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SYNTHESIS OF [3-^{14}C]- AND [5-^{14}C]- LABELLED 5-NITRO-1,2,4-TRIAZOL-3-ONE (NTO) AND STUDY OF ITS CHEMICAL DECOMPOSITION.

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SUMMARY

The chemical decomposition of NTO **1** and its corresponding amine ATO **2** was investigated. To make easier the identification of the decomposition products, we synthesized ^{14}C-labelled NTO and ATO. Our results confirmed the high stability of the NTO triazolone ring. Its scission can be achieved partially by sulfuric acid under intensive heat and pressure. The triazolone ring of ATO was cleaved in alkaline solution. Carbon dioxide is evolved leaving a polar compound assumed to be aminoguanidine. The deamination of ATO was achieved by nitrosation. In dilute HCl (0.15N), 2 equivalents of $NO_2^{\cdot}$ lead to the triazolone **4**, through a radical de-diazotation of the diazo intermediate. With 3 to 10 equivalents of $NO_2^{\cdot}$, the nitrosation leads exclusively to the azide **6**.

Keywords : NTO. Explosives. Triazolones.Deamination.De-diazotation.Nitrosation.

INTRODUCTION

5-Nitro-1,2,4-triazol-3-one is a new stable explosive. Its stability to impact (1) as well as its photo- and thermo- decompositions have been investigated in order to predict any risk and to ensure safe conditions during handling (2-6). The results confirm the stability and the performance of this compound compared to other explosives. NTO is actually produced in many countries, and tested pure or mixed with TNT. As reported for other explosives (7-9), increasing demand for this compound may cause pollution in soils and waters around facilities. In order to prevent such risk and to clean up NTO contaminated industrial wastes, various approaches have recently been developed in our group, including microbial and photochemical remediation. Nevertheless, chemical decomposition of NTO may represent an attractive alternative approach, at least for particular degradative steps.

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Contrary to other nitrotriazoles, only two publications reported the chemical transformations of NTO. The reactions described were the nitro-reduction of NTO to the corresponding primary amine ATO (10,11), and NTO decomposition in refluxed sulfuric acid (12). The chemistry of nitrotriazoles have been reviewed in 1986 by Boyer (13), who confirms the high stability of the nitrotriazolone ring against drastic reaction conditions. Furthermore, oxygen substitution at position 3 made the 1,2,4-triazole ring aromatic, and more stable than aliphatic or cyclic non-aromatic 1,2,4-triazoles (14). Ritchies (15) investigated the structures and energies of NTO tautomers and showed that the 1H-4H tautomer is the most stable. As a consequence, the carbon at position 3 may be considered as a carbonyl group.

In order to complete our knowledge on the reactivity of substituted triazolones, we investigated the chemical decomposition of NTO and ATO. Target regions in these molecules were the nitro group, the primary amine and the cyclic urea. We recently reported a comparison between the chemical and the microbial nitro-reduction of NTO (16). The present work focused on the deamination of ATO and the hydrolysis of the cyclic urea. In order to follow the behaviour of these compounds, and to propose accurate reaction mechanisms, we synthesized the [5-^{14}C]- NTO, [3-^{14}C]-NTO, [5-^{14}C]-ATO and [3-^{14}C]-ATO variants.

MATERIALS and METHODS

The liquid chromatograph is from Waters and consists of a 717 injector, a 600E pump operating at 1 ml/min and a 486 UV-detector set at 220 nm coupled to an HPLC radioactivity monitor LB506 C-1 (Berthold). IR spectra were recorded on a Nicolet 205 FTIR instrument, ^{1}H and ^{13}C-NMR spectra were obtained on a Bruker AM 300 instrument. Mass spectra (MS) were recorded on an AEI MS-50 (electron impact spectra, EI), an AEI MS-9 (chemical ionisation spectra, CI) or a Kratos MS-50 (high resolution mass spectra HRMS).

Chemicals:

5-Nitro-1,2,4-triazol-3-one (NTO) **1** was kindly supplied by the Commissariat à l'Energie Atomique, centre du Ripault, France. Urazole **3** was supplied by Aldrich.

1,2,4-Triazol-3-one **4** was synthesized according to a published procedure (13).

5-amino-1,2,4-triazol-3-one (ATO) **2** 1.3 g of **1** (10mmol) were dissolved in 40 ml of methanol, then 140 mg of Pd/C were added. The hydrogenation vessel was stirred under 30 psi for five hours at room temperature. HPLC analysis shows the total disappearance of NTO and the concomitant formation of the amine **2**. The mixture was filtered and the methanol evaporated under reduced pressure to give 700 mg of yellow powder consisting of pure **2** (70% yield). ^{13}C-NMR : 155.09 (C=O), 147.83 (C=N). IR : 3400, 1700, 1650. EIMS : 100 ($M^{+}\cdot$, 83), 57 (35), 43 (100). HRCIMS : calculated for $C_2H_4ON_4$: $[M+H]^+$ 101.0645, Found : 101.0465. m.p. : 240-245°C. Anal.Calc. for $C_2H_4N_4O$: C 24, H 4, N 55, O 16. Anal. Found: C 24.6, H 3.8, N 54.1 , O 17.4. [5-^{14}C]-ATO and [3-^{14}C]-ATO were prepared from ^{14}C-labelled NTO by a similar procedure.

[5-^{14}C]-Nitro-1,2,4-triazol-3-one or [5-^{14}C]-NTO (figure 1 A)

[5-^{14}C]-NTO was synthesized as shown in figure 1A. [^{14}C]-Sodium formate was obtained from [^{14}C]-carbon dioxide and sodium trimethoxyborohydride (radioactive yield 83 %) (17). [5-^{14}C]-1,2,4-Triazol-3-one was synthesized by refluxing for 5 hours 12.5 mmol, 150 mCi (12 mCi/mmol) of [^{14}C]-sodium formate with 3.6 mmol of semicarbazide hydrochloride in 1 ml of 12 N hydrochloride acid (18). The dried residue was purified by liquid chromatography using Sephadex G-10 eluted with water. 21 mCi of [5-^{14}C]-1,2,4-triazol-3-one were obtained (radioactive yield 14 %). [5-^{14}C]-NTO was obtained by nitration of [5-^{14}C]-1,2,4-triazol-3-one with fuming nitric acid at -5°C (19). To 1 mmol of [5-^{14}C]-1,2,4-triazol-3-one cooled at -5°C, 0.4 ml of fuming nitric acid were added with stirring for 2 min., then the flask was heated slowly to room temperature and stirred for 15 hours. 0.5 ml of ice-water was added and the yellow precipitate filtered and washed three times with 0.5 ml of cold water, 1 ml of cold water then quickly with 2 ml of water at room temperature. 5.7 mCi of white crystals of [5-^{14}C]-NTO were obtained (radioactive yield 45 %). The radioactive purity and the chemical purity were checked by HPLC (column Zorbax SBC-18 elution 0.1 % of trifluoroacetic acid in water; U.V. detection at 220 nm). Radiochemical and chemical purities were better than 99 %. The structural analysis and the specific activity (12.7 mCi/mmol) were measured by mass spectrometry (DCI/CH_4) m/e=130-132. The mass spectrum was in agreement with the mass spectrum of an authentic sample.

5-Nitro-1,2,4-triazol-[3-^{14}C]-one or [3-^{14}C]-NTO (figure 1 B)

[3-^{14}C]-NTO was synthesized as shown in Figure 1B. 500 mCi of [^{14}C]-barium carbonate (specific activity 39.6 mCi/mmol) was heated at 800 °C with ammonia gas to give [^{14}C]-barium cyanamide in a quantitative yield. Then [^{14}C]-barium cyanamide was heated for 4 hours at 50°C with 46 ml of sulfuric acid to give 333 mCi of [^{14}C]-urea (radioactive yield 67 %) (20). [^{14}C]-urea was diluted with cold urea to lower the specific activity to about 25 mCi/mmol. [^{14}C]-urea and 0.83 ml of hydrazine hydrate were refluxed in 5.2 ml of isoamyl alcohol and 5 ml of ethyl alcohol for 12 hours; 125 mCi of [^{14}C]-semicarbazide hydrochloride was obtained (radioactive yield 36 %). The 125 mCi of [^{14}C]-semicarbazide hydrochloride, diluted with 570 mg of cold semicarbazide hydrochloride, was refluxed with 2.2 ml of formic acid and 0.3 ml of water. 62 mCi of 1,2,4-triazol- [3-^{14}C] -one were obtained (radioactive yield 50 %). 9.4 mCi of [3-^{14}C]-NTO were obtained from 14 mCi of 1,2,4-triazol-[3-^{14}C]-one as described for [5-^{14}C]-NTO (radioactive yield 67 %). The radioactive purity and the chemical purity were checked by HPLC (column Zorbax SBC-18 elution 0.1 % of trifluoroacetic acid in water U.V. detection at 220 nm).Radiochemical and chemical purities were better than 99 %. The structural analysis and the specific activity (11.5 mCi/mmol) were measured by mass spectrometry (DCI/CH_4) m/e=130-132. The mass spectrum was in agreement with the mass spectrum of an authentic sample.

^{14}C-counting

Samples of the reaction (50 to 500 µl) were added to 5 ml of aqueous scintillation cocktail (Aquasafe 300 plus from Zinsser Analytic) and counted in a LKB 1214 Rackbeta counter.

Chromatographic methods

TLC analysis was performed on 0.2 mm thick Silica gel plates (DC-Alufolien Kieselgel $60F_{254}$ from Merck, Germany). Spots-associated radioactivity was measured using an automatic TLC linear analyzer, Tracemaster 20, from Berthold. The solvent used for TLC was : chloroform/methanol/acetic acid 50:50:2. For HPLC analysis, we used a porous graphitic column Hypercarb 7 µm, 100 x 4.6 mm I.D (Shandon HPLC, France) (21). The elution gradient consists of : $t_{0\text{-}25min}$: 100 % A (0.05% TFA in water), $t_{30\text{-}45min}$: 100 % B (15% acetonitrile: 0.05% TFA in water), t_{50min} : 100 % A. Radioactivity was measured by a HPLC radioactivity monitor LB506 C-1 (Berthold) (fig 3A).

Urea measurement

Urea formation was determined by two methods: 1) a commercial test based on the formation of a colored complex between urea and diacetyl monoxime ((Sigma Diagnostics, blood urea nitrogen kit), 2) TLC method coupled to radioactivity detection. Spots-associated radioactivity was measured using a linear TLC analyzer Tracemaster 20 (Berthold). Cellulose F plates (Merck) were eluted with butanol-acetic acid-water mixture (50%, 25%, and 25%, respectively).

Nitrite measurement

Nitrite concentrations were determined using a procedure based on the Griess reaction. 50 µl of the solution was added to an equal volume of Griess reagent (5% sulfanilamide in 2N HCl plus 0.5 % N-1-naphtylethylendiamine in 2N HCl) and incubated in a microplate at room temperature for 20 min. The absorbance was measured at 540 nm in a microplate reader (Dynatech), and the concentrations deduced from a standard curve. This curve is linear between 5 and 100 µM of nitrites and the limit of detection is 5 µM.

Reaction conditions

For all the reactions described below, NTO and ATO were treated under the same conditions, in the presence of the appropriate radiolabelled compound.

- In hydrochloric acid: 2 g of NTO (15.4 mmol), were added to 200 ml of HCl 4N. The solution was refluxed for 7 hours. The mixture was cooled and evaporated to give 1.6 g of white powder consisting on 5-chloro-1,2,4-triazol-3-one **5** (13.2 mmol). Yield 85.7%. ^{13}C NMR (DMSO, 300 MHz) δ: 155.1 (CO), 133 (C=N). CIMS : $[M+H]^+$ 120. Anal. $C_2H_2N_3OCl$ required C, 20; H, 1.7; N, 35; O, 13.3; Cl, 30. Found C, 18.5; H, 2.1; N, 34.3; O, 14.6; Cl, 30.7.

- In sulfuric acid: 25 mg of NTO (192.3 µmol), were added to 2.5 ml of H_2SO_4 2N. The mixture was then placed in a sealed vessel and heated at 130°C. Samples were analyzed by HPLC, TLC and radioactivity counting.

- In nitrous acid: 15 mg of ATO (0.15 mmol) and 42 mg of $NaNO_2$ (0.6 mmol, 4 Eq.) were dissolved in 1.5 ml HCl solution (0.15 to 4N HCl). The mixture was then stirred at room temperature. Samples were analyzed by HPLC and radioactivity counting. 1,2,4-Triazol-3-one **4** was obtained by mixing 50 mg of ATO and 70 mg of $NaNO_2$ (2 Eq.) in 10 ml of glacial acetic acid. After 4 hours of reaction, the mixture was evaporated, the residue was resuspended in methanol, filtered and evaporated. The residue was chromatographed on silica gel (Methanol/methylene-chloride 1:1) to offer 32 mg of **4** (74% yield). Analytical data

were identical to those reported by Chipen et al (11). 5-Azido-1,2,4-triazol-3-one **6** was obtained by mixing 50 mg of ATO and 140 mg of $NaNO_2$ (4 Eq.) in 10 ml of HCl 0.15 N. After 1 hour at room temperature, the mixture was deposited on Sephadex G-10 and eluted with water. Compound **6** containing fractions (HPLC) were pooled and evaporated to give 35 mg of yellow powder (55% yield). ^{13}C NMR (DMSO, 300 MHz) δ : 157.6 (CO), 150.4 ($C\text{-}N_3$). HRCIMS : calculated for $C_2H_2ON_6$: $[M+H]^+$ 127.0116, Found : 127.0366.

- in sodium hydroxide solution: 20 mg of NTO (154 µmol) were added to 2 ml of NaOH 4N. The mixture was placed in a sealed vessel and heated at 130°. Samples were analyzed by HPLC, TLC and counting.

RESULTS and DISCUSSION

Synthesis of [3-^{14}C]-NTO and [5-^{14}C]-NTO :

Recently, the synthesis of ^{15}N-labelled NTO has been reported and its photo- and thermal decomposition investigated (22,23). In order to appreciate the carbon behaviour during NTO degradation and to distinguish between the nitro and the urea regions of this molecule, we synthesized [3-^{14}C]- and [5-^{14}C]-labelled NTO (Fig.1). The corresponding [3-^{14}C]- and [5-^{14}C]-labelled ATO were prepared by nitro-reduction. We had previously used these compounds for elucidating the mammalian and the microbial metabolisms of NTO and ATO (24,25), as well as the decomposition of these compounds by advanced oxidation processes (AOPs) (36).

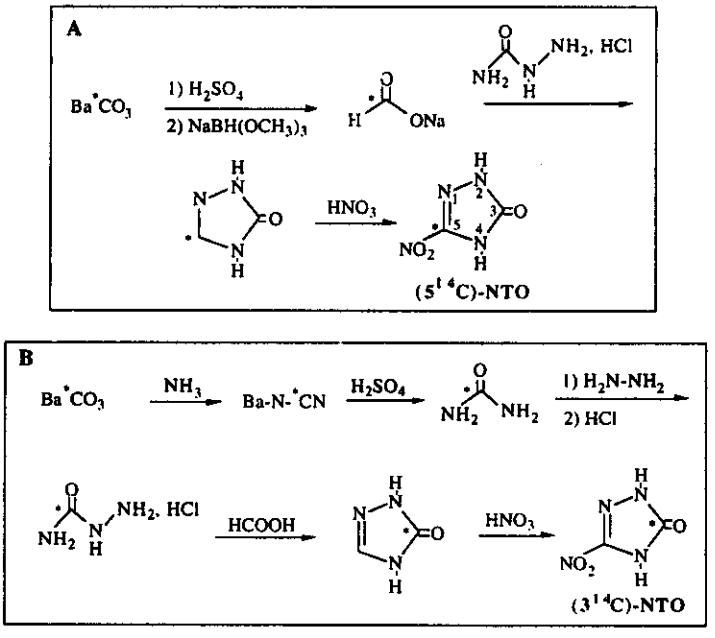

Fig.1. Synthesis of [^{14}C]-NTO.

Deamination of ATO :

The nitro-reduction of nitroaromatics removes the energetic properties of this class of explosives, but generates a new risk due to the cytotoxicity of the derived aromatic primary amines. This risk could be considerably reduced by deamination. We reported previously the nitro-reduction of NTO to ATO (16), and decided to achieve the deamination of ATO by nitrosation (nitrites in HCl). In 4N HCl and 2-4 equivalents of nitrites, the chloro derivative **5** was the major compound obtained (more than 80%) (fig 2).

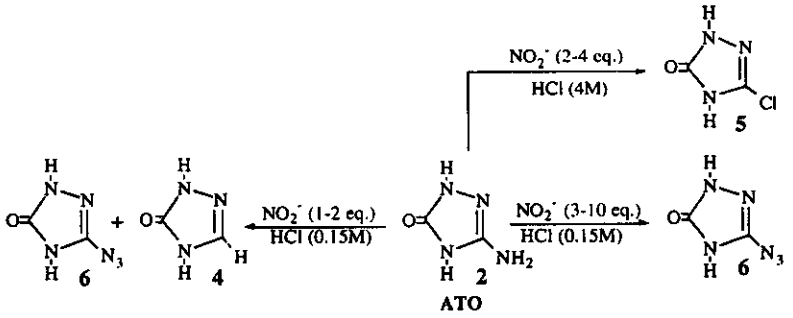

Fig.2. Influence of nitrite and HCl concentrations on ATO nitrosation derivatives

Such a substitution of the amino group by chloride, during the diazotization of 4-N-substituted aminotriazoles, was reported earlier by Gehlen (26). In dilute HCl (0.15 N), nitrite concentration drastically influences the structure of the reaction products (Fig 2). Thus, in the presence of 1 or 2 equivalents of nitrites, we obtained a mixture of the triazolone **4** and the azide **6**, while 3 to 10 equivalents of nitrites lead exclusively to the azide **6**. These results were deduced from HPLC (Fig 3.B), and confirmed by TLC, both coupled to radioactivity detection.

The initial radioactivity associated to ATO was completely recovered in compounds **4** and **6**. All these reactions are complete in a few minutes and leave less than 0.5% of the initial nitrites. Contrary to the deamination of various heterocyclic primary amines (27), we never obtained the expected urazole, which suggests that the diazo intermediate **3** could not be hydrolysed. The formation of **4** as a major derivative with 1 equivalent of nitrites (more than 70%), represent an efficient replacement of the primary amine by hydrogen in mild conditions and in aqueous media. Common procedures for the replacement of an aromatic primary amine by hydrogen involve two separate steps: the diazotization of the amine, and the reduction of the diazo group. An extensive number of reducing agents have been investigated but only a few gave satisfactory results. Hypophosphorous acid remains the standard reductant for diazonium salts (28,29). The reductive de-diazotation can be achieved in a one pot step by the use of alkyl nitrite and cooper (II) halide in boiling THF or dioxan. The solvents serve as hydrogen donors, and the reactions were initiated by light or heat activation (29-31). Only a few examples for such reactions have been reported in the literature, the most successful is the one pot synthesis of the antibiotic nebularine from adenosine (29). Nevertheless, in nitrous acid, adenosine leads to hypoxanthine through the

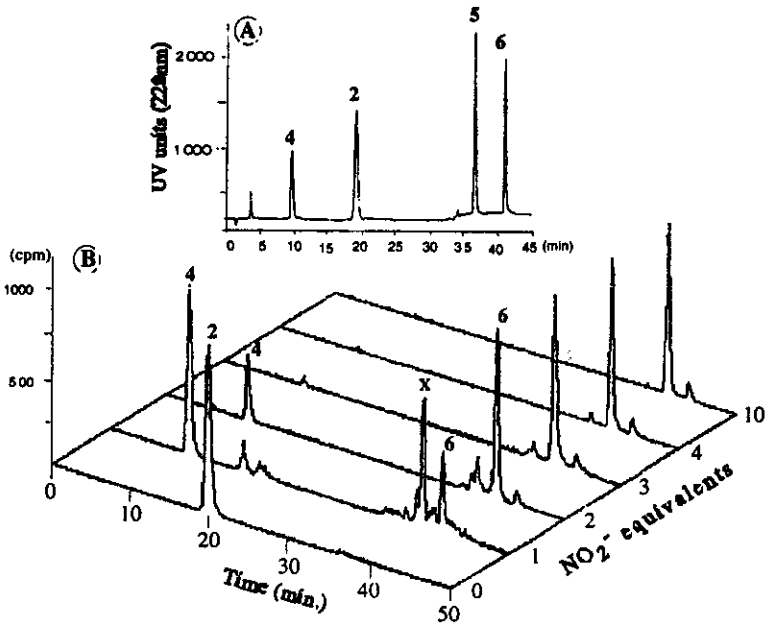

Fig.3. HPLC analysis. A. mixture of standards detected by UV 220nm. B. Superposition of radioactivity-HPLC profiles obtained by nitrosation of $^{14}(C_3)$-ATO at various nitrite concentrations (1 to 10 eq.). Chromatograms correspond to a dilution of the whole reaction medium.

hydrolysis of the diazonium group, which is not observed in our case. As reported in figure 4 (route B), we proposed for ATO a radical mechanism of de-diazotation. Compound **7** (potentially peak X in fig 3.B) leads to **8** via homolytic scission of the N-OH bound, followed by the rearrangement of the radical and the subsequent elimination of nitrogen. **8** may abstract hydrogen from the solvent or from another molecule of ATO to give compound **4**.

The formation of the azide **6** was unexpected (Fig 3). From 3 to 10 eq. nitrites, no **4** was formed thereby excluding a mechanism based on the rearrangement of a diazo-amino dimer intermediate. The more plausible way seemed to be a direct nitrosation of the diazo intermediate. This unusual reactivity of the diazo group is probably favoured by charge migration through the triazolone ring leaving an elecronegative terminal nitrogen (fig 4 route C). ATO is to our knowledge the first example of a primary amine that leads exclusively to an azide derivative through successive nitrosation processes. The diazotization of the acylated 4-N-amino group reported by Gehlen (35) leads also to the azide derivative. However, the mechanism consists of an intramolecular attack of the N-amino substituent by the diazo group and the rearragement of the derived bicyclic compound.

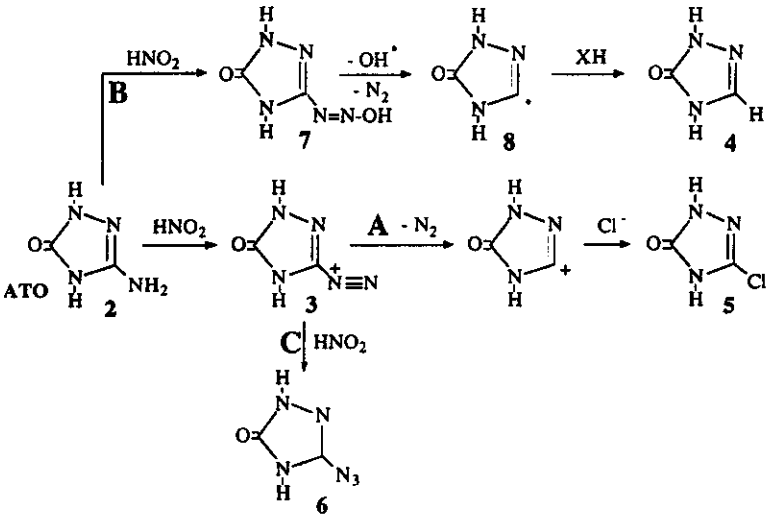

Fig.4. Proposed mechanisms for ATO nitrosation.

Hydrolysis of NTO and ATO :

Ritchies (15) deduced from molecular orbital calculations on NTO **1** and TO **4**, a tautomeric preference for the triazolinone form over hydroxytriazole. This favours the 2,4-dihydro-NTO tautomer where the -NH-CO-HN- group might be considered as a cyclic urea or amide (14). In hydrochloric acid, the triazolone ring of NTO is not affected, while the nitro group is replaced by a chloride leading to the 5-chloro-1,2,4-triazol-3-one **5** in quantitative yield (figure 5). Such a reaction was previously observed for 3-nitro-1,2,4-triazole (19,26,33). In the same conditions, ATO **2** is unaffected.

Hydrolysis of 5-substituted triazolinones in sulfuric acid have been reported earlier (12). The ring is affected, and the rate of degradation depends on the electronic effect of the substituent. In 2N sulfuric acid, NTO is partially degraded, and 40 % of the starting material

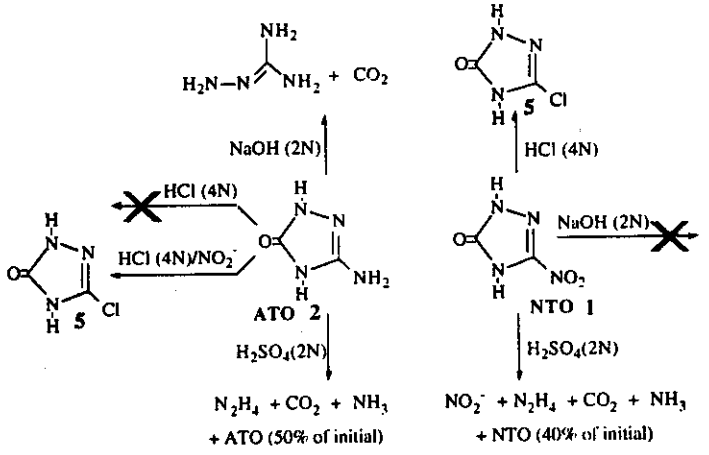

Fig.5. Acid and alkaline hydrolysis of NTO and ATO.

is recovered after 20 hours under reflux. The use of radiolabelled compounds [5-^{14}C]-NTO and [3-^{14}C]-NTO, attests to the mineralization of 45% of the initial radioactivity associated with NTO. Both C-5 and C-3 carbons were eliminated as carbon dioxide. Similar results were obtained for the hydrolysis of ATO **2** but the degradation did not exceed 50%.

Generally, cyclic ureas were hydrolyzed in alkaline solutions (NaOH), leading to a spontaneous decarboxylation and the formation of the diamine derivative (34,35). NTO remains unaffected under a reflux of 2N NaOH for 8 hours. In the same conditions, figure 6 shows that the carbonyl group of ATO is removed as carbon dioxide; the carbon 5 (C-NH_2) is not mineralized and was recovered in water-soluble polar compounds (Rf in TLC analysis between 0.1 and 0.2 cm). No urea was detected in this experiment suggesting that the polar compound probably corresponds to amino-guanidine. Results concerning the hydrolysis of NTO and ATO are presented in figure 5. The differences observed in the hydrolysis of NTO and ATO were due to opposite influences of the nitro and the primary amine groups on the aromaticity of the triazolone ring, and consequently on the reactivity of the carbonyl group.

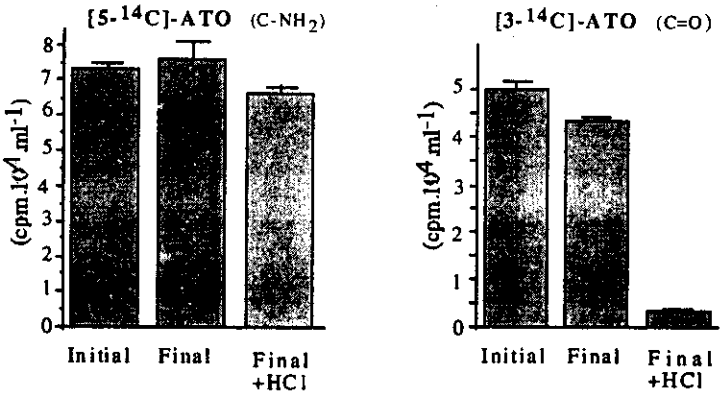

Fig.6. Behavior of labelled carbons 3 and 5, during the alkaline hydrolysis of ATO. HCl is added until acidification of the mixture to allow removing of $^{14}CO_2$ from carbonates.

In conclusion, the triazolone ring of NTO may be degraded in sulfuric acid. however, this degradation is partial and takes place in drastic conditions. Otherwise, the NTO ring is highly stable. ATO can be easily obtained by nitro-reduction of NTO (16). The diazotation of ATO takes place under mild conditions and leads with one equivalent of nitrites to the triazolone **4** as the major compound.

ATO, but not NTO, reacts in alkali as does every cyclic urea. The ring scission is accompanied by the spontaneous mineralisation of carbone 3, and the formation of a polar compound probably aminoguanidine. The mechanisms of formation of **4** and **6** during the nitrosation of ATO, will be further investigated by NMR, using $H^{15}NO_2$ as nitrosating agent.

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