*Tetrahedron* Vol 46, No 5, pp 1679-1686, 1990
Printed in Great Britain

0040-4020/90 $3 00+ 00


# SYNTHESIS AND SPECTROSCOPIC STUDY OF A NOVEL TRICYCLIC SYSTEM CONTAINING THE 1,2,6-THIADIAZINE 1,1-DIOXIDE MOIETY

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(*Received in UK* 15 *November* 1989)

**Abstract.**-3,4,5-Triamino-2H-1,2,6-thiadiazine 1,1-dioxide (**1**) undergoes intermolecular cyclization, under different reaction conditions, to give a novel tricyclic system which shows interesting chelating properties toward ammonium ion A spectroscopic study of this new tricycle and a mechanistic study of the reaction using an $^{15}N$-labelled intermediate has been carried out

During several attempts carried out to synthesize an oxoimidazothiadiazine derivative from the versatile 3,4,5-triamino-2H-1,2,6-thiadiazine 1,1-dioxide (**1**)[1] a bright yellow compound, which was indentified as the novel tricycle system **2**, was obtained The formation of this compound was achieved under very different reaction conditions, through an intermolecular cyclocondensation of **1** A similar cyclocondensation in related aminopyrimidines was described by Taylor and co-workers [2] However, in this case, the course of the reaction is different and the mechanism proposed by Taylor is not exactly the same as that found for aminothiadiazine derivatives

In this paper, a study of the mechanism of the self-condensation of **1**, using an $^{15}N$-labelled intermediate, is reported and the structure of compound **2**, is established by means of nmr, uv and FAB mass spectrometry

## RESULTS AND DISCUSSION

### Synthesis

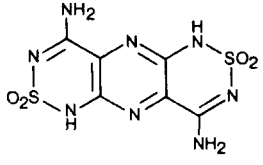
3,4,5-Triamino-1,2,6-thiadiazine 1,1-dioxide **1** is a very useful starting material for the preparation of different purine-like heterocyclic systems[1 3-5] and in no case had problems been found However, when **1** was made to react with methyl chloroformate in DMF/pyridine, a yellow compound, not detected previously, was obtained instead of the expected oxoimidazothiadiazine When methyl chloroformate was substituted by hydrochloric acid and only DMF used as solvent, traces of the same yellow compound together with the

majority 4-amino-1H,4H-imidazo[4,5-c]-1,2,6-thiadiazine 1,1-dioxide[1], were detected. The formation of this imidazothiadiazine derivative is explained by a Vilsmeier type reaction in which phosphorus oxychloride is substituted by hydrogen chloride. On the other hand, the unknown yellow compound was also found when **1** was trimethylsilylated in an attempt to achieve the reaction with methyl chloroformate.

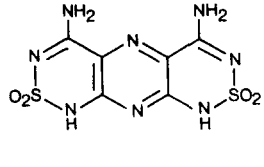
Trials with various combinations of the components of the original reaction mixtures demonstrated that none of the other components were involved and that compound **2** must have originated from the amino derivative **1**.

Two different experimental conditions were shown to be the best for obtaining the new compound. The trimethylsilyl derivative of **1**, heated at 160°C, affords the yellow product in 46% yield. The solution of **1** in DMF and 1mol of pyridine to which drops of hydrochloric acid are added, heated at 100°C, yields the same product (54%). If there is no pyridine in the solution only traces of the yellow compound are detected and if hydrochloric acid is omitted no reaction product is obtained.

On the basis of $^{13}C$-nmr, FAB mass spectometry and analytical data two isomeric structures **2** and **3** were candidates for the new compound. Both are possible through an intermolecular cyclocondensation of **1**. Compound **2** would be formed by reaction of the 4-substituent of one molecule with the 3-substituent of the other, whilst compound **3** would be formed by reaction of the 4- and 3-substituents of one molecule with 4- and 3-substituents of the other respectively.



**2**



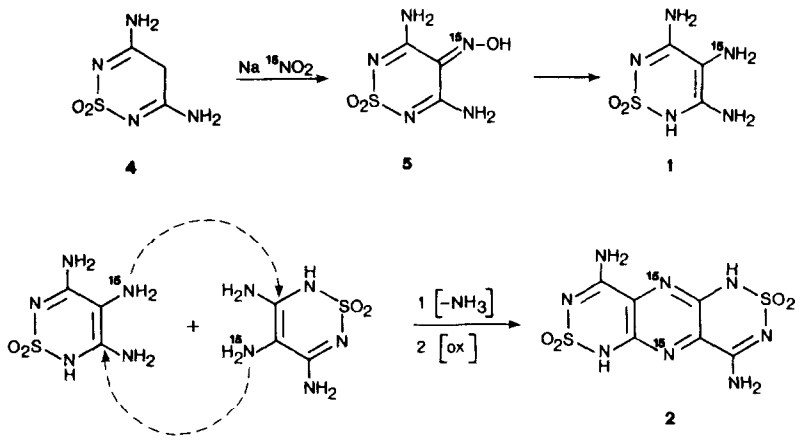
**3**

An oxidative self-condensation of related aminopyrimidines has been reported[2] and, in the majority of those cases, two isomers corresponding to analogous structures of **2** and **3** were identified. In the cases in which only one of the isomers was obtained, the compound corresponded to the structure **3**.

Taylor proposed a mechanism in which the initial step involves oxidation of 5-amino group to the corresponding imine followed, or not, by hydrolysis to the 5-quinone. Subsequent condensation of the 5-quinone or 5-imino with unchanged starting aminopyrimidine gives either or both of the two intermediate anils depending on which amino group of starting material condenses with the 5-keto (or imino) group of the quinone. Ring closure of the anils either by direct loss of ammonia or by preliminary hydrolysis of the other amino groups followed by dehydration leads to one or two isomers. Since it would be expected that the 5-keto group of the quinone would react preferentially with the 5-amino

group of aminopyrimidine the compound corresponding to structure **3** is the one that predominates[2]

In order to establish the mechanism and the structure, **2** or **3**, of the isomer formed, an $^{15}N$-labelled intermediate **5** was prepared, from **4** and $Na^{15}NO_2$ (96% enriched), by a described procedure,[1] to synthesize the triamino derivative **1** labelled at 4-amino group with $^{15}N$ Intermolecular cyclocondensation of labelled **1** yielded a compound, whose $^{15}N$-nmr spectrum shows only one signal corresponding to the two equivalent pyrazine nitrogens, only consistent with structure **2**, as a $^{15}N$-enriched signal The existence of two $^{15}N$-pyrazine atoms is only possible if the $^{15}N$ atoms of the substituent at 4 position of both molecules remain in the final product A probable mechanism that takes into account this fact is depicted in scheme 1




Scheme 1

The more nucleophilic amino group of the 4-position of one molecule attacks the more electron-deficient 3-position of the other with loss of ammonia, and after aromatization compound **2**, with two $^{15}N$-labelled pyrazine nitrogens, is obtained

The mechanism also explains the experimental conditions necessary to obtain **2** In the trimethylsilyl derivative of **1** the nucleophilic character of 4-amino group is enhanced On the other hand, because of the acidic properties of **1**,[6] the presence of pyridine helps to achieve the total solution of **1** in DMF, at room temperature, before the compound is decomposed at higher temperature, whilst acid catalysis (HCl added) seems to be necessary for the reaction to take place as in many other nucleophilic attacks [7]

**Spectroscopic Study**

Compound **2** showed an interesting behavior in relation to the isolation method used Depending on the crystallization procedure compound **2** retains molecules of the solvent

such as DMF, water or pyridine Besides, due to its acid character it could form ammonium salts with the ammonia evolved from the reaction For all these reasons it was very difficult to obtain a correct analysis for **2**. On the other hand, the vapor pressure of the compound was insufficient to allow its mass spectrum in the EI ionization mode to be recorded The molecular weight was unequivocally determined from its mass spectrum registered under FAB conditions using thioglycerol as matrix.

Depending on the isolation method used neutral form **2** or different ammonium salts of **2**, namely **2a**, **2b** and **2c** were obtained Form **2a** was obtained from the reaction mixture on adding acetone and water and it is probably the ammonium monosalt, which crystallizes with water Form **2b** was obtained by recrystallization of **2a** from water acidified with HCl and it is the hemi-ammonium salt Form **2c** was obtained on dissolving **2b** in aqueous ammonia and evaporation to dryness twice, and it is probably the ammonium disalt Finally, free compound **2** could be obtained from **2b** on using an ion-exchange resin.

$^{13}C$- and $^{15}N$-nmr spectra were recorded for forms **2**, **2a** and **2b** as well as the corresponding $^{15}N$-labelled forms For unlabelled **2c** the $^{13}C$-nmr spectrum was registered Only the data obtained from spectra of $^{15}N$-labelled **2**, **2a** and **2b** are gathered in table I, since the chemical shift differences, due to the isotope effects, are less than 0.3 ppm [8a]

$^{13}C$-nmr spectra of the four derivatives show only three signals, indicating the symmetry of compound (**2** or **3**) Assigments were based on reported data of pyrazinothiadiazine 2,2-dioxide derivatives [5 9] As can be seen, whilst the C-4 chemical shift value is almost the same for all the forms studied, the chemical shifts corresponding to C-4a and C-10a have different values for each form The most important difference among forms **2**, **2a**, **2b** and **2c** is found in the C-4a chemical shift, 2 3 ppm between neutral form **2** and its hemi-ammonium salt **2b**, 2 ppm between **2b** and mono-ammonium salt **2a** and 1 1 ppm between **2a** and diamomonium salt **2c**, showing an increased deshielding from **2c** to **2** In the $^{13}C$-nmr proton noise decoupled spectra of $^{15}N$-labelled **2a** and **2b** the signals of C-4 and C-4a are doublets, while in the spectrum of **2** the signals of the three carbons appear as doublets In no case the coupling with more than one $^{15}N$ atom could be observed

TABLE I -Nmr data of compound 2[a]

| | C-4(9) | C-4a(9a) | C-10a(5a) | N-1(6) | N-3(8) | N-5(10) | $NH_2$ | $^{+}NH_4$ |
|---|---|---|---|---|---|---|---|---|
| 2[b] | 157 0(d) $\lvert^2J_{C4\ N5}\rvert$=7 9 | 114 0(d) $\lvert^1J_{C4a\ N5}\rvert$=5 0 | 150 3(d) $\lvert^1J_{C10a\ N10}\rvert$=1 1 | 229 2 | 180 5 | 63 3 | 284 9 | - |
| 2b[c] | 157 0(d) $\lvert^2J_{C4\ N5}\rvert$=7 9 | 111 7(d) $\lvert^1J_{C4a\ N5}\rvert$=5 1 | 149 5(s) | 219 3 | 179 3 | 64 6 | 286 9 | 358 4 |
| 2a[c] | 157 2(d) $\lvert^2J_{C4\ N5}\rvert$=7 9 | 109 7(d) $\lvert^1J_{C4a\ N5}\rvert$=4 6 | 148 9(s) | 211 6 | 190 2 | 69 2(s) | 294 3(t) $^1J_{N\ H}$=-92 3 | 357 7(q) $^1J_{N\ H}$=-71 6 |
| 2c[d] | 157 2 | 108 6 | 149 0 | - | - | - | - | - |

[a] The data correspond to $^{15}N$-labelled compounds in DMSO-$d_6$ Chemical shifts in ppm and J in Hz s, singlet, d, doublet, q, quintuplet
[b] Spectra registered at 60°C and increments of $Cr(acac)_3$ added
[c] Spectra registered at 60°C $^{13}C$-nmr data correspond to proton noise-decoupled $^{13}C$-nmr spectrum
[d] Unlabelleded compound

The absolute value of the coupling constant $^2J_{N-5\ C-4}$ was assigned by comparison with the data reported for substituted $^{15}N$-labelled phenazines,[10] which are a good model, since a similar geometric arrangement of atoms as in compound **2** can be found In phenazines, the $^{15}N$ two bond coupling to C-1 is 8 3 Hz which is very similar to the 7 9 Hz coupling to C-4 found in **2**, **2a** and **2b** Probably the sign of $^2J_{N-5,C-4}$ is negative, since in unsaturated systems the cis arrangement between the nitrogen lone-pair to the $^{13}C$ nucleus involved in the coupling produces couplings in the range of -7 to -11 Hz In our case the $^3J_{N-10\ C-4}$ is not observed although in phenazines the similar coupling has a value of 4 4 Hz [10]

In phenazines, the values of one and two bond couplings for the carbons with similar arrangement of C-4a and C-10a of **2** are found between 1 and 2 Hz, whilst we have found for $J_{N,C-4a}$ values of $\simeq$ 5 and for $J_{N,C-10a}$ values of 1 1 and $<$ 1 Hz These values have been tentatively assigned to one bond coupling, since normally the absolute magnitude of one bond nitrogen-carbon coupling is larger than those across more bonds [8b]

The $^{15}N$-nmr spectra of **2**, **2a** and **2b** exhibit four signals, one for each N-1(6), N-3(8), N-5(10) atoms and $NH_2$ groups according only with structure **2** The spectra of **2a** and **2b** also show the signal corresponding to $^+NH_4$ ion as a quintuplet with 71 6 Hz splitting In the spectra of the $^{15}N$-labelled compound the signals corresponding to the pyrazine nitrogens and ammonium ion are enhanced, the latter less so intensity than the former This fact is not in disagreement with the proposed mechanism since the $^{15}N$-labelled ammonium ion is derived from the decomposition of part of starting material **1**

The $^{15}N$-nmr spectra had to be recorded at 60°C to see the signals corresponding to N-1 and N-3 indicating that a dynamic process takes place, probably the prototropic tautomerism which exists in 1,2,6-thiadiazine 1,1-dioxide derivatives [11] $^{13}C$-nmr spectra of **2**, **2a** and **2b** had also to be registered at 60° to see clearly the C-4a doublet

As in the case of $^{13}C$-nmr spectra, some differences in chemical shifts could be observed in $^{15}N$-nmr spectra of **2**, **2a** and **2b** However, the major difference found among $^{15}N$-nmr spectra of **2** and those of ammonium salts is that in the case of **2** addition of $Cr(acac)_3$ was necessary to see the pyrazine nitrogens This fact indicates that the $T_1$ relaxation time of those nitrogens is larger in **2** than in **2a** and **2b**, probably, because in the latter compounds pyrazine nitrogens can relax through the protons of the ammonium ion

But the most important differences between nmr data of **2**, **2a** and **2b** are found in $^1H$-nmr spectra The $^1H$-nmr spectra of hemi-salt **2b** and labelled **2b** show an interesting feature that does not appear in those of **2**, **2a** and **2c** In the spectrum of **2b**, a triplet fine structure at 7 05 ppm with a coupling constant of 51 1 Hz appears, together with the signals of the non-equivalent protons of both $NH_2$ groups, which are shown in the spectra of all the compounds in the range of 8 80-7 85 ppm On heating up to 70°C this triplet does not change while the two $NH_2$ signals at 8 30 and 7 85 ppm are broadened and collapsed into a singlet at 7 80 ppm

In the spectrum of $^{15}N$-labelled **2b** the signal at 7 05 ppm is due to the superposition of a triplet (J=51 5 Hz) and a doublet (J=71 5 Hz) indicating the presence of $^{14}NH_4^+$ and $^{15}NH_4^+$. $^{14}NH$ and $^{15}NH$ resonances can exhibit triplet and doublet fine structure, respectively, in tetrahedral symmetrical $^{14}NH_4$ and $^{15}NH_4$ ions[12], in absence of protons exchange processes[13] These conditions seem to be found in **2b** DMSO solution, while in **2a** and **2c** DMSO solutions the normal dynamic processes affecting $NH_4^+$ cations are produced, exhibiting broad $NH_4^+$ resonances

These facts could be explained if one thinks in **2b** as a complex in which one tetrahedral $NH_4^+$ ion is retained and protected of exchange processes between two molecules of **2**, or two $NH_4^+$ among four molecule of **2** etc building a fully symmetrical package Up to now, and with the available data it is not possible to indicate a more accurate structure of the complex **2b**

The complex **2b** is not destroyed on dissolving it in DMF since its $^1H$-nmr spectrum is the same after this treatment Only, if **2b** is dissolved in alkaline medium the complex disappears to form alkaline salts The uv spectrum of **2** and **2b** are the same when they are registered a pH=1 and in pure water but they are different at pH=10, in contrast with the behavior of related pyrazinothiadiazine derivatives,[9] whose uv spectra at pH=1 (neutral from) are different to those at pH=7 and pH=10 (anion)

Unfortunately, no suitable crystal for X-ray analysis were available, to indentify the structure of complex **2b**

## EXPERIMENTAL

$^1H$-nmr spectra were recorded at 200 MHz on a Bruker AM-200 and at 300 MHz on a Varian XL-300 spectrometer, using DMSO-$d_6$ as solvent Typical acquisition parameters were spectral width, 4 5 KHz, data size, 32 K, acquisition time 3 5 s and pulse angle (53°) Decoupled $^{13}C$-nmr spectra were recorded on the same spectrometer operating at 50 MHz and 75 MHz respectively. Typical conditions were spectral width 1 6 KHz, acquisition time, 0 9 s, data size 32 K and pulse angle (42°) $^{13}C$-nmr coupled spectra were recorded under the above conditions using a gated decoupling sequence pulse with a 3 s delay to build up the NOE $^{15}N$-nmr spectra were obtained on a Varian XL-300 spectrometer operating at 30 4 MHz using the following conditions spectral width 15 KHz, data size 32 K, 50° pulse angle and 5 s pulse repetition The nitrogen shielding values are reported with respect to external neat nitromethane, an increase in shielding being a positive increment

Mps were determined on a Kofler apparatus and are uncorrected Ir and uv spectra were recorded on Perkin Elmer 257 and Perkin Elmer 550 SE spectrophotometers respectively ZAB-HF instrument was used for record mass spectra (MS) Elemental analyses were carried out by the Organic Chemistry Department of Centro Nacional de Química Orgánica, CSIC, Madrid

**4,9-Diamino-1H,6H-pyrazino[2,3-c : 5,6-c']-di-(1,2,6-thiadiazine)-2,2,7,7-tetraoxide (2)**
Method A.

To a stirred suspension of **1** (0 44 g, 2 5 mmol) in HMDS (15 mL) and pyridine (5 mL), under nitrogen, was added a catalytic amount of ammonium sulfate and then refluxed for 5 5 h Evaporation of the solvent to dryness left the trimethylsilyl derivative of **1** as a colourless syrup It was heated at 150°C for 30 m to give a yellow solid crude which was recrystallized twice from water and then from dilute hydrochloric acid to yield **2b** as bright yellow needles (0 2 g, 46%) mp > 300°C $^1$H-nmr δ 8 30 (brs, 4H, $NH_2$, exch ), 7.85 (brs, 4H, $NH_2$, exch ), 7 05 (t, 4H, J=51 1 Hz, $NH_4^+$), 5.70 ppm (brs, 3H, NH, exch.) Ir (KBr) $\nu_{max}$ 3550, 3500, 3400, 3300, 3200 ($NH_2$, NH), 1660, 1570 (C=N), 1310-1300, 1180-1160 $cm^{-1}$ ($SO_2$) Uv ($H_2O$) $\lambda_{max}$ 226, 290, 413 sh, 420, 429 (sh) nm $\lambda_{max}$ ($H_2O$, pH=1) 226, 290, 413 (sh), 420, 429 (sh) nm $\lambda_{max}$ ($H_2O$, pH=10). 203, 246, 295, 395 nm MS ($FAB^+$). m/z 319 ($MH^+$, 100) Anal Calcd for $C_6H_6N_8O_4S_2$ $\frac{1}{2}NH_3$ $H_2O$ C, 20 90, H, 2,78; N, 34 53 Found C, 20 57, H, 2 80, N, 33,75

An aqueous solution of **2b** was passed through 50 ml (wet volume) of Amberlite IR-120 ($H^+$) cation-exchange resin and eluted with water The eluted was evaporated to dryness *in vacuo* yielding free compound **2** which was recrystallized from water mp > 300°C $^1$H-nmr δ 8 53 (s, 2H, $NH_2$, exch ), 8 20 (s, 2H, $NH_2$), 4 30 ppm (brs, NH, $H_2O$) Ir (KBr) $\nu_{max}$· 3600-2600 ($H_2O$), 3400, 3300, 3150 ($NH_2$, NH), 1660, 1600 (C=N), 1320, 1180-1140 $cm^{-1}$ ($SO_2$) Uv ($H_2O$) $\lambda_{max}$ 226, 290, 413 (sh), 420, 429 (sh) nm

Method B

To a warmed stirred mixture of **1** (1 g, 5 6 mmol) in DMF (15 mL) and pyridine (0 25 g) concentrated hydrochloric acid (1 5 mL) was slowly added The resulting bright yellow solution was heated at 110°C for 8 h After cooling to room temperature acetone (30 mL) was added and the red-orange oil so obtained was decanted and treated with water to yield **2a** as a yellow solid (0 5 g, 54%) mp > 300°C ($H_2O$) $^1$H-nmr δ 8 80 (brs, 2H, $NH_2$, exch.), 8 30 (brs, 2H, $NH_2$, exch ), 6 00 (brs, 5H, NH, $NH_4^+$, exch ) On dissolving the compound **2a** in dilute hydrochloric acid, compound **2b** was crystallized and it showed to be identical with the product isolated by the method described above

**Acnowledgment**.-We thank Dra Cristina Suárez (CIEMAT, Spain) to supply $Na^{15}NO_2$. This work was supported by research grant n ° 86-0431 from CICYT, Spain

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