Nenitzescu Indole Synthesis: 1929-2019 Unexpected Formation of a Pyrrole-Azepine Hybrid in the Nenitzescu Indole Synthesis: A Reinvestigation

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Abstract. The condensation of 1,4-benzoquinones with enamines reported ninety years ago is a name reaction known as the Nenitzescu indole synthesis which has proved to be a very useful method for obtaining both 5-hydroxyindoles and nonindole derivatives. An unexpected compound containing two condensed azepine rings was isolated in 1988 from the reaction between 1,4-benzoquinone and ethyl 3-aminocinnamate performed in 1-butanol. The reinvestigation of the proposed bisazepine structure by X-ray analysis revealed instead a pyrrole-azepine hybrid having the two heterocycles rings connected by a double bond.

Keywords: Nenitzescu 5-hydroxyindole synthesis, X-ray diffraction, pyrrole, azepine

1.Introduction

Nenitzescu 5-hydroxyindole synthesis from 1,4-benzoquinones and enamines was reported as early as 1929 and proved to be the most useful synthetic procedure for the synthesis of the 5-hydroxyindole framework [1-10]. Developments in the synthetic aspects, mechanism and applications of the Nenitzescu indole synthesis have been reviewed over time in the reports dedicated to this reaction or included in reviews having as subject 'indole' [3-10]. The 5-hydroxyindole core is widely distributed among natural compounds such as 5-hydroxytryptophan, the neurotransmitter serotonin, the hormone melatonin, melatonin pigments, marine alkaloids, the alkaloid bufotenin which is present in plants, mushrooms and in the skin of some toad species. Also, many synthetic 5-hydroxyindoles resulting from the Nenitzescu process and their chemical transformation products have been found to possess antitumor, antimicrobial, antibacterial and anti-inflammatory activities [8,9]. For example, indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid] is a non-steroidal anti-inflammatory drug (NSAID) which was marketed for human use in 1963. The high pharmaceutical potency of natural and synthetic compounds containing a 5-hydroxyindole moiety stimulated new explorations in the field of the Nenitzescu reaction [8-12].

The original Nenitzescu 5-hydroxyindole synthesis is shown in Scheme 1 and is represented by condensation between 1,4-benzoquinone **1** and ethyl β-aminocrotonate **2** to afford ethyl 2-methyl-5-hydroxyindole-3-carboxylate **3** [1]. Performing the reaction under reflux in acetone has resulted in a 46% yield of the indole derivative **3**. Even though the yields are low and only a few methods are known for obtaining 5-hydroxyindoles, the Nenitzescu reaction remains the method of choice due to its experimental simplicity, accessibility and the large variety of possible starting materials.
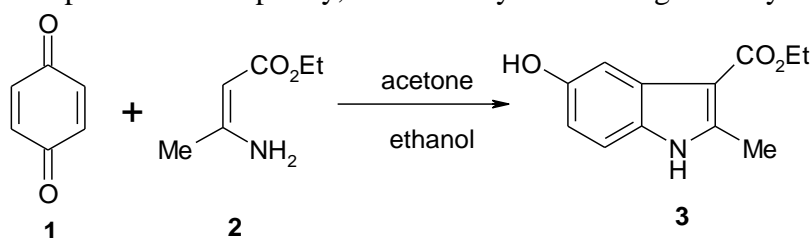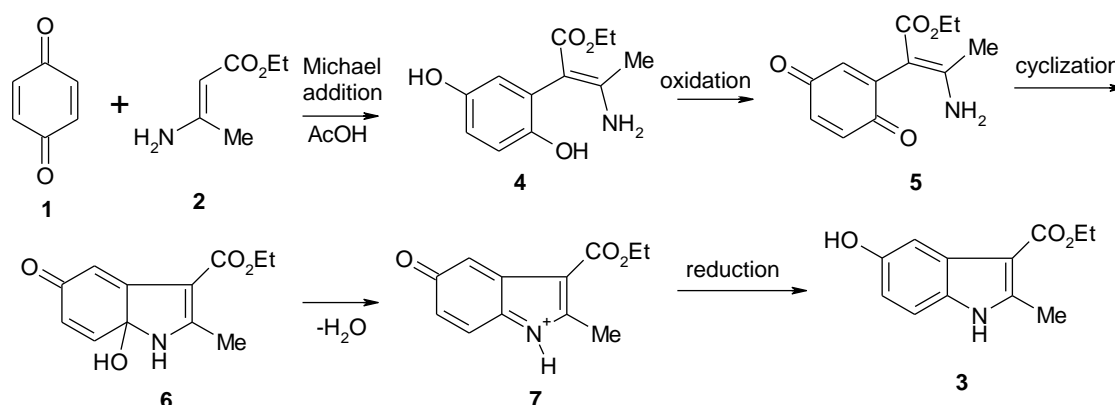

Scheme 1. Nenitzescu 5-hydroxyindole synthesis

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The extension of the Nenitzescu reaction by varying the structure of the quinone and/or the enamine has also proved to be a fruitful synthetic procedure for compounds incorporating the 5-hydroxyindole moiety, such as pyrido[2,3-b]indoles [13], benzocarbazoles [14,15], furo[3,2-h]indoles, furo[2,3-g]indoles [16], dihydrobenzo[g]indoles [17], benzo[g]isoquinoline[18], pyrrolo[2,3-h] quinolines [19], benzofuro[3,2-c]carbazol[20] and others.

The reaction mechanism for the formation of 5-hydroxyindoles is complex and the role of intermediate **4** (Scheme 2) in the formation of 5-hydroxyindoles was proposed by its discoverer in 1929 and confirmed initially on the basis of experiments performed by Raileanu and Nenitzescu in 1965 [2] and then in 1971 [3]. A similar mechanism was proposed by Allen in 1966 [21] and substantiated by evidence emanating from further research studies made in this field [21-27]. The generally accepted mechanism for the formation of 5-hydroxyindoles, the so-called Nenitzescu-Allen mechanism, includes, in the first step, the Michael addition of the enamine **2** to the C=C bond of 1,4-benzoquinone **1**. The oxidation of hydroquinone derivative **4** leads to the corresponding quinone **5** which undergoes cyclization to carbinolamine **6** followed by elimination of water to form cycloimmonium salts **7**. Under the reaction conditions, the intermediate **7** undergoes reduction to give the 5-hydroxyindole derivative **3**. The enaminohydroquinone derivative **4**, the so-called Michael adduct, was isolated in a few cases and transformed into the corresponding indole only under special reaction conditions.

Scheme 2. The Nenitzescu reaction mechanism

Although the condensation between 1,4-benzoquinones and enamines is known as the Nenitzescu 5-hydroxyindole synthesis, the process is more complex and intermediates of hydroquinones analogous to **4**, quinones **5** and carbinolamines **6** were isolated in many cases and under special reaction conditions were transformed into the corresponding 5-hydroxyindoles [3]. An important feature of the Nenitzescu reaction is the acquisition of 6-hydroxyindoles, 4,5-dihydroxyindoles and more frequently 5-hydroxybenzofurans and condensed 5-hydroxybenzofurans as final reaction products. As a consequence, this name reaction was also extended to instances when nonindolic heterocyclic systems were obtained, particularly to benzofuran derivatives. The formation of compounds with unexpected structures has also been observed with benzoquinones and enamines under Nenitzescu reaction conditions [13,28,29]. From the Nenitzescu reaction between ethyl 3-aminocinnamate and 1,4-benzoquinone in 1-butanol, Raileanu and Palaghita [28] isolated in 20% yield a yellow compound which was proposed as having the unexpected diazaheptalene structure **8** (see below) on the basis of elemental analysis, IR and NMR spectroscopy. To our knowledge the formation of compounds with a bisazepine ring from enamines and quinones had not previously been reported under the Nenitzescu reaction conditions. Here we report the reinvestigation by X-ray analysis of the compound isolated from the interaction of ethyl 3-aminocinnamate with 1,4-benzoquinone in 1-butanol, previously proposed as having the structure **8**. As discussed below, the X-ray analysis established that the structure of the product is instead a pyrrole-azepine hybrid.
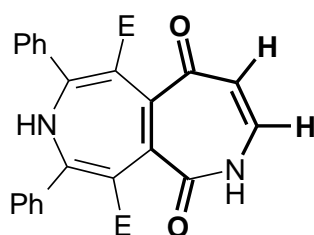
8: Proposed structure 1988

2.Materials and methods

The yellow compound with the proposed structure **8** was obtained by the procedure described by Raileanu and Palaghita [28]. It was purified by crystallization from methanol and the analytical data from IR spectra, NMR spectra and elemental analysis matched those reported in the literature [28].

NMR spectra were recorded on a Varian Gemini 300BB spectrometer at 300 MHz for H-NMR and 75 MHz for C-NMR.

The single crystal used for X-ray diffraction analysis was obtained by crystallization of the yellow compound from methanol. Intensity data were collected on a Nonius Kappa CCD four-circle diffractometer using graphite-monochromated MoKα-radiation (λ = 0.71073 Å) with the crystal maintained at 113(2) K with a nitrogen cryostream cooler (Oxford Cryosystems, UK). Data-reduction included Lorentz-polarization corrections but absorption for the small crystal specimen was negligible. The structure was solved using direct methods. Following location of C, N and O atoms and their refinement by full-matrix least-squares with isotropic displacement parameters, they were refined anisotropically. All H atoms were subsequently located in difference Fourier syntheses and were added to the model in idealized positions with isotropic displacement parameters (U_{iso}) in the range 1.2-1.5 those of their parent atoms. A summary of the salient data is as follows:

Formula: $C_{28}H_{24}N_2O_6$, M = 484.49 g mol^{-1}, crystal dimensions 0.120 × 0.080 × 0.030 mm^3, μ(MoKα) = 0.093 mm^{-1}, Lp-corrections applied, space group $P2_1/c$ (No. 14), V = 2450.64(14) Å^3, Z = 4, D_c = 1.313 g/cm^3, F_{000} = 1016, $2\theta_{max}$ = 51.4°, 8995 reflections collected, 4629 unique (R_{int} = 0.0663). Final $GooF$ = 0.934, $R1$ = 0.0470, $wR2$ = 0.0899, R indices based on 2481 reflections with $I > 2\sigma(I)$ (refinement on F^2), 327 parameters, zero restraints. Full details of the data-collection, crystal data and programs employed in the analysis are listed in the CIF file which has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1950826). It can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.ca.ac.uk).

3.Results and discussions

The structure of compounds resulting from the condensation between 1,4-benzoquinones and enamines is strongly influenced by the solvent nature, which is well exemplified (Scheme 3) by Raileanu and Nenitzescu [2,28]. When the interaction between *p*-benzoquinone and ethyl 3-aminocinnamate was performed in acetic acid the reaction led to the expected ethyl 2-pheny-5-hydroxyindole-3-carboxylate **9** in 46% yield [2]. When the synthesis was performed in acetone, chloroform or dichloromethane, formation of the indole **9** was unsuccessful (Scheme 3). The condensation of *p*-benzoquinone with ethyl 3-aminocinnamate in benzene or chloroform at room temperature or under reflux gives enamine hydroquinone **10** in 25 % yield. It should be mentioned that the formation of hydroquinone derivative **10** is accompanied by quinone **11** (ca. 3.5 %) and hydroquinone. Heating compound **10** in acetic acid in the presence of a catalytic amount of quinone affords the indole **9**. Based on these transformations and others results described in the literature, Raileanu and Nenitzescu elaborated in 1965 the mechanism for the formation of 5-hydroxyindoles. A

year later a similar mechanism was proposed by Allen Jr. [21]. Continuing their research on the interaction between *p*-benzoquinone and ethyl 3-aminocinnamate, Raileanu and Palaghita[28] performed this reaction in 1-butanol under reflux. From the reaction mixture 4-enamino-5-hydroxyindole **12** and a yellow compound were isolated. Based on IR and NMR spectroscopy the structure of the yellow compound was assigned as the 2,8-diazaheptalenedione derivative **8**. The formation of an azepine structure under the conditions of the Nenitzescu synthesis has not been reported in literature, except in the work of Raileanu and Palaghita[28].
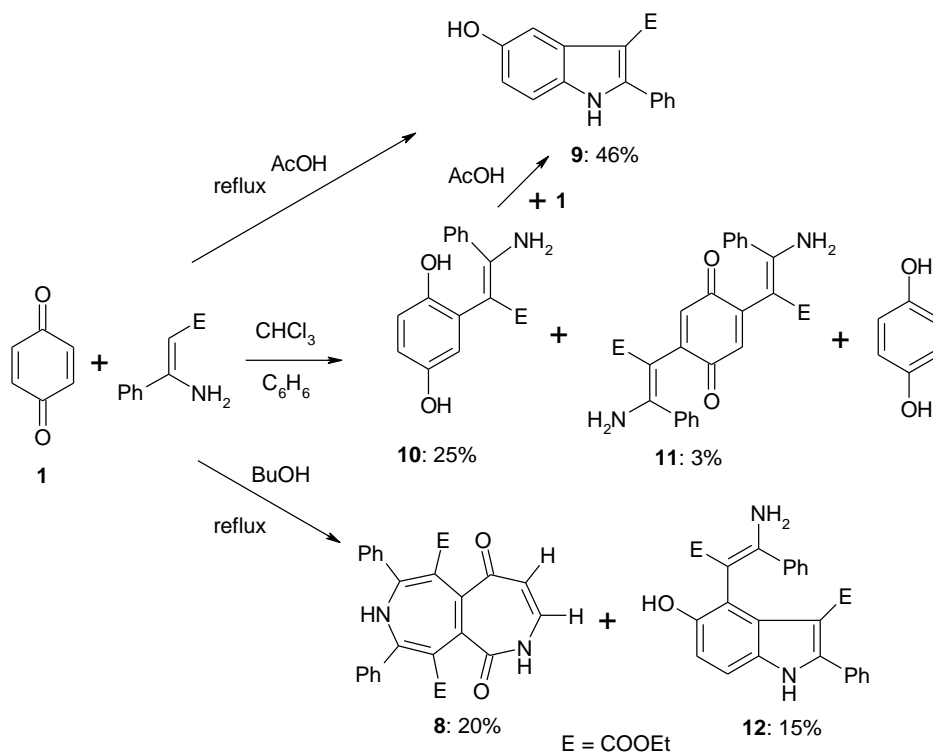
Scheme 3. The influence of the solvent nature in the Nenitzescu reaction [2,28]

From the H-NMR spectrum of the proposed condensed bisazepine derivative **8** it was reported that for one of the two ester groups the methylenic protons are magnetically non-equivalent. The phenomenon was explained [28] as being due to the steric hindrance of one of the two phenyl groups. Usually, the non-equivalence of methylene protons is due to hindered rotation about a double bond or when protons are placed in a chiral environment (chiral solvent, central chirality, axial chirality, elicoidal chirality)[30-33]. In order to identify the source of magnetic non-equivalence for the methylenic protons we reinvestigated the structure of the yellow compound by X-ray diffraction, which was found to correspond to **13** (Figure 1).
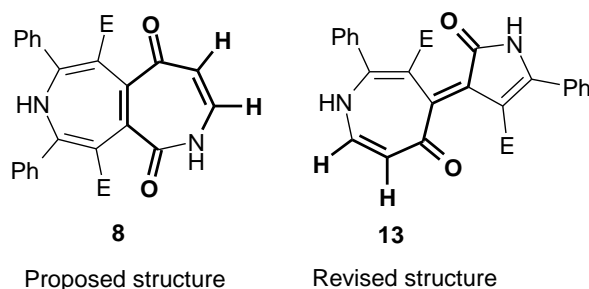

Figure 1. Proposed **8** and revised structure **13** of the
by-product in the Nenitzescu reaction

The molecular structure of the yellow product **13** determined by X-ray analysis is shown in Figure 2 and the feature of primary interest, owing to its rare occurrence in the context of this report, is the presence of the pyrrole and azepine rings linked by the double bond C5=C20 (1.349(3) Å). Consequently, the six atoms C4-C5-C6 (azepine ring) and C21-C20-C24 (pyrrole ring) are coplanar with a root-mean-square deviation of only 0.041 Å. Several crystal structures found in the Cambridge Crystallographic Database (CSD)[34] feature linked azepine and pyrrole rings but in these cases the individual rings are generally fused with other ring systems. Figure 2 also shows the boat-like conformation of the 7-membered ring in **13**, with the locations of the double bonds. A search in the CSD for structures containing the azepine ring with the same double-bond arrangement revealed that e.g. *cis-* and *trans*-dimethyl 4-benzyl-2,5,7-trimethyl-4,5-dihydro-azepine-3,6-dicarboxylate also display boat-like conformations and endocyclic bond lengths and angles that are similar to those found in **13**.

Regarding the above-mentioned magnetic non-equivalence of the methylene protons of one of the two ester groups in the H-NMR spectrum of **13**, a detailed examination of pertinent intra- and intermolecular distances derived from the X-ray model (Figure 2) provides a rationale for this observation. The intramolecular distances O33···H35A and O33···H35B are quite distinct, namely 2.48 Å and 2.90 Å respectively, while for the methylene group at C18, the two corresponding O16···H distances are very similar (2.63 and 2.70 Å). Further asymmetry, consistent with the observed magnetic non-equivalence, is indicated when pertinent intermolecular interactions are considered; thus, it is also observed that one of the H atoms of the methylene group on C35 engages in an intermolecular C-H···O hydrogen bond [C35-H35A···O25[a] (a = 1-x,-1/2+y,1/2-z)] with H···O 2.53 Å and C···O 3.448(3) Å, while the other (H35B) is not involved in such hydrogen bonding. Instead, for the two methylene H atoms on C18, neither is engaged in C-H···O H-bonding.

The crystal structure of **13** features a complex network of hydrogen bonds based on two unique classical bonds involving N-H donors and carbonyl oxygen atom acceptors, namely N1-H···O8[b] (b = x,1/2-y,1/2+z) with N···O = 2.710(3) Å, and N22-H(22) ···O33[c] (c = 1-x,1/2+y,1/2-z) with N···O = 2.918(2) Å. Both carbonyl oxygen atoms O16 and O25 engage in C-H···O hydrogen bonds (C···O distance range 3.248(3) - 3.448(3) Å) which contribute to the crystal cohesion.
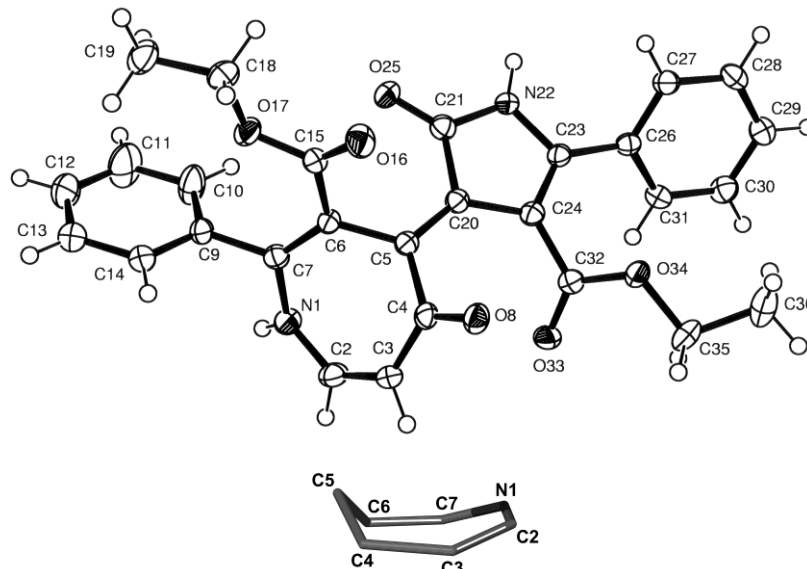
Figure 2. The molecular structure of the yellow compound **13** with non-hydrogen atoms drawn as thermal ellipsoids at the 50% probability level (top) and a perspective view of the boat-like conformation of the azepine ring showing the two endocyclic double bonds (bottom). Bond lengths in the 7-membered ring are: N1-C2 1.360(3), C2-C3 1.345(3), C3-C4 1.426(3), C4-C5 1.497(3), C5-C6 1.486(3), C6-C7 1.351(3), C7-N1 1.395(3) Å.

4.Conclusions

The originally proposed structure (**8**) of the yellow compound resulting from the Nenitzescu reaction between *p*-benzoquinone and ethyl 3-aminocinnamate in 1-butanol was revised based on its analysis by X-ray diffraction. The latter showed unequivocally that the molecule has the structure **13**, in which a pyrrole ring and an azepine ring are connected by a C=C double bond. To our knowledge this is the first example in which this structural arrangement has been reported to emanate from the Nenitzescu synthesis. In addition, ring-opening of the 1,4-benzoquinone ring during the course of the Nenitzescu indole reaction has been observed for the first time.

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