On the Amination of Pyrimido[5,4-*e*]1,2,4-triazines in Liquid Ammonia

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When dissolved in liquid ammonia 5-chloro-1,2-dihydropyrimido[5,4-*e*]-1,2,4-triazine (**1**) and 5-methoxypyrimido[5,4*e*]-1,2,4-triazine (**4**) quickly convert into 5-aminopyrimido[5,4-*e*]-1,2,4-triazine (**2**). When **2** is kept in liquid ammonia containing an excess of potassium permanganate, 3,5-diaminopyrimido[5,4-*e*]-1,2,4-triazine (**5**) is formed.

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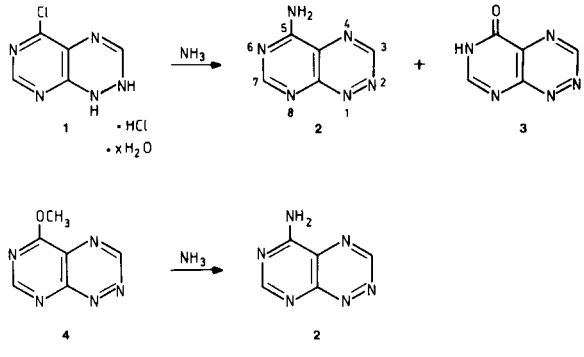
The study of the reactivity of mono- and bicyclic azaheterocycles towards liquid ammonia has ongoing interest in our laboratory [1]. Our knowledge of the chemistry of quinolines [2], purines [3] and pteridines [4,5] in liquid ammonia induced us to study the amination of the pyrimido[5,4-*e*]-1,2,4-triazines (7-azapteridines). These compounds posses a higher C=N/C=C-ratio than pteridines and consequently, they are more susceptible to nucleophilic attack. Moreover, since in our laboratory the reactions of pyrimidines [6] and triazines [7-10] in liquid ammonia are well studied, it offered us the possibility to examine the effect of their fusion on the reactivity in liquid ammonia. Two research groups [11,12] have studied in detail the synthesis of the pyrimido[5,4-*e*]-1,2,4-triazines and their behaviour in nucleophilic substitutions: however, the reactivity towards liquid ammonia has not been investigated. The parent compound has a limited stability under normal working conditions; as the hydrochloride of 5-chloro-1,2-dihydropyrimido[5,4-*e*]-1,2,4-triazine (**1**) is synthetically most easily accessible [13] we commenced our work with a study of the solvolytic behaviour of **1** with liquid ammonia. Aminolysis of **1** was found to take place easily and was already completed after having kept the reaction mixture for 10 minutes at −70°, 5-aminopyrimido[5,4-*e*]-1,2,4-triazine (**2**) being obtained [14]. Pyrimido[5,4-*e*]-1,2,4-triazin-(6*H*)-5-one (**3**) was also present in the product mixture (combined isolated yields 80%). The structures of compounds **2** and **3** were determined on the basis of ^{1}H- and ^{13}C-nmr data (Tables 1 and 2).

Scheme 1



The formation of **3** was explained by the presence of water in the very hygroscopic hydrochloride **1** [15]. As the amounts of water, adsorbed to **1**, are variable, it leads to variable ratios of compounds **2** and **3** (up to 1:2) as is observed in several solvolysis experiments.

Under similar conditions, aminolysis of 5-methoxypyrimido[5,4-*e*]-1,2,4-triazine (**4**) also yields **2**; compound **3** was not found, as proved by tlc analysis and ^{1}H-nmr spectra of the reaction mixture. Compound **4** is not hygroscopic, explaining the absence of **3**.

The solvolysis of compound **4** in liquid ammonia was studied by ^{1}H-nmr spectroscopy. Dry ammonia was condensed into a cooled (−70°) nmr tube containing solid **4**, and after shaking the tube in order to dissolve some of the solid, the spectrum of the solution was measured at −45°. This spectrum exhibts only two sharp resonances at 10.08 and 8.57 ppm (relative to δ_{NH_3} = 0.95). These chemical shifts are the same as the H-3 and H-7 resonances of 5-aminopyrimidotriazine **2** in liquid ammonia. Since the ^{1}H-nmr spectra of DMSO-d_6 solutions of compounds **2** and **4** are clearly distinct (Table 1), these measurements unequivocally lead to the conclusion that during solvolysis in liquid ammonia the methoxy group in **4** is almost instantaneously replaced by the amino group. In addition, the presence of merely the two sharp low field resonances indicates that in the liquid ammonia the amino compound **2** is *not* in equilibrium with a detectable amount of a covalent amino σ-adduct. In case an σ-adduct should have been formed, one of the ring hydrogen resonances (H-3 or H-7) must have undergone an appreciable upfield shift with respect to their original positions. This has actually not been observed.

Reactions in Liquid Ammonia/Potassium Permanganate.

Recently we have found that pyrimidines and triazines are very susceptible to amination, when treated with liquid ammonia/potassium permanganate [16,17,18]. Based on that experience, we examined the replacement of the hydrogens in the pyrimidotriazine in **1** and **4**, when treated with liquid ammonia/potassium permanganate.

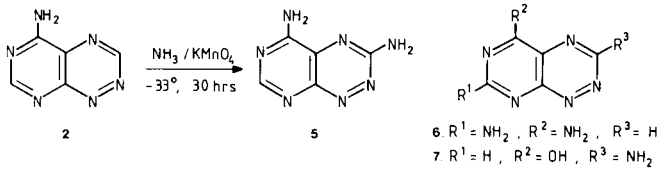
Table 1

^{1}H-NMR (90 MHz) Data, δ/ppm, of the Pyrimido[5,4-*e*]-1,2,4-triazines **1**-**7** in DMSO-d_6 (δ_{TMS} = 0)

Compound	δ (H-3)	δ (H-7)	δ (H substituent)		
1	6.33	7.38	6.2 (very broad)		
2	10.13	8.70	8.9 (broad)		
	10.08	8.57	–		liq NH_3 at −45° with δ_{NH_3} = 0.95
3	10.08	8.48	–		
4	10.31	9.17	4.28		
5	–	8.30	7.7	8.3	
6	9.48		7.0	8.1	
7		8.09	7.9	4.2	

Analysis (tlc, silica gel, 10% ethanol in ethyl acetate) of the product mixture obtained after treatment of **1** showed that besides products **2** and **3** (Rf = 0.34) a third product was present (Rf = 0.24). This bright yellow product could be isolated and was unequivocally identified as 3,5-diaminopyrimido[5,4-*e*]-1,2,4-triazine (**5**) (total yield about 80%). The structure assignments of **5** was based on comparison of the ^{1}H-nmr data (Table 1) with those of reference compounds as 5,7-diaminopyrimido[5,4-*e*]-1,2,4-triazine (**6**) and 3-amino-5-hydroxypyrimido[5,4-*e*]-1,2,4-triazine (**7**) and supported by ^{13}C-nmr data, showing no ^{13}C-H coupling in the coupled spectrum for C-3 and C-5 (see Table 2).

Scheme 2



Reaction of 5-chloro-3-methyl-1,2-dihydropyrimido-[5,4-*e*]-1,2,4-triazine (**8**) with liquid ammonia/potassium permanganate yielded only the 5-amino compound **9** and 5-hydroxy compound **10**; no trace of a 5,7-diamino compound was detected. It is evident that position 3 in **2** is more susceptible to nucleophilic attack than position 7 [19]. Even by blocking of position 3 with a methyl group, position 7 is not attacked and 5,7-diamino formation does not occur. Compound **4** reacts similarly as **1** on treatment with liquid ammonia/potassium permanganate, **2** as well as **5** being produced. Since we noticed that the yield of **5** from **1** increased when the reaction time increased, we reacted 5-aminopyrimidotriazine **2** with refluxing liquid ammonia (−35°), containing potassium permanganate, for 30 hours and found that compound **5** was obtained in about a 65% yield.

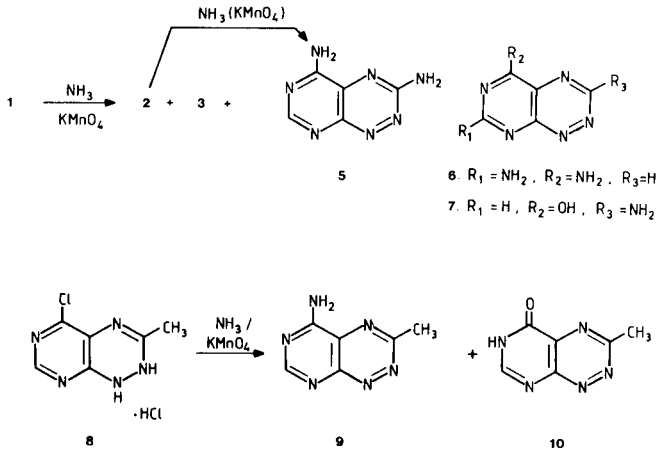
Table 2

^{13}C-NMR Data, δ/ppm (J/Hz) [a] of the Pyrimido[5,4-*e*]-1,2,4-triazines **1**, **8**, **2**, **4** and **5** in DMSO-d_6 (δ DMSO = 39.7)

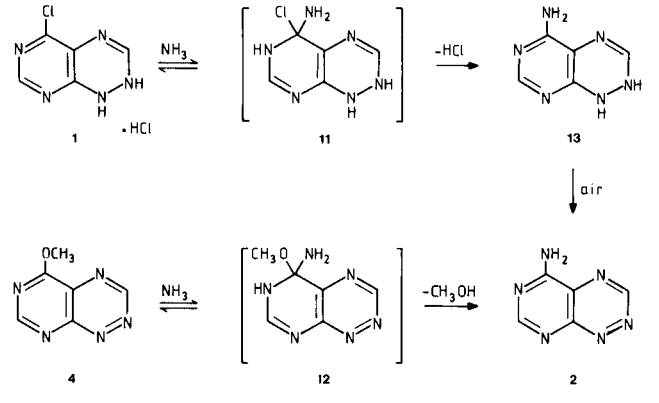
Compound	C-3	C-5	C-7
1 [b]	140.2 (205)	131.5 (15)	152.3 (209)
8	146.5	132.9 (13)	153.0 (205)
2	154.0 (211)	164.2 (9)	160.2 (200)
4	158.6 (209)	169.0	155.7 (193)
5	161.5	162.9	153.8 (200)

[a] The figures in parentheses denote the values of the coupling constants observed in the coupled spectrum. [b] The parent 4-chloro compound, obtained after treatment of **1** with a slight excess of base show the C-3 at 139.3 ppm, the C-5 at 133.3 ppm and the C-7 at 153.4 ppm.

Scheme 3



Scheme 4



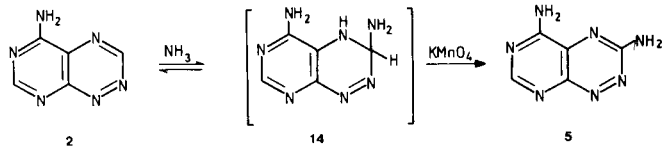
Discussion.

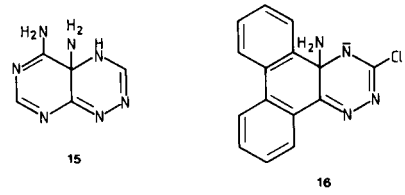
Reported studies on the reactivity of pyrimido[5,4-*e*]-1,2,4-triazines have shown that in these compounds C-5 is the most susceptible position to nucleophilic attack [11,12]. This result runs parallel to findings from our studies on the amination of other fused pyrimidines.

Although we could not obtain nmr spectroscopic evidence for their existence, the transient σ-adducts **11** and **12** are believed to be intermediates in the formation of **2**. The ^{13}C-nmr spectroscopy of a solution of compound **1** in liquid ammonia only supports the intermediacy of the 1,2-dihydro compound **13**. This latter compound belongs to a class of compounds known to be readily oxidized [14]. Oxidative introduction of the second amino substituent in the 5-aminopyrimidotriazine **2** has no precedent in literature.

No nmr spectroscopic indication has been obtained for the presence of a detectable amount of the precursor of **5**, *i.e.* the 3,5-diaminodihydropyrimidotriazine **14**. Intermediate **14** is present in the far-to-the-left equilibrium with **2**; oxidation of **14** into **5** by permanganatee causes a shift of the equilibrium **2** ⇄ **14** to the right. It is very interesting that the introduction of an amino group at the C-4 position, located between two nitrogen atoms in the 1,2,4-triazine ring *i.e.* C-3, has scarcely been observed. All experimental work [7-10] and theoretical considerations indicate that position 5 and not position 3 of the non-fused triazine ring is most susceptible for Chichibabin amination. In case position 5 in the non-fused triazine ring is blocked by a substituent, *i.e.* the phenyl group, the amination at C-3 only takes place to a very small extent [10]. Therefore the introduction of the amino group at C-3 in a pyrimido[5,4-*e*]-1,2,4-triazine ring by a Chichibabin type amination is unprecedented and provides the first example of a C-3 substitution into the 1,2,4-triazine ring. It can be suggested that a small percentage of **2** is also in equilibrium with the bridgehead σ-adduct **15**, although this adduct cannot lead to an amino product on oxidation. The possibility for the occurrence of such an adduct is based on the fact that a similar adduct **16** has firmly been established [21] (based on ^{15}N-labelling studies) in the potassium amide induced amino-dechlorination in 3-chlorophenanthro[9,10-*e*]-1,2,4-triazine.

Scheme 5





EXPERIMENTAL

The ^{1}H-nmr spectra were obtained using a Varian EM 390 with TMS as the internal standard. The ^{13}C-nmr spectra were measured on a Bruker CXP-300 spectrometer operating at 75.460 MHz. The spectra were run with a sweep width 15.000 Hz, using quad detection mode with 8 K data (Hz/pt 3.7), pulse width 12 μs and pulse delay 2 s. Some spectra were also measured with a sweep width of 4.000 Hz, using 16 K data (Hz/pt 0.49), pulse 20 μs and pulse delay 2 s.

Preparation of Starting Materials.

The pyrimido[5,4-*e*]-1,2,4-triazines **1** [13], **2** [14] and **4** [22], **6** [23] and **7** [24] were synthesized according to procedures, described in the literature.

Amination Experiments.

The procedures of the solvolysis experiments of the various pyrimidotriazines are almost identical whether or not potassium permanganate is present. The difference lies in a reduction of the volume of methanol used to extract the reaction product(s) after evaporation of the ammonia. In a typical example, the 5-methoxypyrimidotriazine **4** (2.5 mmoles) was added all at once to a cooled (−70°) purple solution of potassium permanganate (10 mmoles, 1.58 g) in dry liquid ammonia (100 ml) being distilled over sodium . After stirring at −70° for half to two hours the ammonia was evaporated overnight. The residue (free of ammonia) was extracted 2-3 times with 200-300 ml of boiling methanol. The collected brownish solution was partially concentrated (100-200 ml) and filtered over silica gel in order to remove residual manganese dioxide. The silica gel was washed with methanol until the washing was almost colourless. The yellow solution was evaporated and the yellow product mixture analysed.

Chromatrography over silica gel (Merck, Kieselgel 60) using 5% ethanol in dichloromethane as eluent gave first the yellow 5-aminopyrimidotriazine **2** (in case of solvolysis of **1** mixed with 5-hydroxypyrimidotriazine **3**). Its mass spectrum shows characteristic peaks [24] at m/z 149 (100%, M$^+$) and 121 (160%, M$^+$ −28); for nmr data see Tables 1 and 2.

The product obtained is identical to that obtained after the reaction of **1** with sodium azide in refluxing methanol [14].

Using 10% ethanol in dichloromethane the 3,5-diaminopyrimidotriazine **5** was eluated and isolated as yellow crystals which could be recrystallized from water (mp ∓ 340°, lit [25] ∓ 340°). Its mass spectrum shows m/z 163 (100%, M$^+$), 135 (100%, M$^+$ −28) and 108 (30%, 135-27). For nmr-data see Tables 1 and 2.

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