vacuum. In the presence of water, **4** hydrated across the N(5)–C(6) azomethine bond to form the σ-adduct **9c**, which in turn ring-opened to furnish two rotamers (**10** and **11**) of 5-amino-6-(*N*-methylformamido)-*as*-triazin-3(2*H*)-one. The intermediacy of **9c** and the rapid cleavage of this adduct to **10** and **11** was verified by adding one drop of D_2O to a solution of **4** in $(CD_3)_2SO$ and following the reaction by ^{1}H NMR spectroscopy. As shown in Fig. 2, **9c** is formed and it immediately ring-opens. The entire process was completed in *ca.* 15 min.



Scheme 2

Depending on the mode of cleavage of the imidazoline ring of **9c**, two structures are possible, *i.e.*, 5-amino-6-(*N*-methyl-

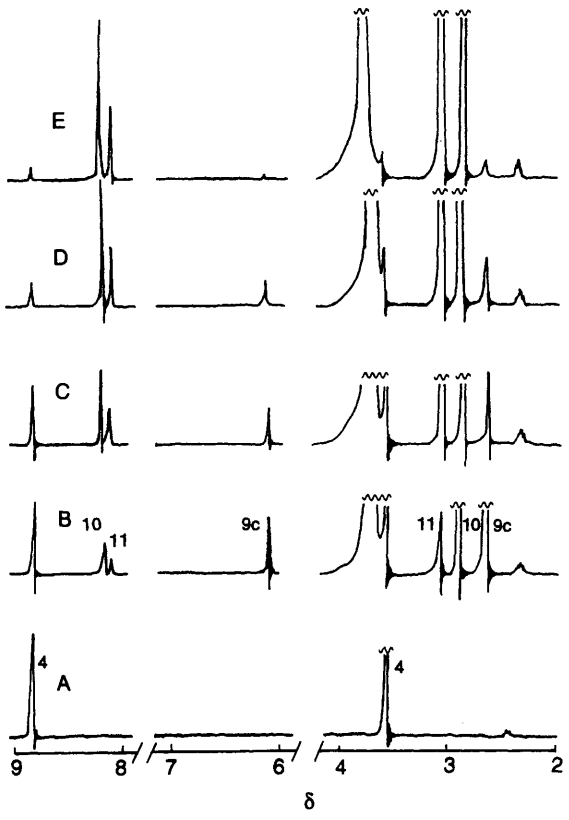
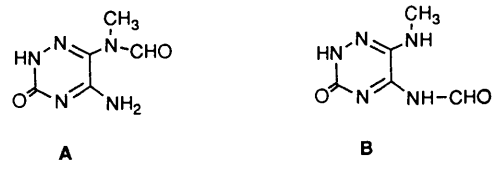


Fig. 2 A, ^{1}H NMR spectrum of pure 7-methylimidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (**4**) in $(CD_3)_2SO$. B, One drop of deuterium oxide (D_2O) added to the sample of **4** and the spectrum run immediately. The signals of **9c**, **10** and **11** are visible. C, The spectrum of **4** after 3 min exposure to D_2O. D, The spectrum of **4** after 9 min. The signals of **4** and **9c** decrease as they convert (**4** ⟶ **9c** ⟶ **10** + **11**) into **10** and **11**, whose signals become more intense. E, The spectrum obtained after 15 min indicating the ring-opening process is complete. This experiment was conducted at room temperature at 90 MHz.



formamido)-*as*-triazin-3(2*H*)-one (**A**) and 5-formamido-6-methylamino-*as*-triazin-3(2*H*)-one (**B**). Structure **B** was eliminated after examination of the ^{1}H and ^{13}C NMR spectra of the ring-opened material. In the ^{1}H NMR spectrum (Fig. 3) of this material, the signals for the methyl groups (at high field) are sharp singlets. If **B** were present, then one of these methyls should appear as a doublet since it would be coupled to the proton of the methylamino group. This characteristic spin pattern is present in all of the 6-methylamino-*as*-triazines described in this paper (Table 2). Likewise, the N(6)H resonance should appear as a quartet in the range δ 6–7 ppm. Neither of these spin patterns are present in the spectrum depicted in Fig. 3. Furthermore, in the carbon-13 spectrum of this material both methyl resonances are downfield from those methyl signals associated with the methylamino groups of **1a**, **3**, and **7** (Table 3). It is worth mentioning that the proton and carbon chemical shifts of the methyl groups of **10** and **11** are nearly identical with the *N*-methyl chemical shifts of *N*,*N*-dimethylformamide (DMF, see Tables 2 and 3). A thorough investigation[6] of 5-amino-6-(*N*-methylformamido)-*as*-triazin-3(2*H*)-one (**A**) showed that it existed as two restricted rotamers, *i.e.*, **10** and **11**. The predominant rotamer is **10** and the proton chemical shifts

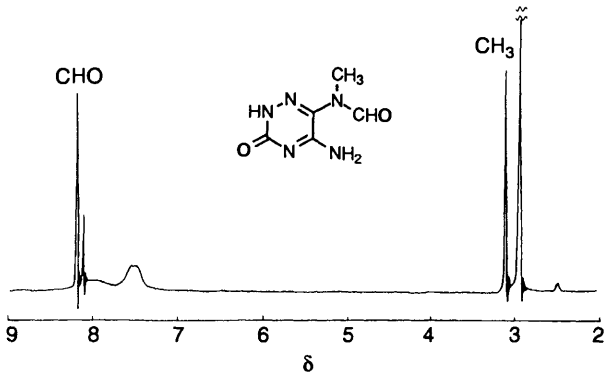
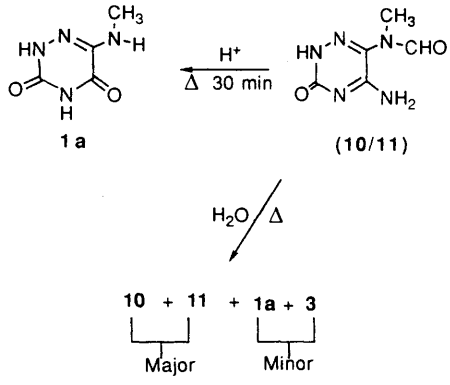


Fig. 3 Spectrum of the rotamers **10** and **11** in $(CD_3)_2SO$ at 298 K at 90 MHz

(observed at 90 MHz) of these rotamers coalesce around 60 °C.

Unlike **9a** and **9b**, heating the solid mixture of **10** and **11** under vacuum did not furnish **4**. In fact, this 6-azapurine was only obtained from **10** and **11** when the mixture was subjected to the original conditions of ring closure with TEOF or TMOF. When an aqueous solution of **10** and **11** (Scheme 3) was heated



Scheme 3

overnight and the solution taken to dryness *in vacuo*, two additional components were found in the residue. The structures of these minor components were identified as **1a** and **3** by ^{1}H NMR and UV spectroscopy. These *as*-triazines arise from decarbonylation and hydrolysis. The rotamers **10** and **11** are still the major constituents of this new mixture, however, their relative ratios have changed considerably. It appears that the rotamer **11** is preferentially hydrolysed in hot aqueous solution and is the primary source of the minor components. In hot, 0.01 mol dm^{-3} hydrochloric acid, hydrolysis of **10** and **11** is rapid (30 min) and **1a** is the sole product.*

Based on the combined spectral and chemical data, it can be concluded that **4** undergoes addition of methanol, ethanol and water across the N(5)–C(6) azomethine bond to give the respective σ-adducts **9a–c**. In the latter case, the σ-adduct **9c** experiences ring-opening and gives exclusively 5-amino-6-(*N*-methylformamido)-*as*-triazin-3(2*H*)-one, which exists as the two rotamers **10** and **11**.

* The amino and methylthio substituents on the C(5) position of the *as*-triazin-3-one ring are quite sensitive to nucleophilic displacement or hydrolysis. For example, recrystallization of **2** from water causes hydrolysis of the 5-methylthio function and provides minor amounts of **1a**. When **3** was dissolved in water and the solution was held at a gentle boil overnight, a portion (*ca.* 25%) was converted into **1a**. On the other hand, **5** is stable under the latter conditions, but attempted ring closure of **5** to **6** with formic acid furnished only **14** (N. C. Motola, M.S. Thesis, University of Rhode Island, Kingston, RI, 1979).

Table 3 Summary of carbon-13 chemical shifts[a]

Compd.	C(3)	C(5)	C(6)	NCH_3	CHO
as-Triazines					
1a	148.9_4	154.7_4	143.6_6	27.7_5	
1b	145.7_7	179.8_9	145.9_5	28.6_2	
2	151.8_3	167.2_9	142.7_0	28.5_2	
3	154.9_1	154.1_6	137.5_2	28.0_8	
5	154.4_2	153.4_9	136.5_0		
7	154.3_6	152.2_9	137.8_8	27.5_3	
10	154.8_9	157.4_2	132.6_7	30.9_2	162.6_0
11	154.8_9	156.8_0	131.8_9	34.6_0	164.3_0
12	154.8_0	155.7_4	129.2_6		162.4_8
		154.6_6	128.1_5		162.2_7
13	155.4_6	154.7_7	130.3_4	28.1_1	163.4_7
		156.2_1	129.4_5		163.0_4
14	149.3_1	154.8_1	144.0_2		

Compd.	C(3)	C(4a)	C(6)	C(7a)	CH_3 [position]
Imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one					
4	156.1_8	162.0_9	163.3_5	137.0_0	30.3_6 [N(7)]
6	155.0_1	153.9_8	155.3_2	144.6_0	
8	155.8_0	153.5_8	157.9_6	145.5_3	29.9_5 [N(5)]
9a	152.0_1[b]	153.8_4[b]	100.4_5	141.3_2	48.4_5 [OCH_3], 27.5_1 [N(7)]

[a] Carbon spectra were obtained on Varian CFT-20, Bruker AM-300 and AM-400 spectrometers. Compounds were dissolved in $(CD_3)_2SO$ and chemical shifts are expressed in parts per million with respect to Me_4Si. [b] These assignments can be reversed.

The syntheses of imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (**6**) and 5-methylimidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (**8**) were conducted in the same manner as that of 7-methylimidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (**4**). The diamino-*as*-triazine synthons **5** and **7** (Scheme 1) were ring-closed with TEOF, TMOF or diethoxymethyl acetate (DEMA) to provide **6** and **8**, respectively, in good yield (Table 1). Since **4** underwent covalent addition with alcohols and water, we speculated that **6** and **8** should also form covalent σ-adducts. Unlike **4**, these heterocycles could be recrystallized from either methanol or a methanol–ethanol mixture without any detection of intermediates such as **9a** and **9b**; however, they did hydrate when recrystallized from water.

The pattern of hydration of **6** and **8** was the same as for **4**. Water added across the N(7)–C(6) azomethine bond and the σ-adducts opened to their respective C(6)-formamides **12** and **13**. Since these heterocycles hydrate in the same manner, for the sake of brevity, the discussion that follows will focus only on the hydration of **8**.

The hydration of **8** (and **6**) was not as easy as that described for **4**. A sample of **8** in $(CD_3)_2SO$ was quite stable to D_2O (one drop) at room temperature and over an extended period of time, but eventually it provided a ^1H NMR spectrum as shown in Fig. 4. At no time could proton chemical shifts similar to those assigned to the C(6)H and N(7)CH_3 of **9c** be detected. The spectrum illustrated in Fig. 4 was also obtained on dissolution of **8** in hot (*ca.* 90 °C), glass-distilled water; the solution was maintained at this temperature for 5 min, and then allowed gradually to cool to room temperature. The crystalline material which precipitated was dissolved in $(CD_3)_2SO$ and it displayed the identical proton spectrum shown in Fig. 4. A thorough ^1H and ^{13}C NMR investigation of this material established the structure as 6-formamido-5-methylamino-*as*-triazin-3(2*H*)-one (**13**). In the proton spectrum (Fig. 4), the signals centred at δ 11.63, 9.77 and 7.87 exchanged with deuterium oxide and the doublet at δ 2.80 collapsed to a singlet. The carbon chemical shift of the methyl group resonated in the same region as the methylamino carbon of **1a**, **3** and **7** (Table 3). These spectral features are consistent with structure **13**.

Like 5-amino-6-(*N*-methylformamido)-*as*-triazin-3(2*H*)-one

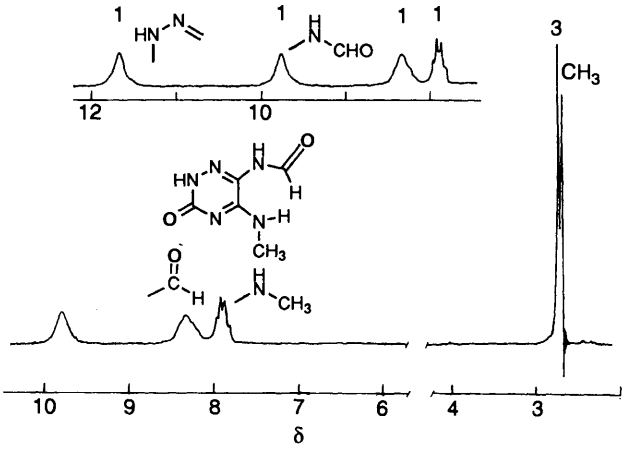
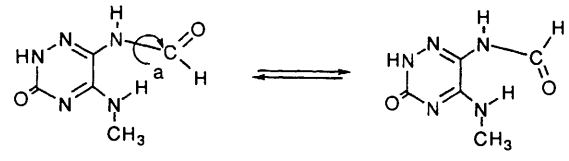


Fig. 4 The spectrum [90 MHz; $(CD_3)_2SO$] resulting from the hydration of **8**. The integration from left to right is 1:1:1:1:3. The resonances at δ 11.63, 9.77 and 7.87 exchange with deuterium oxide. After exchange the doublet centred at δ 2.80 collapses to a singlet. Besides the singlet at δ 2.80, the broad singlet at δ 8.30 remains in the exchanged spectrum.



13A **13B**

$\Delta G^{\ddagger}_{312}(a) \cong 64$ kJ mol^{-1}

(**10** and **11**), 6-formamido-5-methylamino-*as*-triazin-3(2*H*)-one (**13**) exists as an intimate mixture of rotamers (**13A** and **13B**). Using a Bruker AM-300 MHz spectrometer, the coalescence temperature (T_c) for the chemical shifts of the formyl proton was determined to be 312 ± 1 K and the populations of **13A** and **13B** were found to be nearly equivalent.* Another interesting

* The ratio of **13A**:**13B** was determined to be 56:44. The same ratio was established for **12A**:**12B**.

aspect of **13** (**A** + **B**) is that it reverts back to **8**. Bringing a ^1H NMR sample of **13** in $(CD_3)_2SO$ (Fig. 5) to a boil promoted ring-closure. Monitoring of the reaction by ^1H NMR indicated that **13** completely reverted to **8** in less than 30 min. Based on these experiments and the structure of **13**, we conluded that **8** (and **6**) hydrated in a similar fashion (Scheme 4) as **4** to furnish the adduct **9e** (and **9d**). Once formed, this adduct immediately ring-opens to provide **13** (and **12**). It appears that **9e** (and **9d**) is more labile than **9c** and thus eludes detection by ^1H NMR spectroscopy.

5-Methylimidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (**8**) and its hydrolysis product **13**, experience further breakdown on continued heating in water. When **8** was dissolved in hot water and held at a gentle boil for 1 h, ring-opening to **13** occurred accompanied by partial hydrolysis of the formamido group. A spectral examination (^1H and ^{13}C NMR) of the dried residue indicated that both **13** and **7** were present, with **13** predominating. Both of these *as*-triazines could be identified by their distinctive proton and carbon chemical shifts. Continued heating of an aqueous solution of **8** for 24 h led to an equimixture of **7** and 6-amino-*as*-triazin-3,5-dione[7] (**14**). Their formation results, as depicted in Scheme 4, from hydrolysis of **13**, to give **7**, followed by hydrolysis of the C(5)-substituent. Imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (**6**) followed the same pattern of hydrolysis.

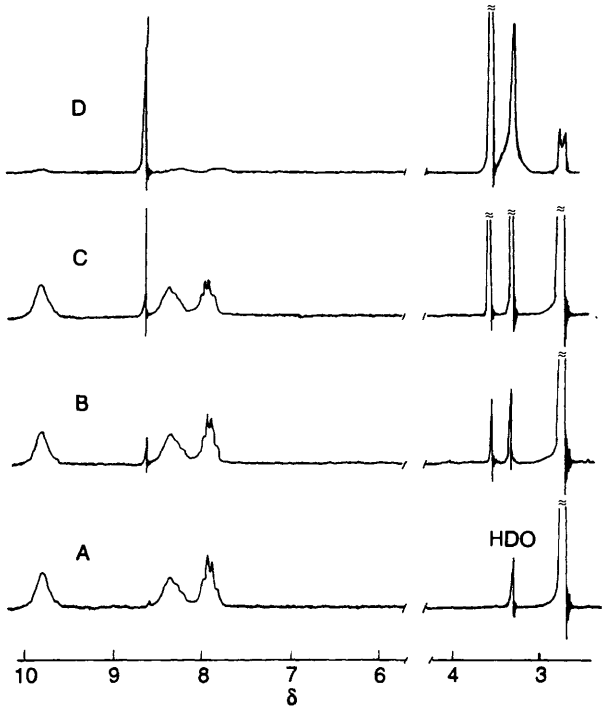


Fig. 5 Spectra which result after heating **13A** and **13B** in boiling $(CD_3)_2SO$. A, The mixture of the proposed intermediates before heating. B, After heating for 5 min. C, After heating for 10 min. D, After heating for 20 min. Only **8** is visible after 30 min.

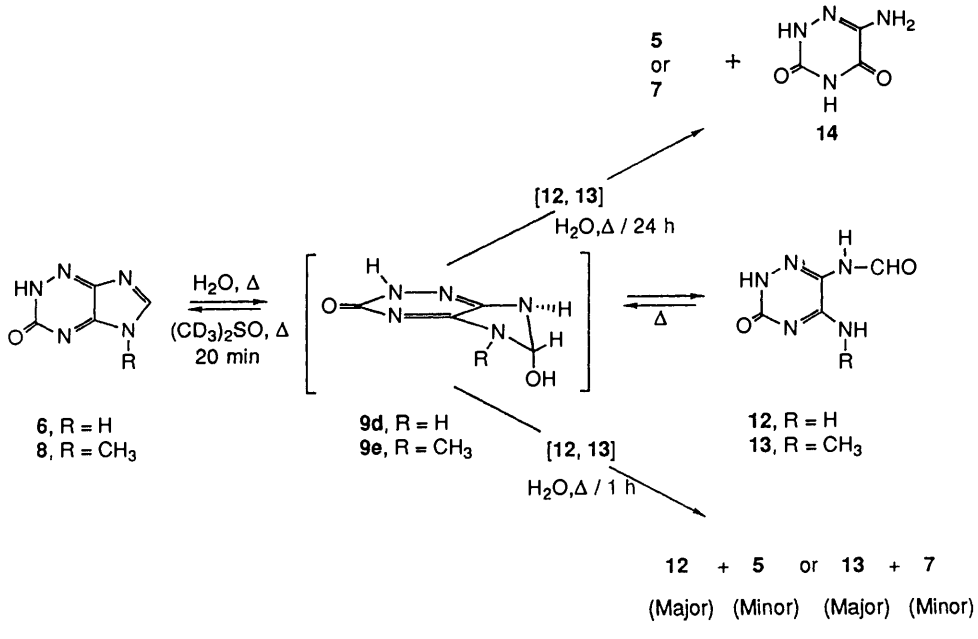
In conclusion, the ease and convenience of synthesizing imidazo[4,5-*e*]-*as*-triazines (6-azapurines) from 5,6-diamino-*as*-triazines is again demonstrated.[1,3] The targeted imidazo-[4,5-*e*]-*as*-triazin-3-(2*H*)-ones prepared in this study were shown to be quite sensitive to covalent addition by water and certain alcohols. The pattern of addition was the same for the three 6-azapurines examined and occurred on the azomethine bond[8,9] located in the imidazole portion of this ring system. We are continuing our efforts to synthesize other imidazo[4,5-*e*]-*as*-triazines and to investigate their unique chemical properties.

Experimental

Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. The ultraviolet absorption spectra were obtained on a Beckman DB-GB grating spectrometer. All solvent proportions are by volume unless otherwise stated. Evaporations were performed with a Buchi Rotovapor at 50 °C. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

Synthesis

General Cyclization Procedure to the Imidazo[4,5-e]-*as-triazine Ring System.—Method A.* To a well-stirred suspension of either **3**, **5** or **7** in 25 cm^3 of the specified trialkyl orthoester (Table 1) was added concentrated hydrochloric acid (HCl, 2 cm^3). This mixture was heated at reflux (oil bath, 130 °C) for 18 h. The reaction mixture was allowed to cool to room



Scheme 4

temperature and the solid was collected by filtration, washed with cold, absolute alcohol (as determined by the alkyl substituent on the orthoester) and air-dried. If desired, this material can be recrystallized from the solvent listed in Table 1.

In the case of **4**, the alcohol generated during ring-closure should be distilled off as it is formed. Also this heterocycle cannot be washed or recrystallized as it is extremely susceptible to covalent addition of alcohol and water.

Method B. The amino-*as*-triazines **5** and **7** were heated with diethoxymethyl acetate (DEMA, 10 cm^3) at 50 °C for 16 h. After this period, the reaction solution was allowed to cool, diluted with absolute ethanol (10 cm^3) and refrigerated (*ca.* 5 °C) for 18 h. The crystalline precipitate that formed was collected by filtration, washed with cold ethanol (5 cm^3), and air-dried. A second crop could be obtained by evaporating the filtrate under diminished pressure and collecting the crystalline residue with a minimal amount of cold absolute ethanol.

6-*Methylamino*-3-*oxo*-3,4-*dihydro*-as-*triazine*-5(2H)-*thione* (**1b**).—6-Methylamino-*as*-triazin-3,5(2*H*)-dione[4] (**1a**, 8.52 g, 60 mmol), phosphorus pentasulfide (6.66 g, 30 mmol, Alfa), and pyridine (150 cm^3, containing 0.6% water)* were heated at reflux for 3 h with vigorous stirring. The reaction mixture was allowed to cool and stand at room temperature for 16 h. The clear, reddish-brown solution was decanted from the reaction flask and the pyridine removed under diminished pressure (water bath, 60 °C). The residue which remained was covered with 200 cm^3 of distilled water, boiled for 10 min, and allowed to stand at 4 °C for 18 h. The precipitate was collected by filtration, resuspended in 140 cm^3 of distilled water, and carefully basified to pH 10 with concentrated ammonium hydroxide (NH_4OH). The mixture was treated with Norit (optional), filtered through a Celite pad, and the pad washed with (3 × 20 cm^3) basic water (pH 10). The combined wash and filtrate was acidified by dropwise addition of 6 mol dm^{-3} HCl to pH 4. During this process, **1b** precipitated as a yellow-orange solid. The solid was collected by filtration, washed with cold, distilled water (3 × 20 cm^3), and air-dried to provide **1b** (7.25 g, 76%): m.p. 275–278 °C (decomp.) (Found: C, 30.3; H, 4.1; N, 35.1; S, 19.88. $C_4H_6N_4SO$ requires C, 30.37; H, 3.82; N, 35.42; S, 20.27%); λ_{max}/nm (pH 1) 372 (ε/dm^3 mol^{-1} cm^{-1} 4590), 303 (10 210) and 244 (10 130); λ_{max}(MeOH)/nm 375 (ε/dm^3 mol^{-1} cm^{-1} 4590), 303 (9970) and 245 (9650); λ_{max}/nm (pH 11) 318 (ε/dm^3 mol^{-1} cm^{-1} 11 080), 248sh (8860) and 228 (11 870).

6-*Methylamino*-5-*methylthio*-as-*triazin*-3(2H)-*one* (**2**).—To a stirred suspension of **1b** (3.16 g, 20 mmol) in absolute ethanol (300 cm^3) was added sodium hydroxide (NaOH) solution (1 mol dm^{-3}; 20 cm^3). Upon addition of the NaOH solution, **1b** dissolved and within minutes precipitated as the sodium salt. This mixture was stirred for 30 min at room temperature and then methyl iodide (5.0 cm^3) was added to it in one portion. Stirring was continued at room temperature for 6 h, after which the excess solvent was removed under diminished pressure to furnish **2** as a light-yellow, crystalline solid (85–90% average yield). This product is sufficiently pure to be used directly in the preparation of **3**. Recrystallization of this solid from distilled water afforded 2.27 g of **2**† (66%): m.p. 214–216 °C (Found: C, 34.75; H, 4.7; N, 32.4; S, 18.6. $C_5H_8N_4SO$ requires C, 34.87; H, 4.68; N, 32.53; S, 18.62%); λ_{max}/nm (pH 1) 353 (ε/dm^3 mol^{-1} cm^{-1} 2170), 284 (7920) and 239.5 (15 770); λ_{max}(MeOH)/nm 360 (ε/dm^3 mol^{-1} cm^{-1} 2410), 280 (8710) and 241 (17 910); λ_{max}/nm (pH 11) 302 (ε/dm^3 mol^{-1} cm^{-1} 3720) and 229 (13 780).

5-*Amino*-6-*methylamino*-as-*triazin*-3(2H)-*one* (**3**).—*Method A.* 6-Methylamino-5-methylthio-*as*-triazin-3(2*H*)-one (**2**, 1.72 g, 10 mmol) was dissolved in methanolic ammonia (150 cm^3, saturated at 0 °C) and kept at room temperature for 24 h in a pressure bottle. During this period, **3** gradually crystallized out of solution. The excess gases were vented off and the crystalline solid was recrystallized from water to afford **3** (1.30 g, 95%) as light-yellow needles: m.p. > 300 °C (Found: C, 33.85; H, 5.0; N, 49.65. $C_4H_7N_5O$ requires C, 34.04; H, 5.00; N, 49.62%); λ_{max}/nm (pH 1) 328 (ε/dm^3 mol^{-1} cm^{-1} 3670), 242sh (12 700) and 223 (18 070); λ_{max}(MeOH)/nm 310 (ε/dm^3 mol^{-1} cm^{-1} 3330), 249.5sh (9740) and 227 (21 170); λ_{max}/nm (pH 11) 302 ε/dm^3 mol^{-1} cm^{-1} 3330), 240sh (9030) and 230 (17 220).

Method B. 6-Methylamino-5-methylthio-*as*-triazin-3(2*H*)-one (**2**, 0.172 g, 1 mmol), formamide (4 cm^3) and 20 cm^3 of absolute methanol were refluxed for 2 days. The solvent was evaporated off under diminished pressure and the residue triturated with anhydrous ether (15 cm^3). The resulting solid was collected by filtration, washed with ether (3 × 10 cm^3), and air-dried to provide **3** (90 mg, 64%). NMR (^1H and ^{13}C) spectra indicated that this product was identical with **3** prepared from method A.

Covalent Addition of Water and Alcohols

Addition of Methanol to 7-*Methylimidazo*[4,5-e]-as-*triazin*-3(2H)-*one* (**4**): Formation of **9a**.—7-Methylimidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (**4**; 151 mg, 1 mmol) was dissolved in 10 cm^3 of anhydrous methanol and refluxed 20 h. The solution was allowed to cool and then it was refrigerated (4 °C) for 16 h. The white needles which formed were collected by filtration, washed with cold, anhydrous methanol (2 cm^3) and dried in an Abderhalen at 65 °C for 4 h. This crystalline material (134 mg) was a mixture of starting material and **9a** (TLC; chloroform–methanol 4:1) and the identification was confirmed by a rigorous NMR analysis.

Addition of Absolute Ethanol to 7-*Methylimidazo*[4,5-e]-as-*triazin*-3(2H)-*one* (**4**): *Formation of* **9b**, **10** *and* **11**.—This experiment was identical with that for the addition of methanol, with the exception that absolute ethanol (taken from a fresh, unopened bottle) was used. The crystalline material (116 mg) obtained from this experiment was a mixture of **9b**, **10** and **11**. The structures of these three heterocycles were identified *via* exhaustive NMR analyses.

Conversion of **10** *and* **11** *into* 7-*Methylimidazo*[4,5-e]-as-*triazin*-3(2H)-*one* (**4**).—To a stirred suspension of **10** and **11** (338 mg, 2 mmol) in TEOF (25 cm^3) was added 1.0 cm^3 of concentrated hydrochloric acid. The reaction was heated at reflux overnight and the ethanol formed during cyclization was continuously distilled off. After the reaction had cooled to room temperature, the suspended solid was collected by filtration. The material was dried in an Abderhalen at 78 °C for 4 h. The procedure afforded 258 mg of **4** (86%) which was identical (^1H and ^{13}C NMR) with the authentic heterocycle prepared from **3**.

Conversion of Imidazo[4,5-e]-as-*triazin*-3(2H)-*one* (**6**) *into* (**12**).—Imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (**6**, 274 mg, 2 mmol) was dissolved in hot, distilled water (*ca.* 90 °C), maintained at this temperature for 5 min, and then the solution was allowed to cool and come to room temperature. The crystalline material was collected by filtration, air-dried, and then dried in an Abderhalen for 12 h at 110 °C. This procedure

* If the water content of the pyridine used for this reaction is 0.1%, **1b** and 6-methylamino-*as*-triazine-3,5-dithione are obtained in near equal amounts; see ref. 7.

† See footnote * on p. 2566.

furnished **12** in near-quantitative yield (Found: C, 30.8; H, 3.25; N, 45.15. $C_4H_5N_5O_2$ requires C, 30.97; H, 3.25; N, 45.15%); λ_{max}/nm (pH 1) 285 (ε/dm^3 mol^{-1} cm^{-1} 4590) and 224sh (11 470); λ_{max}(MeOH)/nm 266sh (ε/dm^3 mol^{-1} cm^{-1} 6050) and 227 (10 700); λ_{max}/nm (pH 11) 301 (ε/dm^3 mol^{-1} cm^{-1} 5120), and 238 (15 980).

Conversion of 5-*Methylimidazo*[4,5-e]-as-*triazin*-3(2H)-*one* (**8**) *into* (**13**).—This procedure was identical with that described for the covalent addition of water to **6**. As in the case of **6** and **12**, a near-quantitative yield of **13** was obtained from **8** (Found: C, 35.7; H, 4.2; N, 41.6. $C_5H_7N_5O_2$ requires C, 35.51; H, 4.17; N, 41.40%); λ_{max}/nm (pH 1) 284 (ε/dm^3 mol^{-1} cm^{-1} 6290) and 227sh (11 840); λ_{max}(MeOH)/nm 265sh (ε/dm^3 mol^{-1} cm^{-1} 7370); λ_{max}/nm (pH 11) 300 (ε/dm^3 mol^{-1} cm^{-1} 6630) and 241 (16 440).

Aqueous Hydrolysis of 5-*Methylimidazo*[4,5-e]-as-*triazin*-3(2H)-*one* (**8**) *to* **7** *and* **14**.—5-Methylimidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (**8**; 302 mg, 2 mmol) was dissolved in distilled water (15 cm^3) and the solution held at a gentle boil for 24 h. After this period, the water was removed *in vacuo* (water bath, 60 °C) and the resulting crystalline material was dried in an Abderhalen (110 °C) for 20 h. The ^{1}H NMR and ^{13}C NMR spectra indicated that **7** and **14** were present as a 1:1 mixture. Their structures and ratio were verified by subjecting a 1:1 mixture of authentic **7** and **14** to a rigorous NMR analysis.

A similar experiment conducted on **6** afforded **5** and **14**. Like **7**, a 1:1 mixture of **5** and **14**, was obtained as was confirmed by an NMR (^{1}H and ^{13}C) analysis.

NMR

The proximity of certain proton or carbon chemical shift values made the signal assignment of certain compounds somewhat difficult since it was not possible to proceed by analogy with similar heterocycles.[10] Regarding the proton spectra, the assignment of NH resonances was feasible using the linewidth variation as a function of temperature. Assignment of carbon chemical shifts was determined by coupled and/or partially decoupled spectra. Temperature studies allowed the lines in exchange to be distinguished. The spectrometers used for this study are listed in Tables 2 and 3.

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