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SYNTHESIS OF THE 4-HYDROXYIMINO-3-CARBOXAMIDE-2-QUINOLONE WITH A NEW HETEROCYCLIZATION MECHANISM OF THE REACTION BETWEEN CARBON SUBOXIDE AND 2-AMINOBENZAMIDOXIME

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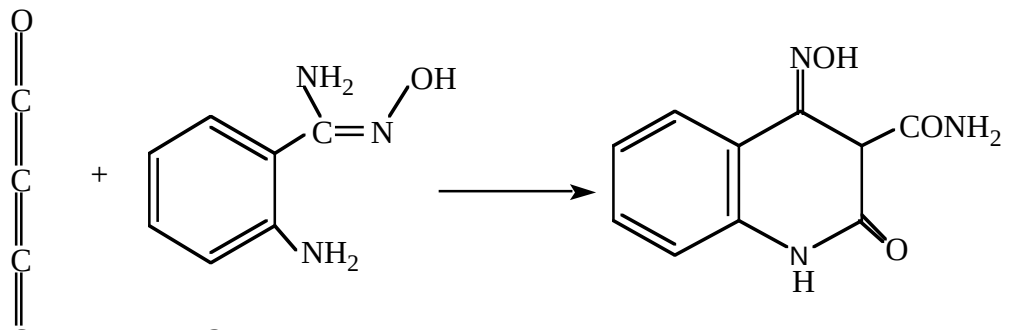
Abstract - Synthesis of the 4-hydroxyimino-3-carboxamide-2- quinolone with a new heterocyclization mechanism of the reaction between carbon suboxide and 2-aminobenzamidoxime is reported. Its formation is also supported by charge calculations.

The 2-quinolone nucleus has attracted considerable attention because of its biological interest. Its structure is present, for example, in furoquinolinones[1] and it represents a useful isoster of coumarin ring in which the atom of oxygen is substituted by the nitrogen atom. Although many methods are available for the preparation of 2-quinolones, [2] very little is known about their direct synthesis starting from 2-aminobenzaldoximes.

As part of an ongoing investigation aimed to the study of the interaction of 2-quinolones with the HIV reverse transcriptase binding sites, we studied the reaction of carbon suboxide (C_3O_2)[3] (**1**) with the *syn*-2-aminobenzamidoxime (**2a**) (the reaction with the *anti*-isomer is not reported because we did never isolate the *anti*-2-aminobenzamidoxime because of its rapid interconversion). [4]

Reaction between carbon suboxide (**1**) and 2-aminobenzamidoxime (**2**) leads to the formation, as the unique product, of the 4-hydroxyimino-3-carboxamide-2-quinolone (**3**) (93% yield) (Scheme 1). The

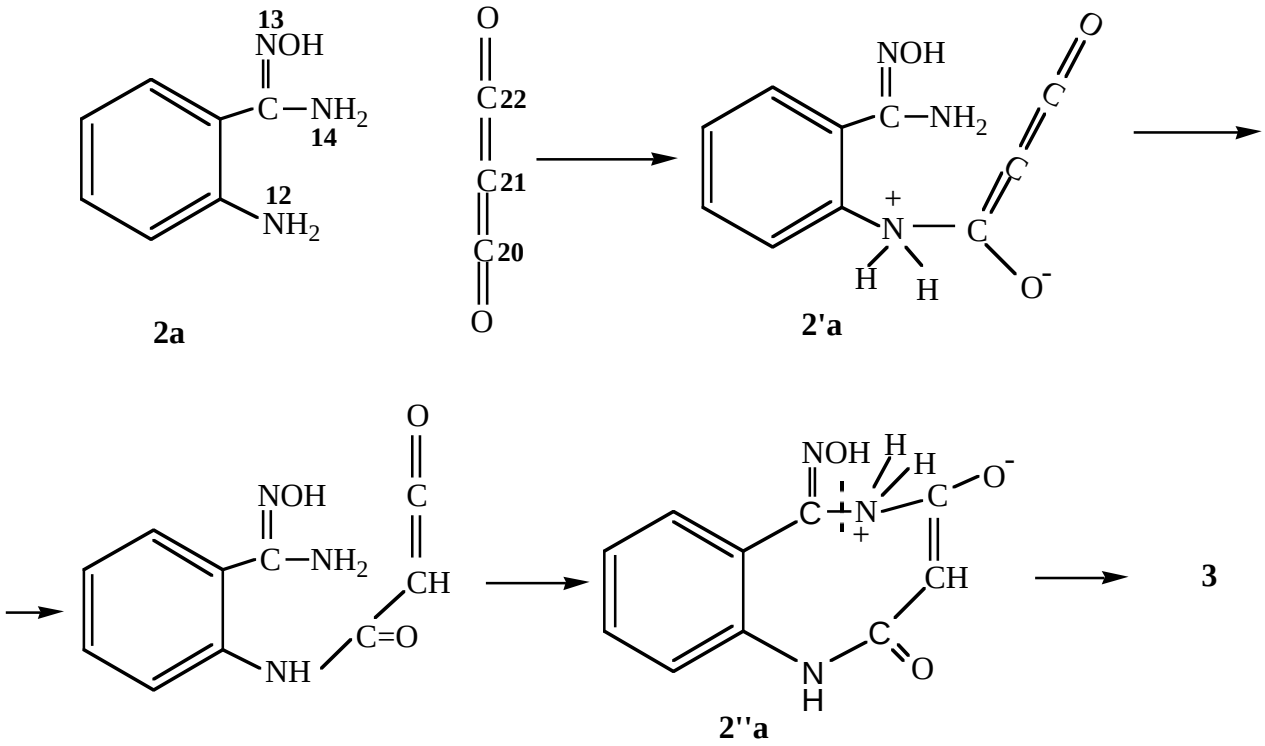


1 **2** **3**

Scheme 1

proposed mechanism (Scheme 2) involves a first attack of the N12 to the C20 of carbon suboxide to give the intermediate (**2'a**) and a second attack of the N14 to the C22 of carbon suboxide to give **2"a** intermediate which rearrange to provide **3**.

Following some calculations using molecular mechanics, semiempirical and *ab initio* methods we showed evidence of the mechanism of the heterocyclization which exclude the involvement of the oximic nitrogen N13. For this computational analysis we have considered the neutral form of the intermediate compound (**2'a**) (see Scheme 2).



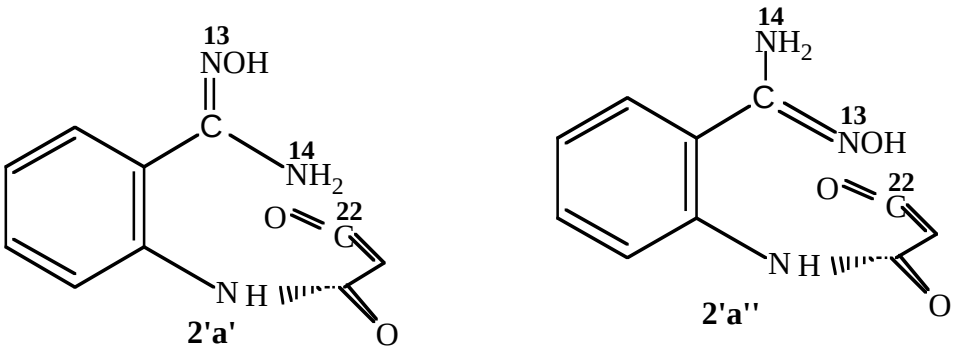
Scheme 2

A conformational search of the compound (**2'a**) has been carried out using the Monte Carlo algorithm[5] as implemented in the MacroModel[6] package ver.6.0 energy minimising with the MMFF force field.[7] We have randomly generated 1000 conformations of **2'a** and minimised with the Truncate Newton Conjugate Gradient until the standard convergence criterion of 0.01 kcal/Å-mol has been reached. The few number of rotable bonds ensure a quick convergence in the Monte Carlo search as revealed by the average number of duplicate conformation larger than 30.

The putative conformers related to the two possible mechanism, i.e. the N14 or the N13 attack to the C22 carbonyl carbon have been isolated within the most populated conformations and respectively named **2'a'** and **2'a''**(Scheme 3).

Energetically they appear to be equally stable and probable, so we have concentrated our attention in the formal charge distribution that, at least in the first part of the heterocyclization, plays an important role in

the intramolecular attack preference. For this purpose we have also adopted the semiempirical AM1 and STO-3G* methods[8] that, in contrast to the molecular mechanic charge distribution of MMFF, are dependent to the conformations (**2'a'**) and (**2'a''**). The results are summarised in Table 1.



Scheme 3: Schematic representation of the two conformers (**2'a'**) and (**2'a''**) compatible with the heterocyclization mechanism.

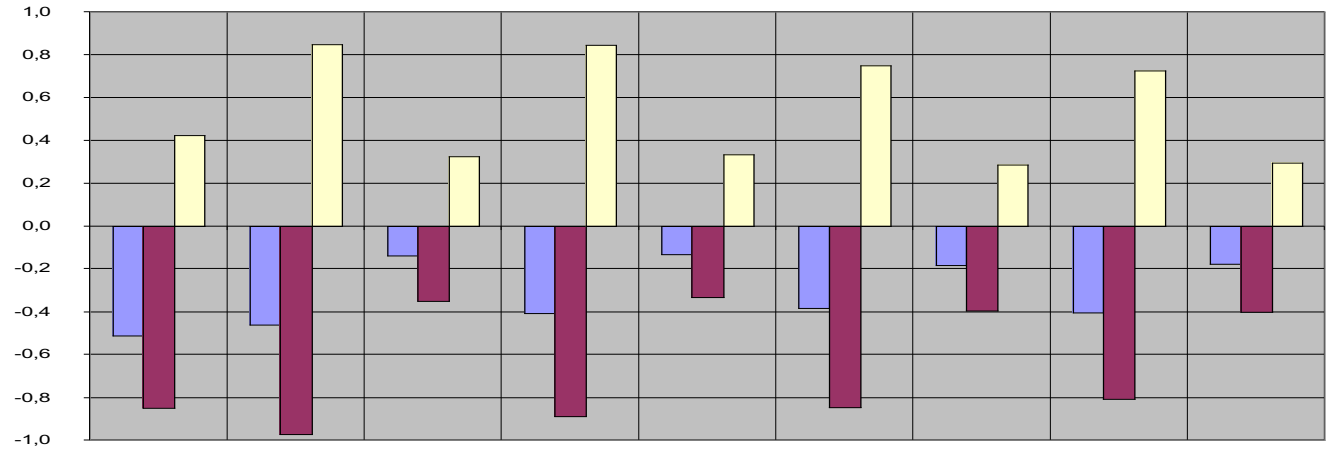
The comparison reveals a very consistent qualitative charge distribution. In all cases the carbon C22 is adequately positive charged, so that it can accept the nuclephilic attack from one negative charged nitrogen. The evaluation of the formal charge distribution of the two putative nitrogen atoms always reveals the amine N14 more negative than the oxime N13.

In order to better display the charge distribution around the considered conformations (**2'a'**) and (**2'a''**) we have also performed the AM1 potential surface density calculation clustering in five colors the corresponding electrostatic values (Figure 1).

Also graphically it is worth to note that only in the conformation (**2'a'**) we can appreciate a better complementarily between the positive density surface corresponding to the C22 and the negative one of the N14.

EXPERIMENTAL

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 spectrophotometer on potassium bromide mulls. ^{1}H-NMR and ^{13}C-NMR spectra were performed on a Brüker 200 MHz apparatus and the chemical shifts (δ) referred to tetramethylsilane. Microanalyses were taken on a Carlo Erba 1106 Analyser. MS spectra were recorded with a QMD 1000 instrument (Fisons instruments) at 70 eV using a direct inlet system. Reagent-grade commercially available reagents and solvents were used. All solvents were rigorously dried before use according to standard methods. [9]



	MMFF	AM1 EF 2'a'	AM1 MU 2'a'	AM1 EF 2'a"	AM1 MU 2'a"	STO3G* EF 2'a'	STO3G* MU 2'a'	STO3G* EF 2'a"	STO3G* MU 2'a"
N13	-0,513	-0,464	-0,139	-0,409	-0,131	-0,384	-0,182	-0,404	-0,178
N14	-0,850	-0,971	-0,351	-0,890	-0,335	-0,849	-0,393	-0,810	-0,402
C22	0,422	0,848	0,325	0,843	0,334	0,748	0,283	0,722	0,296

Table 1: 2'a Formal charge comparison on the three atoms N13, N14 and C22 obtained with MMFF (unique conformation) and with AM1 and STO 3G* on the conformation (**2'a'**) and (**2'a''**) using the Electrostatic Fit (EF) and the Mulliken (MU) variation.

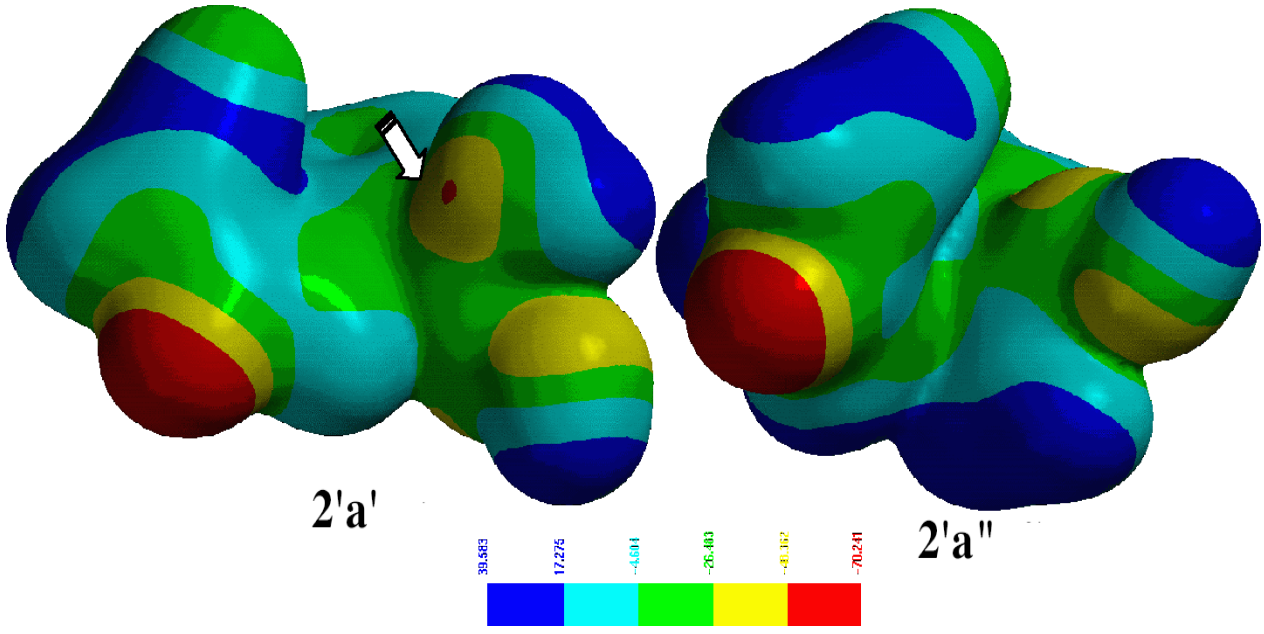


Figure 1: Electrostatic potential surface computed with AM1 on the energy minimised conformer (**2'a'**) and (**2'a''**). The spectrum of five colors red, yellow, green, turquoise and blue respectively indicates most negative, partial negative, neutral, partial positive and most positive density surfaces. The arrow indicates a remarkable negative red surface onto the amine N14 not present on the conformation (**2'a''**) onto the oxime N13.

Preparation of 4-hydroxyimino-3-carboxamide-2-quinolone (**3**)

C_3O_2 (**1**) (2.5 mL, 36 mmol), measured at –75 °C, were added at rt under stirring, to a solution of the oxime (**2**)[10] (5.44 g, 36 mmol) in anhydrous acetone (500 mL) (the water content, detected with KF analysis, was 13-18 ppm). The mixture was kept under stirring at rt for 72 h and the resulting solution was evaporated under reduced pressure to yield a crude residue. The latter was purified from acetone to give **3** (7.34 g, 93%), mp 210-212 °C; IR, ν_{max}: 3580-3200, 1690, 1640, 1628; ^{1}H NMR (DMSO-d_6): δ 10.75 (s, 1H, OH, D_2O exch.), 8.33-8.29 (d, J= 3.34 Hz, 1H, NH) , 7.53-7.19 (m, 6H, Ar-H + NH_2 D_2O exch.), 3.80 (s, 1H, CH); ^{13}C NMR: δ 167.85 (C), 163.85 (C), 156.20 (C), 136.26 (C), 130.68 (CH), 128.90 (CH), 123.55 (CH), 121.27 (CH), 120.80 (C), 41.3 (CH); m/z=219 (M^+, 11%). Anal. Calcd for $C_{10}H_9N_3O_3$: C 54.80; H, 4.14; N,19.16. Found: C, 54.72; H, 4.10; N, 19.20.

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