SYNTHESIS OF NEW 1-HYDROXYINDOLES FUNCTIONALIZED ON POSITION 3 BY CYCLIZING REDUCTION

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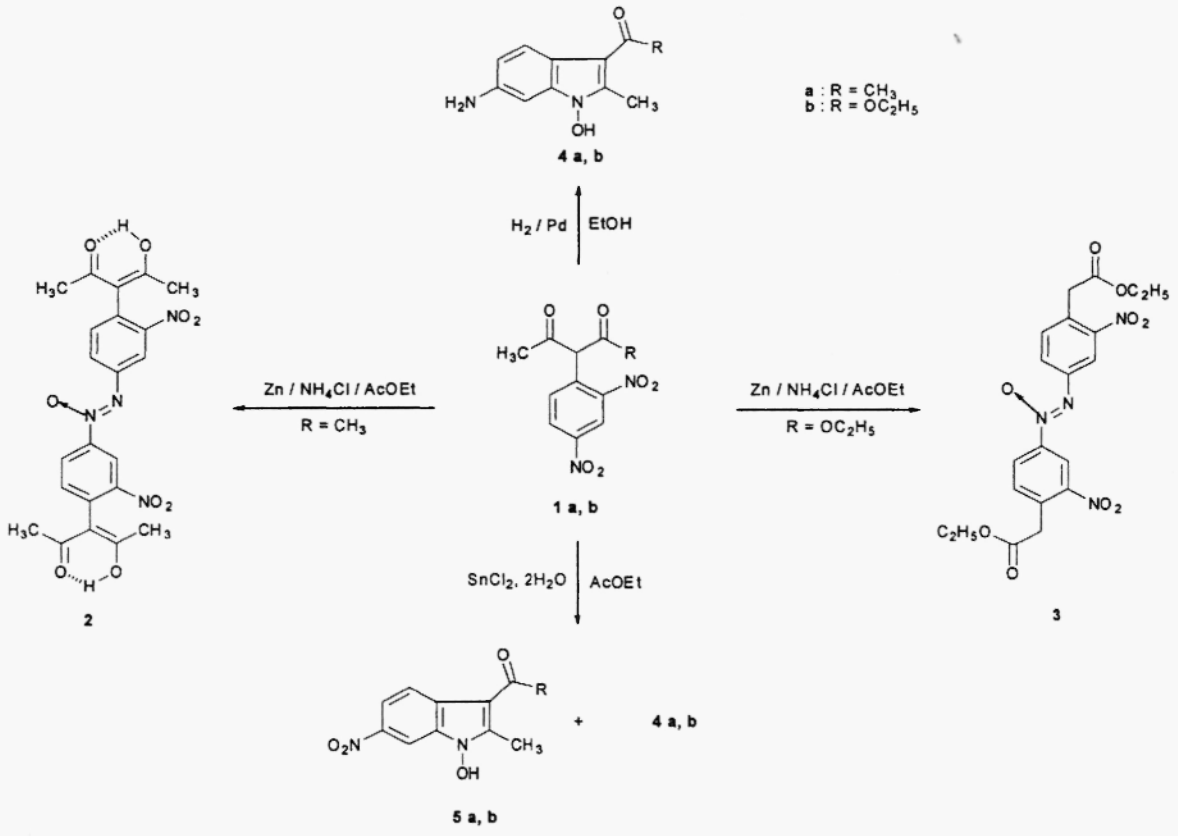
Abstract : Cyclizing reduction of α-(2',4'-dinitrophenyl) β-dicarbonyl compounds : **Ia,b** by two different ways leads to the formation of 1-hydroxyindole derivatives. The chemical way gave, in presence of tin (II) chloride dihydrate, compounds **4a,b** and **5a,b** while the catalytic way gave only compounds **5a,b** in the presence of palladium on activated carbon in ethanol.

The 1-hydroxyindoles present some interesting properties in pharmacology as well as in agrochemistry (1-3). In order to prepare new 1-hydroxyindole derivates functionalized on position 3 we have examined the reductive cyclization of α-(2',4'-dinitrophenyl) β-dicarbonyl compounds **Ia,b**. In this approach we have tried to avoid the desacylation reactions already known for that sort of compounds (4) and to orient the reaction to the obtention of the expected compounds by using adapted reducing agents.

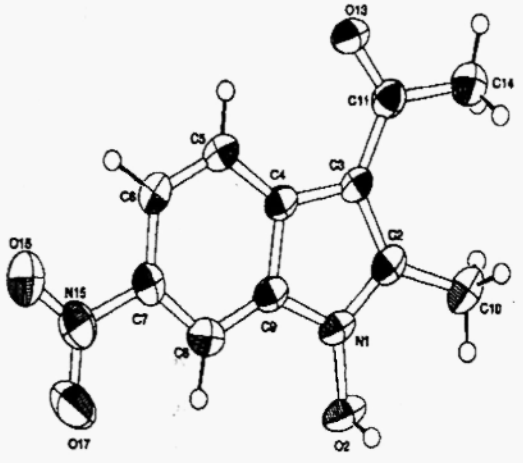
The literature concerning the synthesis of 1-hydroxyindoles is very poor. The following methods are normally used : electrochemical (5) or chemical (6-8) reduction of α-(o-nitrophenyl)ketones by zinc in the presence of ammonium chloride, the cyclization of the o-nitrobenzylidene catalyzed by a base (9) in the presence of potassium cyanide, and the oxydation of the indole derivatives, performed by perchloric acid and $FeCl_3$ (10) or by H_2O_2 in presence of sodium tungstate (11).

In our experiments we have first tried the above chemical method, but we find out that only the azoxy compounds **2, 3** can be prepared (scheme). Derivative **3** comes from a deacylation and a partial reduction reaction. Taking these results into account, we have experimented the use of respectively powdered iron in ethanol, or hydrogen in the presence of Pd / C at 10 % or $SnCl_2$ in ethyl acetate. We have obtained the 1-hydroxyindoles **4a,b** and **5a,b** weathever the quantity of the $SnCl_2$ or the duration of the hydrogenation, whereas the use iron does not allow to isolate identifiable products.



Scheme

The structure of the products has been determined by classical spectroscopic methods (^{1}H or ^{13}C NMR, MS and IR) and by the crystallographic structure of compound **5a** (12) as shown in the figure . The ^{1}H NMR spectra of compounds **2** and **3** show the presence of two ABC systems for the aromatic protons of both rings and the absence of the signal related to the acetyl group in compound **3**. The enolic form of compound **2** is clearly



Figure

indicated by the presence of two signals at about 13 ppm, each of them integrating one proton, and the absence of the signal for the proton in α of the carbonyl group.

Therefore the α-(2',4'-dinitrophenyl) β-dicarbonyl compounds we have studied here have a different behaviour than the α-(o-nitrophenyl) ketone. Some authors, working under the same experimental conditions have directly obtained N-H indole derivatives (13-18). This difference in the reactivity be due to the electronic effects created by the second nitro group in para of the benzenic ring and probably to the presence of carbonyl groups in position 3.

In conclusion, it has been possible for us to prepare new 1-hydroxyindoles derivatives functionalized on position 3, which could be used as stating material in the synthesis of several heterocyclic systems.

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EXPERIMENTAL

General

Melting points were determined on a büchi-tottoli apparatus and are incorrected. Spectra were recorded using the following instruments IR : Perkin-Elmer 577 spectrometer (KBr disks) ; ^{1}NMR : Bruker AC-250 (250 MHz) spectrometer, chemical shifts are given in δ ppm downfield from TMS internal standard ; MS (EI or DCI) Nermag R 10-10 C spectrophotometer; RX : Euraf Nonius CCD diffractometer.

Synthesis of compounds 2 and 3

A mixture of 3.8 mmol of **1a,b** , 22.8 mmol of ammonium chloride and 2 g of zinc was stirred for one day in 50 ml ethyl acetate at room temperature. The filtrate was then concentrated and purified by chromatography on silica gel.(hexane / ethyl acetate 90/10)

2 : 4,4'-di(1-acetyl-propan-2-one-yl)-3,3'-dinitro-azoxybenzene

yield : 20 %. m.p. 195°C (hexane). IR (KBr): 3650 cm^{-1} (νOH), 1600 cm^{-1} (νC=O), 1520 and 1340 cm^{-1} (νNO2). SM/FAB (m/z = 484). ^{1}H NMR ($CDCl_3$) δ ppm: 1.87 (s, 12H), 7.40-7.70 (2d, 2H), 8-8,70 (2dd, 2H), 8.80-8.92 (2d, 2H), 13.20 (s,OH), 13.24 (s,OH). 13C NMR (CDCl3) δ ppm: 24.16, 109.06, 109.67, 119.04, 121.36, 126.39, 130.1, 132.54, 134.48, 135.10, 143.53, 147.77, 150.49, 150.58.

3 : 4,4'-di (ethoxycarbonylmethyl)-3,3'-dinitro-azoxybenzene

Yield: 25 %. m.p. 130°C (hexane). IR (KBr) : 1730 cm^{-1} (νC=O), 1510 and 1340 cm^{-1} (νNO2). SM/FAB (m/z = 460). ^{1}H NMR ($CDCl_3$) δ ppm: 1.09-1.27 (t, 6H), 3.97-4.23 (q, 4H), 4.15 (s, 4H), 7.50-9 (m, 6H).

^{13}C NMR ($CDCl_3$) δ ppm: 13.95, 38.70, 60.73, 118.92, 120.74, 126.86, 130.40, 131.41, 134.20, 134.29, 134.87, 142.42, 146.54, 148.27, 169.29, 169.52.

Synthesis of compounds 4a,b

I g of compound **1a,b** and 1.1 g of Pd/C at 10 % in 50 ml of ethanol is introduced into an hydrogen reactor. The mixture is first degazed under reduced pressure and then left at normal pressure. When the reaction is finished (end of hydrogen consumption), the solution is quickly filtered under vacuum and then concentrated under reduced pressure.

4a : 3-acetyl-6-amino-1-hydroxy-2-methylindole

Yield: 80 %. m.p. 208°C (Ethanol). IR (KBr): 1637 cm^{-1} (νC=O), 3543-3408 cm^{-1} (νOH, νNH2). ^{1}H NMR (DMSO-d6) δ ppm: 2.44 (s, 3H), 2.60 (s, 3H), 5.00 (s, NH2), 6.50-6.55 (dd, 1H), 6.55-6.60 (d, 1H), 7.66-7.70 (d, 1H), 11.23 (s, OH).

^{13}C NMR ($CDCl_3$) δ ppm: 11.04, 30.68, 92.08, 108.58, 111.65, 113.25, 120.85, 134.61, 138.44, 144.59, 192.08.

4b : 6-amino-3-ethylcarbonyl-1-hydroxy-2-methylindole

Yield: 70 %. m.p. 225°C (Ethanol). IR (KBr): 1660 cm^{-1} (vC=O), 3340 cm^{-1} (vOH), 3260 cm^{-1} (vNH2). ^1H NMR (DMSO-d6) δ ppm: 1.31-1.36 (t, 3H), 2.59 (s, 3H), 4.21-4.28 (q, 2H), 4.98 (s, NH2), 6.50-7.63 (m, 3H), 11.17 (s, OH). ^{13}C NMR ($CDCl_3$) δ ppm: 14.38, 18.51, 62.56, 96.02, 101.65, 115.48, 117.42, 124.78, 138.59, 142.88, 144.68, 168.97.

Synthesis of compounds 5a,b

3.8 mmol of compound **1a,b** and 24 mmol of tin (II) chloride dihydrate were dissolved in 50 ml ethyl acetate. The mixture is then stirred for one hour and neutralized by a solution of Na_2CO_3 (1M). The products are extracted with ethyl acetate and purified by chromatography on silica gel. (hexane/ethyl acetate 80/20). The products are isolated in the following order: **5a** then **4a** (**5b** then **4b**).
The total yield is about 90 %.

***5a** : 3-acetyl-1-hydroxy-2-methyl-6-nitroindole*
Yield: 45 %. m.p. 200°C (dichloromethane). IR (KBr): 1330 and 1490 cm^{-1} (vNO2), 1650 cm^{-1} (vC=O), 3400 cm^{-1} (vOH). SM/FAB (m/z = 234).
^1H NMR (DMSO-d6) δ ppm: 2.60 (s, 3H), 2.80 (s, 3H), 8.00-8.10 (dd, 1H), 8.20-8.27 (d, 1H), 8.27-8.30 (d, 1H), 12.40 (s, OH).
^{13}C NMR ($CDCl_3$) δ ppm: 11.48, 30.61, 104.93, 109.55, 116.79, 120.89, 126.40, 131.50, 142.25, 146.41, 192.53.

***5b** : 3-ethylcarbonyl-1-hydroxy-2-methyl-6-nitroindole*
Yield: 40 %. m.p. 205°C (dichloromethane). IR (KBr): 1335 and 1505 cm^{-1} (vNO2), 1660 cm^{-1} (vC=O), 3400 cm^{-1} (vOH). SM/FAB (m/z = 264).
^1H NMR (DMSO-d6) δ ppm: 1.26-1.44 (t, 3H), 2.69 (s, 3H), 4.17-4.43 (q, 2H), 7.97-8.20 (m, 3H), 12.42 (s, OH).
^{13}C NMR ($CDCl_3$) δ ppm: 10.81, 14.29, 59.46, 99.23, 105.07, 116.63, 120.63, 126.59, 131.42, 142.28, 147.11, 163.84.

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12. Crystal data for 5a: C11 H10 N2 O4 ; chemical formula weight: 234.211; experimental crystal description: needle, yellow, crystal size max: 0.35 mm, crystal size mid: 0.15 mm, crystal size min: 0.10 mm; symmetry cell setting: monoclinic, symmetry space group name h-m: P21/c. Cell length a: 4.7039 (2) A°, cell length b: 16.2930 (10) A°, cell length c: 14.3990 A°, cell length beta: 96.547 (4)A°, cell volume: 1096.40 (5) A°3, cell formula units z: 4. Diffraction radiation type: Mo-Kα, radiation wavelength : 0.71073 A°. Cell measurement device: Enraf Nonius CCD. Experimental absorption correction: none. Diffraction reflections number: 7916, reflections number total: 2169, reflections number observed: 2058. Refinement data: refine is structure factor coefficients: F2. Refine is R factor observed 0.051, refine is wR factor observed: 0.054, refine is number reflexions 1740, refine is number parameters: 15 . Atom type scattering source: Waasmaier, D. & Kirfel, A. (1995). Acta Cryst. A 51, 416-431.
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