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2,2′-Diphenyl-$\Delta^{3,3'}$-bi-3*H*-indole-1,1′-dioxide: Competitive Demethylation and Redox Reactions

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Competitive demethylation and redox reactions induced by 2,2′-diphenyl-$\Delta^{3,3'}$-bi-3*H*-indole-1,1′-dioxide, **1** (dinitrone) on several nitrogen bearing compounds (pyridines, amides, indoles, hydrazones and amines) are reported.

(Keywords: 2,2′-Diphenyl-$\Delta^{3,3'}$-bi-3H-indole-1,1′-dioxide; Demethylation; Oxidation)

2,2′-Diphenyl-3,3′-bi-3H-indol-1,1′-dioxid: Kompetitive Demethylierung und Redoxreaktionen

Es wird über kompetitive Demethylierungen und Redoxreaktionen an stickstoffhaltigen Verbindungen (Pyridine, Amide, Indole, Hydrazone und Amine) berichtet, die durch das Dinitron 2,2′-Diphenyl-3,3′-bi-3*H*-indol-1,1′-dioxid induziert werden.

Introduction

Previous investigations demonstrated that the reaction of 2,2′-diphenyl-$\Delta^{3,3'}$-bi-3*H*-indole-1,1′-dioxide (**1**) with hydrogen donors leads to redox products (2,2′-diphenyl-$\Delta^{3,3'}$-bi-3*H*-indole, **2** and 2,2′-diphenyl-$\Delta^{3,3}$-bi-3*H*-indole-1,1′-dihydroxide, **3**) [1]. It was also shown that compound **1** is not able to form "transient" molecular associations as some similar nitrones [2–4]. On the other hand some preliminary data of demethylation reactions induced by **1** on aromatic amines or aromatic hydrocarbons (e.g. toluene and xylene) were also reported [5].

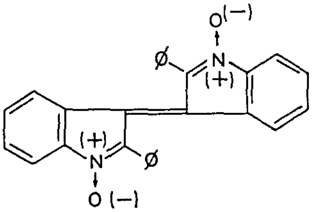
In this paper some nitrogen containing organic compounds are examined in order to prove a general behaviour of **1** in demethylation-oxidation reactions. Table 1 reports a list of these compounds and the corresponding reaction products.

Results and Discussion

In the reaction of isomeric picolines (see analogy with toluene and xylene reactivity [5]) with **1** the position of the methyl group in the pyridine ring is important. Redox products are obtained in acceptable yields. Compounds **2** and **3** (as reduction products), are obtained in the case of 2-picoline, together with pyridine aldehyde and carboxy pyridine (as oxidation products). The presence of pyridine (as demethylation product) is easily verified.

3-picoline undergoes almost complete redox reaction giving **2** and nicotinic acid. In all cases no hydroxymethylpyridines are recovered. Literature reports show that pyridone derivatives are always present in the demethylation reaction of picolines catalyzed by organic (penthylnitrite-sodium methoxide [6]) or inorganic (selenium dioxide [7], vanadium pentoxide [8], copper sulfate [9]) compounds at high temperatures (300–400 °C). In all cases the reactions are not selective.

No report can be found on the demethylation-oxidation reaction of dimethylaminopyridines. **1** gives with 4-dimethylaminopyridines almost quantitatively compound **2** and 4-methylaminopyridine, whereas N,N-dimethylaniline with **1** forms N-methyl,N-hydroxyaniline together with N-methylaniline [5]. Some aniline derivatives give quinolines, via dealkylation-cyclization reaction in the presence of concentrated sulfuric acid [10]; N-demethylation of 3-phenyl-1-methylurea [11] and catalytic decomposition of diazonium chlorides from substituted benzanilines [12], provide some examples of amide dealkylation.



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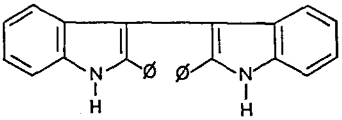

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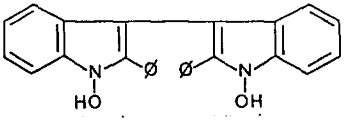

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In our case, reactions of **1** with N,N-dimethylformamide, N,N-dimethylacetamide or tetramethylurea leads to demethylated derivatives. In the case of tetramethylurea, a mixture of reaction products was obtained. Neither reaction nor molecular association were observed in the reaction of **1** with non-isomerizable phenylhydrazones. On the other hand, isomerizable phenylhydrazones are quantitatively dehydrogenated by **1**, with formation of the corresponding phenylazoalkenes [5].

The use of inorganic catalysts such as $AlCl_3$ [13], Ni/Al_2O_3 [14] for ring demethylation and KOH [15] for N-demethylation in the indole ring is reported in the literature. With nitrone **1**, N-demethylation of N-methyl-2-phenylindole (leading to 2-phenylindole), surprisingly succeeds only in the presence of benzene as solvent. Experiments on other substrates are in progress in order to achieve a better understanding on the reaction mechanism that may be a hydrogen extraction or an electron transfer process.

Although the literature contains many reports on the demethylation reaction of aromatic amines [16], the use of **1** for the above substrates may furnish an alternative tool for alkyl group abstraction.

Experimental

2,2'-Diphenyl-$\Delta^{3,3'}$-bi-indole-1,1'-dioxide (**1**) was obtained according to *Colonna* [17]. Benzaldehyde and Benzophenonemethylphenylhydrazone were prepared according to Ref. [18]. All compounds and solvents were Fluka RP-ACS grade reagents and purified before use. High Pressure Liquid Chromatography was performed with a Perkin-Elmer HPLC s.3 instrument using CH_3CN/H_2O (65/35 ratio) as solvent, a C18 SIL-X-10 column (flow rate of 1.5 ml/min and $\lambda = 254$ mm).

Reaction of Picolines with Dinitrone 1

The isomeric picolines and **1** (ratio 5/1) were mixed and warmed at 140 °C for 14 h under a nitrogen stream. During this times gaseous reaction products were trapped through absorption in cold water. The only gaseous compound obtained, as indicated in Table 1, was formaldehyde as evidenced by appropriate tests (*Tollens* and Resorcinol reagents).

The reaction mixture was cooled at room temperature and treated with hot benzene: the undissolved portion was the pyridinecarboxylic acid (with some traces of dinitrone **1**) as shown by mixed melting point with reference compound and by infrared spectra.

The benzene solution was cooled and *n*-hexane added; the precipitate contained compounds **2** and **3**, the latter was present in the reaction of 2-picoline with **1**. They were separated and purified on alumina column (using benzene as solvent).

Quantitative HPLC analysis of a small portion of the mother liquors allowed the identification of all the reaction products. The remaining portion of the solution was evaporated to dryness, dissolved in a small amount of boiling ethyl

Table 1

Donor	Reduction product			Demethylation—oxidation products							
	1	2	3								
2-Picoline	traces	50	20	picolinaldehyde	20	picolinic acid	5	pyridine	42	formaldehyde	+
3-Picoline	traces	88		nicotinaldehyde	18	nicotinic acid	60	pyridine	5	formaldehyde	−
4-Picoline	traces	55		isonicotinaldehyde	13	isonicotinic acid	10	pyridine	31	formaldehyde	+
4-Dimethylamino-pyridine	traces	90	traces			4-aminomethylpyr.	83			formaldehyde	+
N,N-Dimethyl-formamide	traces	45	traces			N-methylformamide	35			formaldehyde	+
N,N-Dimethyl-acetamide	traces	52	traces			N-methylacetamide	47			formaldehyde	+
Tetramethylurea	traces	37		unidentified products						formaldehyde	+
Benzaldehydemethyl-phenylhydrazone											
Benzophenonemethyl-phenylhydrazone											
N-Methyl-2-phenyl-indole	traces	traces	traces	2-phenylindole[b]						3	+[b]

[a] (+) or (−) denote presence in a few percents or absence, respectively, of the compound; the number indicates the amount (%) obtained

[b] Only in benzene as solvent

alcohol and treated with a concentrated alcoholic solution of 4-nitrophenylhydrazine. The solution after boiling for half an hour was cooled, the precipitate collected and characterized as the 4-nitrophenylhydrazone of the corresponding aldehyde through mixed melting point with an authentic sample and infrared spectra.

Reaction of 4-Dimethylaminopyridine with **1**

The reaction conditions were the same as used for the reaction of picolines with **1**. The reaction mixture, dissolved in hot benzene, was cooled ans small amounts of *n*-hexane were added: almost pure biindole **2** was collected. The solution, after quantitative HPLC measurements, was evaporated to dryness. Crude 4-aminomethylpyridine was recovered and characterized by infrared and NMR measurements.

Reaction of Amides with **1**

The reaction conditions were the same used for the reaction of picolines with **1**. Biindole **2** was isolated as in the case of 4-dimethylaminopyridine. From the benzene *n*-hexane solution, N-methylamides were characterized with HPLC, infrared and NMR techniques.

Reaction of Benzaldehyde- and Benzophenomethylphenylhydrazone with **1**

The reaction conditions were the same used for the reaction of picolines with dinitrone **1**. The mixture was disolved in small amount of hot benzene and cooled. Unchanged **1** precipitated from the solution. The filtrate was evaporated to dryness giving, after purification from benzene-*n*-hexane, the starting hydrazone.

Reaction of N-Methyl-2-phenylindole with **1** *in Benzene Solution*

N-Methyl-2-phenylindole and **1** (ratio 5/1) were dissolved in anhydrous benzene and the resulting solutions, after mixing, were refluxed for 20 h under nitrogen. After this time, the volume of solution was reduced to few ml and hexane added. **2** was recovered as a colourless solid (few percent). The solution was analyzed by HPLC: together with N-methyl-2-phenylindole, the demethylated derivative (2-phenylindole) was easily evidenced.

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