



## 'Interrupted' diazotization of 3-aminoindoles and 3-aminopyrroles



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### ABSTRACT

'Interrupted' diazotization of 3-aminoindoles and 3-aminopyrroles, achieved by quenching with cold water immediately after the addition of nitrite, led, in good yields, to stable compounds whose structures were identified to be the diazonium species with nitrate as the counter ion, which show no saline character.

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### 1. Introduction

3-Diazoindoles were first reported in the first decade of the last century by diazotization of the corresponding 3-aminoindoles with sodium nitrite in acetic acid and subsequent neutralization with sodium carbonate performed after several hours and at low temperatures. The yields at that time were quite low.<sup>1</sup>

In 1938, in an attempt to optimize the yield of 3-diazo-2-phenylindole **2** by diazotization of the corresponding 3-aminoindole **1**, Capuano, immediately after the addition of the nitrite, 'interrupted' the reaction by adding cold water and extracting with ether. Slow evaporation of the ethereal solution allowed the isolation of a crystalline compound having gross formula C<sub>14</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>, corresponding to the addition of N<sub>2</sub>O<sub>3</sub> to the aminoindole. It showed no saline character, and in the solid state sheltered from the light proved to be indefinitely stable, but slowly decomposed in acetic acid to give 3-diazo-2-phenylindole and nitrous acid (Scheme 1).<sup>2</sup>

Capuano stated that 'the new compound is an intermediate between the starting amino compound and the final diazo derivative' but he did not propose any structure. For this compound, many years later, the structure was tentatively suggested to be **3** (Fig. 1).<sup>3</sup>

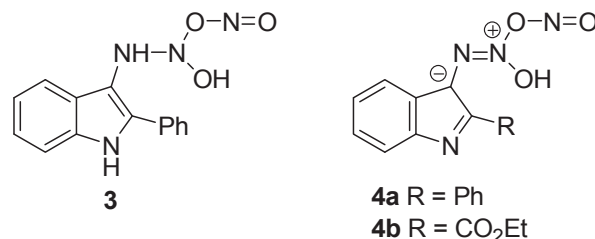
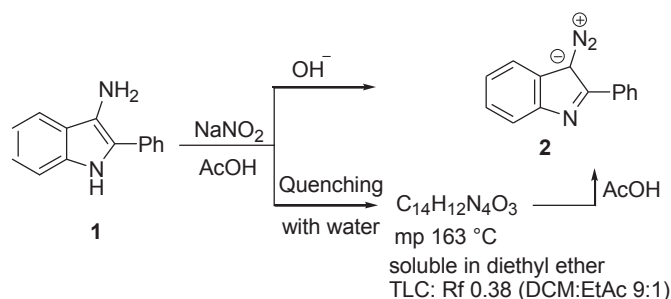


Fig. 1. Proposed structures of compounds obtained from 'interrupted' diazotization.

Recently, we decided to carry out the same reaction, as described, because of our interest in the reactivity and synthesis of diazo pyrroles and indoles as key intermediates in the synthesis of antineoplastic agents.<sup>4–16</sup>

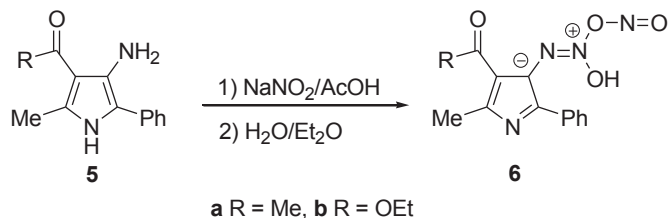
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From the reaction, we isolated a compound having the same mp and identical chemical behavior described by Capuano. However, the elemental analysis was compatible with a gross formula of  $C_{14}H_{10}N_4O_3$  that has two hydrogen atoms fewer than the structure proposed earlier.

## 2. Results and discussion

The IR spectrum exhibited a very broad absorption band centered at  $2925\text{ cm}^{-1}$  typical of an NH or OH heavily involved in hydrogen bonding and a strong absorption at  $2171\text{ cm}^{-1}$  attributable to a diazo like group. The  $^{13}\text{C}$  NMR spectrum showed a pattern compatible with a 3H-indole structure typical of 3-diazoindoles.<sup>17</sup> In fact, the C-3 carbon signal was found at  $79.5\text{ ppm}$  while the C-2 and C7a carbons were found at  $155.9$  and  $135.4\text{ ppm}$ , respectively.

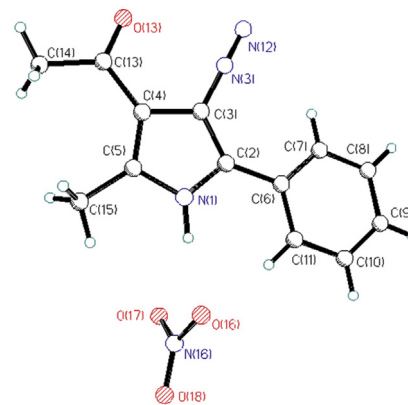
Due to the above-described evidence we assigned to the compound the structure **4a** (R=Ph). Next, we tried to generalize this sort of reaction, and it was found that 3-amino-2-ethoxycarbonylindole under the same conditions afforded a compound, with similar chemical behavior and spectral data, to which the structure **4b** (R=CO<sub>2</sub>Et) was assigned. Also for this compound the  $^{13}\text{C}$  NMR showed signals compatible with a 3H-indole structure having the C-3 carbon at  $73.0\text{ ppm}$  and C-2 and C-7a carbons at  $148.6$  and  $145.6\text{ ppm}$ , respectively. However, on the basis of the experimental evidence described below, such structures were found to be incorrect.



The ‘interrupted’ diazotization of related 3-aminopyrroles **5** furnished compounds analogous to those obtained in indole series, to whom was initially assigned the incorrect structures **6**. Such compounds showed, in the IR spectra, a broad absorption centered at  $2643\text{ cm}^{-1}$  and a diazo like band at  $2197\text{--}2212\text{ cm}^{-1}$ . The  $^{13}\text{C}$  NMR spectra showed the C-3 carbon at  $85.8\text{--}86.0\text{ ppm}$ , the C-2 carbon at  $139.7\text{--}141.0\text{ ppm}$ , while C-4 and C-5 carbons were found at  $110.6\text{--}120.4\text{ ppm}$  and  $150.7\text{--}150.8\text{ ppm}$ , respectively. Such pattern is in agreement with a 3H-pyrrole structure similar to that of 3-diazopyrroles.<sup>18</sup>

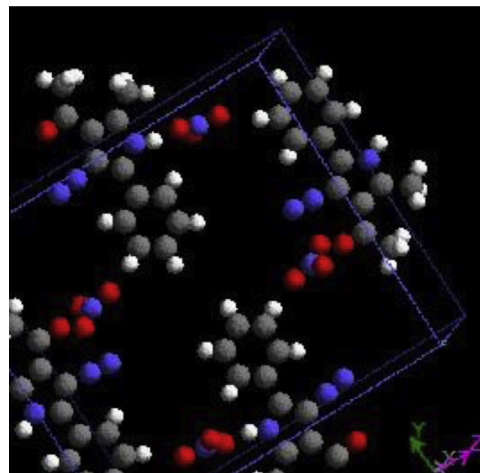
Compound **6a**, obtained from 4-acetyl-3-amino-5-methyl-2-phenylpyrrole (**5a**), gave crystals suitable to perform a single crystal X-ray analysis.<sup>19</sup> Unexpectedly, the ORTEP representation gave the structure in which a diazonium cation was present with a nitrate as counter ion, therefore a 1H-pyrrole structure.

This structure was in complete disagreement with the chemical behavior we observed and the IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral data. However, a careful investigation of the bond distances revealed them compatible with a certain character of 3H-like pyrrole structure.<sup>3</sup> In fact C(2)–N(1) distance is shorter than the C(5)–N(1) distance [ $1.352(3)$  and  $1.375(3)\text{ Å}$ , respectively] and C(4)–C(5) distance was shorter than C(2)–C(3) [ $1.366(3)$  and  $1.381(3)\text{ Å}$ , respectively]. The C(3)–N(3) distance is  $1.353(3)\text{ Å}$  resulting intermediate between a single and a double bond and shorter than the corresponding average C–N bond length [ $1.40(2)\text{ Å}$ ] of aromatic diazonium compounds but close to the values in aliphatic diazo compounds ( $1.32\text{ Å}$  in diazomethane).



ORTEP representation for **6a**

The N–N distance of the diazonium group is  $1.101(3)\text{ Å}$ , which is close to the N–N distance of diazo group in diazomethane ( $1.113\text{ Å}$ ) suggesting a ‘carbanionic’ character of the sequence C(3)–N(3)–N(12) bearing a negative charge on the carbon and a positive charge on N(3). Analysis of the crystal lattice showed that the distance between the terminal nitrogen of the diazo group and the closest oxygen of the nitrate (N(12) and O(17), respectively, according to the ORTEP numbering) is compatible with an interaction ( $1.17\text{ Å}$ ) and the distance between the immonium proton N(1)H and either of the oxygens of another nitrate ion is too long to justify a bonding interaction ( $1.99\text{ Å}$ ). Moreover, ab initio calculations for compound **6a**, performed by Hartree–Fock method at 6-311G level by starting from PM3 preoptimized geometries, and using as an input the X-ray coordinates or the same constitution optimized at first by molecular mechanics and then defining a distance of  $2.0\text{ Å}$  between N(12) and O(17), confirmed an interatomic distance of  $1.41\text{ Å}$ .



Crystal lattice for **6a**

These results prompted us to take  $^{15}\text{N}$  NMR spectra of compounds **2** and **4** (R=Ph) labeled selectively with  $^{15}\text{N}$  in the side chain. Thus, we prepared compound **1** labeled in the amino group by nitrosation of 2-phenylindole with 10%  $^{15}\text{N}$  labeled sodium nitrite and subsequent catalytic reduction of the nitroso group. The putative product of the interrupted diazotization **4a** labeled at the side chain in all three nitrogen atoms or in the N-2 and N-3 by  $^{15}\text{N}$  was obtained by performing the interrupted diazotization on the labeled or non labeled 3-amino-2-phenylindole **1**.

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