Ring Opening in the Amination of 3-X-1,2,4-Triazines [1,2]. A ^{15}N Study

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Evidence, based on ^{15}N-labelling studies, has been obtained that the amino-dechlorination of 3-chloro-1,2,4-benzotriazine by potassium amide in liquid ammonia occurs according to an $S_N(AE)^{ipso}$ process, while the amino-dechlorination of 3-chlorophenanthro[9,10-*e*]-1,2,4-triazine reacts for more than 90% according to a process involving a ring opening reaction [$S_N(ANRORC)^{ipso}$ substitution].

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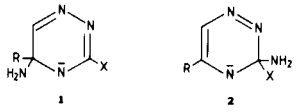
Detailed studies of the mechanism of the amination of 5-R-3-X-1,2,4-triazines with potassium amide in liquid ammonia have shown [1,3] that the formation of the corresponding 3-amino-1,2,4-triazines proceeds according to two competitive routes: *i* an $S_N(ANRORC)$ pathway [4], involving as initial step the addition of the amide ion at C-5, yielding 5-amino-3-X-dihydro-1,2,4-triazinide (**1**), *ii* an $S_N(AE)^{ipso}$ substitution at C-3, involving intermediate **2**. The character of the leaving group X determines the contribution of each of the competitive pathways [3]. In case

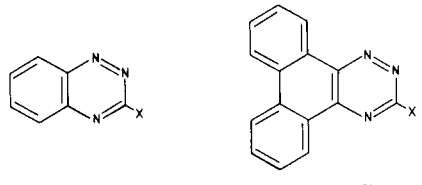
Scheme 1



1 **2**

X = Cl, Br, I, SCH_3, the $S_N(ANRORC)$ mechanism is the main pathway, while in case X = F, $^+N(CH_3)_3$, the $S_N(AE)$ substitution is strongly favored. The $S_N(ANRORC)$ mechanism also occurs as main reaction pathway, when a phenyl group is present at C-5; evidently this bulky group does not prevent addition of the amide ion to that position. These results induced us to study the occurrence of the $S_N(ANRORC)$ process in the amination of two annellated 1,2,4-triazines *i.e.* 3-chloro-1,2,4-benzotriazine (**3a**) and 3-chlorophenanthro[9,10-*e*]-1,2,4-triazine (**4a**).

Scheme 2

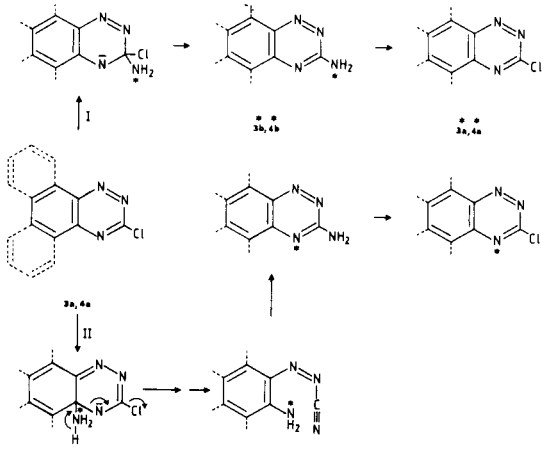


3a: X = Cl
3b: X = NH_2

4a: X = Cl
4b: X = NH_2

Treatment of the compounds **3a, 4a** with four equivalents of potassium amide in liquid ammonia (−33°, 30 minutes) gave the corresponding 3-amino-1,2,4-triazines (**3b, 4b**) in yields of 35 and 85% respectively. In order to investigate whether in these amination reactions an S_N(ANRORC) mechanism would be involved we reacted **3a** and **4a** with ^{15}N-labelled potassium amide in ^{15}N-labelled liquid ammonia containing about 4.5% excess of ^{15}N, and converted the labelled 3-amino compounds obtained [we refer to these compounds as **3*b** and **4*b** (* = ^{15}N)] by diazotization in concentrated hydrochloric acid into the corresponding 3-chloro compounds **3*a** and **4*a**. It is evident that **3*a** and **4*a** do not contain excess of nitrogen-15, if the $S_N(AE)$ process (route I) is operative in the amination, while amination according to the $S_N(ANRORC)$ process (route II) would give **3*a, 4*a** being nitrogen-15 labelled in the heterocyclic ring and having the same percentage of nitrogen-15 as present in the 3-amino compounds **3*b, 4*b**.

Scheme 3



From the results of the mass spectrometric measurements of the starting materials **3a, 4a**, and 3-amino compounds **3*b, 4*b** and the 3-chloro compounds **3*a, 4*a** (see Table) it is clear that, surprisingly, the amination of

3a occurs nearly exclusively by route I [S_N(AE)] and the amination of **4a** nearly exclusively by route II [S_N(ANRORC)] [5]. It has been established [6] that the addition of the amide ion to an azine is charge-controlled and consequently

Table

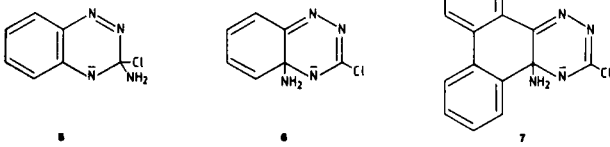
Percentage of Excess of ^{15}N in **3a**, **4a**, **3*b**; **4*b**, **3*a** and **4*a** as Established by Mass-spectrometric Measurements [a]

Compound	% ^{15}N-excess	% S_N(ANRORC) mechanism
3a	0.0	
3*b	4.4	4.5 ± 5
3*a	0.2	
4a	0.0	
4*b	4.3	93 [b] ± 5
4*a	4.0	

[a] Accuracy ± 0.2%. [b] The experiment was carried out in duplicate.

the addition preferably takes place at the position with the lowest electron density. Calculations show [7] that position 3 in benzo-1,2,4-triazine has the lowest electron density. In the σ-adduct formed from **3a**, *i.e.* **5**, the 6π-aromatic benzene ring is still maintained.

Scheme 4



Both arguments lead to the conclusion that addition at C-3 in **3a** is strongly favored. That the preferred formation of adduct **5** rather than **6** is not primarily due to the steric hindrance is convincingly demonstrated with the 3-chloro compound **4a**, which reacts, as we have seen, to 94% according to the S_N(ANRORC) mechanism *via* adduct **7**. The steric environment on that particular bridge carbon atom is not very different in **3a** and in **4a**. The preferred formation of **7** certainly reflects the decreased aromatic character of the central ring in **4a**.

EXPERIMENTAL

The following starting materials and reference compounds were prepared by procedures given in the literature: 3-chloro-1,2,4-benzotriazine (**3a**) [8], 3-chlorophenanthro[9,10-*e*]-1,2,4-triazine (**4a**) [9], 3-amino-1,2,4-benzotriazine (**3b**) [10] and 3-aminophenanthro[9,10-*e*]-1,2,4-triazine (**4b**) [11].

Amination Procedure.

To 25 ml of dry liquid ammonia in a 50 ml three-necked flask, equipped with a dry ice/acetone condensor, were added a few crystals of ferric nitrate and 160 mg (4 mmoles) of potassium. After the mixture was stirred for 30 minutes, 1 mmole of **3a** or **3b** was added with the exclusion of moisture. The reaction was terminated by addition of 220 mg (4 mmoles) of ammonium salt. After the ammonia was evaporated the residue was thoroughly extracted with warm chloroform. The residual material, after evaporation of the solvent, was purified by column chromatography (silica, chloroform-acetone in the ratio 10:1).

The amination with ^{15}N-labelled potassium amide in ^{15}N-labelled ammonia was caried out in the same manner. ^{15}N liquid ammonia was prepared from ^{15}N-labelled ammonium nitrate by treatment with a concentrated solution of potassium hydroxide.

Conversion of Components **3*b** and **4*b** into **3*a** and **4*a** Respectively.

Both conversions were performed by the procedure as described for the conversion of unlabelled **3b** and **3a** [8].

REFERENCES AND NOTES

[1] Part **30** on the S_N(ANRORC) mechanism. For part **29** see A. Rykowski and H. C. van der Plas, *J. Heterocyclic Chem.*, **19**, 653 (1982).

[2] Part **8** on the Chemistry of Triazines; for part **7** see ref [1].

[3] A. Rykowski and H. C. van der Plas, *J. Org. Chem.*, **45**, 88 (1980).

[4] For more examples of this method, see H. C. van der Plas, *Acc. Chem. Res.*, **11**, 462 (1978) and references cited therein.

[5] An S_N(ANRORC) mechanism is indicated if any excess of ^{15}N is found in the compounds **3*a** and **4*a** formed from **3*b** and **4*b** respectively. The decrease in ^{15}N content from 4.3% in **4*b** to 4.0% in **4*a** indicates that 4.0/4.3 × 100 = 93% of **4b** is formed by S_N(ANRORC) mechanism. The percentage of S_N(ANRORC) for transformation of **3a** into **3b** was calculated in the same way.

[6] H. Hirota, H. Masuda, Y. Hamada and I. Takeuchi, *Bull. Chem. Soc. Japan*, **52**, 1498 (1979); H. J. W. van den Haak, H. C. van der Plas and A. van Veldhuizen, *J. Org. Chem.*, **46**, 2134 (1981).

[7] S. C. Wait, Jr. and J. W. Wesley, *J. Mol. Spectrosc.*, **19**, 25 (1966).

[8] F. Arndt and B. Rosenau, *Chem. Ber.*, **50**, 1248 (1917).

[9] P. V. Laakso, R. Robinson and H. P. Vandrewala, *Tetrahedron*, **1**, 103 (1957).

[10] F. Arndt, *Chem. Ber.*, **46**, 3522 (1913).

[11] J. Thiele and R. Bihan, *Ann. Chem.*, **302**, 299 (1898).