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An unexpected route for the synthesis of a new spiroheterocyclic system from ninhydrin

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ABSTRACT

The reaction of ninhydrin with amines leads to the formation of Ruhemann's purple. This study presents the synthesis of Ruhemann's purple and a new benzo-fused spiroheterocyclic system by the reaction between ninhydrin and phenylethylamine. The structure was established using spectroscopic data and X-ray crystal structure analysis.

We have observed that the hydroxylation degree on the aromatic ring influences the reactivity of β-phenylethylamines to non-enolizable aldehydes. The product obtained depends on the hydroxylation degree of the original phenylethylamine ring. When the reaction is performed between dopamine and formaldehyde, the corresponding 1,2,3,4-tetrahydroisoquinoline is obtained by a Pictet–Spengler reaction; when the reaction is performed between tyramine and formaldehyde, an azacyclophane is obtained by a double aromatic Mannich reaction; and when the reaction is performed between phenylethylamine and formaldehyde, a triple amine–aldehyde condensation leads to the corresponding hexahydro-1,3,5-triphenyl-1,3,5-triazine.[1–3]

On the other hand, ninhydrin **1** is a highly electrophilic tricarbonyl compound derived from indane. The electrophilic character is high due to the presence of three consecutive electron-withdrawing groups, the most electrophilic of which is carbon 2. The presence of three electrophilic groups makes it very interesting from a chemical perspective, and it has been the object of many studies aimed at obtaining heterocyclic compounds with great structural diversity.[4]

The reaction of ninhydrin **1** with amines usually leads to a single product known as Ruhemann's purple **2**; as a result, it is used in a variety of analytical techniques.[5–9] This reaction starts with the formation of a Schiff base, which tautomerizes and hydrolyzes to form an aldehyde and Ruhemann's purple **2** by interaction with a second molecule of ninhydrin (Scheme 1).[9]

Recent studies showed that dopamine **3** (3,4-dihydroxyphenethylamine) does not form the expected Ruhemann's purple **2** and, when reacting with ninhydrin, produces a mixture of spiro-tetrahydroisoquinoline-type **4** regioisomers by a Pictet–Spengler condensation (Scheme 2).[10]

We here extend our studies on the reactivity of phenylethylamines and describe the reaction of β-phenylethylamine with ninhydrin as a synthetic method to produce a new benzo-fused spiroheterocyclic system. The synthesis described involves a tricomponent condensation between phenylacetaldehyde generated in situ, phenylethylamine, and ninhydrin.

Our studies show that phenylethylamine **5** exposed to ninhydrin **1** does not present the usual behavior described for amines and, along with Ruhemann's purple **2**, predominantly produces a compound that is violet in solution form and colorless in the solid state **6**.[11] The analysis of ^{1}H NMR and ^{13}C NMR spectra showed a greater number of signals than those expected for the Schiff base or the corresponding tetrahydroisoquinoline. The additional signals indicate the presence of a third aromatic unit with two aliphatic carbons, most likely from a phenylacetaldehyde molecule formed in situ.

The structure of the new compound was determined by IR spectroscopic analysis, NMR (^{1}H, ^{13}C, COSY, HMQC and HMBC) and mass spectrometry (EI-MS and ESI-MS). In the HMBC experiment, we obtained key data that assisted in determining the structure,

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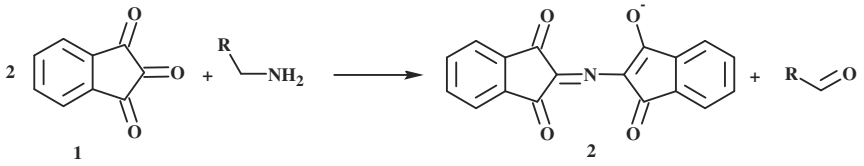
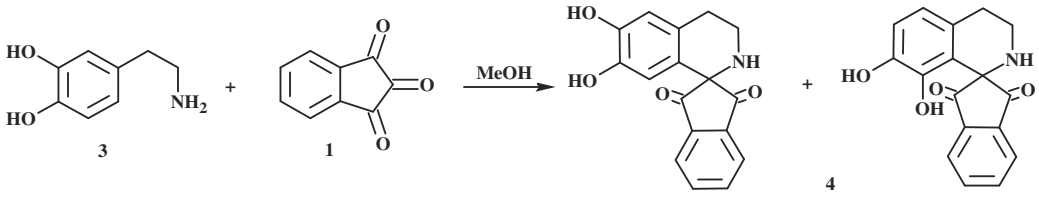


Scheme 1. Ruhemann's purple formation from ninhydrin.



Scheme 2. Reaction of dopamine with ninhydrin.

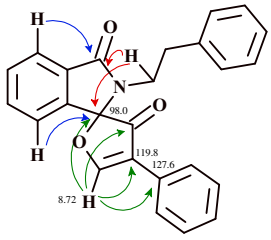


Figure 1. Selected HMBC correlations of spiro[furan-2,1′-isoindoline] **6**.

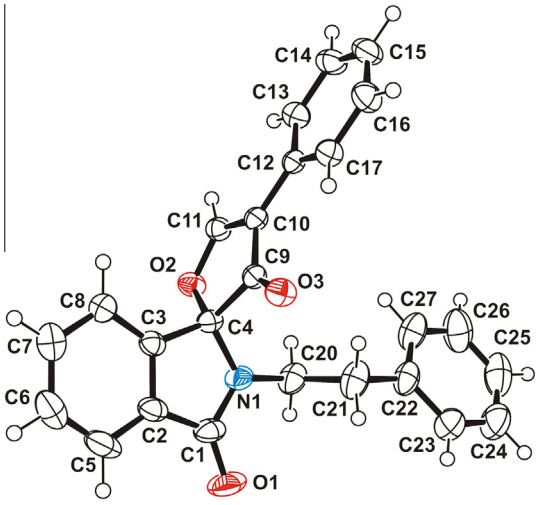
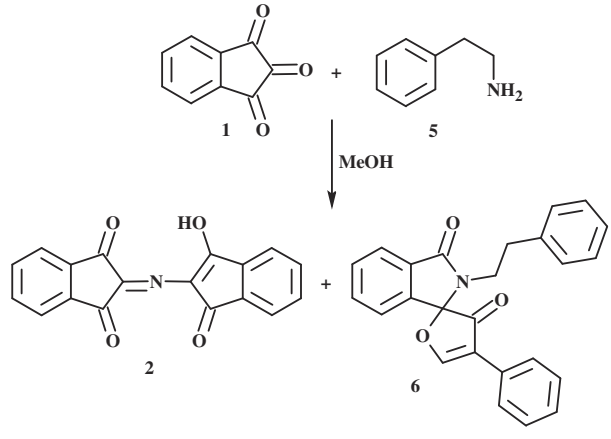


Figure 2. ORTEP diagram of one of the two crystallographically independent molecules of the spiro[furan-2,1′-isoindoline] **6**.

such as a proton at 8.72 ppm that correlates with two sp^2 carbons at 119.8 and 127.6 ppm and with a quaternary sp^3 carbon at 98.0 ppm. The sp^2 carbons were assigned to the unit from the phenylacetaldehyde, whereas the sp^3 carbon was assigned to the unit from ninhydrin. According to the correlation of the protons from the adjacent aromatic ring and the aliphatic protons from the phenylethylamine, we established that this carbon is linked to three electron-withdrawing groups (Fig. 1). The structure of this product was confirmed by X-ray crystallography (Fig. 2). The resulting compound corresponds to a spiro[furan-2,1′-isoindoline] **6** product of the three-component reaction between ninhydrin **1**, phenylethylamine **5,** and phenylacetaldehyde (Scheme 3). The distances and bond angles within the spiroheterocyclic fragment are similar to those found in the structure of 5-methyl-3*H*, 3′*H*-spiro[benzofuran-2,1′-isoindole]-3,3′-dione.[12]

Previous studies have demonstrated that the imine or enamine produced by the condensation between 1,3-dicarbonyl compounds and primary amines reacts with ninhydrin to form dihydroxyindenopyrrole hemiaminals. It was also demonstrated that the oxidative cleavage of certain dihydroxy-indenopyrroles and the subsequent hydrolysis and cyclization yield spiro[isobenzofuran-1,6′-pyrrolo[2,3-d]pyrimidine]-2′,3,4′,5′-tetraones.[13–15]

Initially, a mechanism similar to that proposed for 1,3-dicarbonilic compounds was suggested for the formation of compound **6**.[13–15] To confirm this mechanism, first, the imine was synthesized from the phenylacetaldehyde and phenylethylamine, and then, it was reacted with ninhydrin. Under these conditions, it was not possible to obtain experimental evidence of the formation of **6**, which would make it possible to propose that the formation of this spiroheterocycle follows a different mechanism. When the three-component reaction between ninhydrin **1**, phenylethylamine **3** and recently distilled phenylacetaldehyde was performed, and when ninhydrin and phenylacetaldehyde



Scheme 3. Reaction of ninhydrin with phenylethylamine.

mixture was first reacted, followed by the addition of phenylethylamine, complex mixtures were obtained and it was not possible to obtain experimental evidence of the formation of **6**. Compound **6** was obtained only when phenylacetaldehyde was generated