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Oxidation of Indoles and 1,2-Dihydro-3*H*-indol-3-ones.

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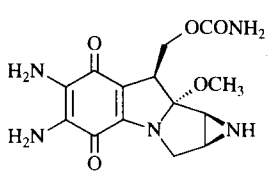
Abstract: *2-Hydroxy-1,2-dihydro-3H-indol-3-ones* ***3*** *were obtained from 1,2-dihydro-3H-indol-3-ones* ***2*** *by using various conditions (m-CPBA or sodium azide) depending on substituent in 1-position. The reactivity of hydroxyketones* ***3*** *is examined and oxidation of 1-(phenylsulfonyl)indole by m-CPBA is described.*

The oxidative metabolism of aromatic substrates in cells is an important pathway for their detoxification. In the case of indole derivatives, tryptophane-2,3-dioxygenases result mainly in C_2-C_3 scission of the pyrrole ring.[1] The oxidation of indoles leads to a number of compounds depending on the nature of substituents on the indole nucleus and more particularly on the pyrrole moiety. The nature of oxidizing agents also plays an important role during oxidation (dimethyldioxirane, peracidic compounds, Davis' reagent or others).[2-8]

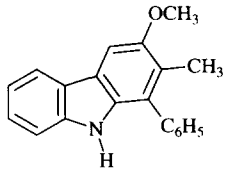
Adam *et al* have studied recently the photooxygenation of *N*-acetylindole and its reactivity with dimethyldioxirane.[9] Mechanistic aspects of the reaction of singlet oxygen with indoles have been reviewed by Foote.[3] Sakamoto *et al* carried out an extensive work on oxidation of *N*-acetylindoles; depending on the oxidizing agents and the solvent used, the nature of the products differed slightly. The use of MoO_5 / HMPA in dichloromethane afforded directly the 1-acetyl-2-hydroxy-1,2-dihydro-3*H*-indol-3-one[5] or 1-acetyl-2-methoxy-1,2-dihydro-3*H*-indol-3-one by using methanol as solvent.[10,11] Oxidative rearrangement of quinolinone with sodium dichloroisocyanurate also provided 1-acetyl-2-hydroxy-2,5-dimethylindol-3-one.[12,13]

2–Hydroxy carbonyl compounds are potential intermediates for the synthesis of various natural products.[14] Sakamoto[15,16] used 1-acetyl-2-methoxy-1,2-dihydro-3*H*-indol-3-ones as starting materials to construct a carbon-carbon bond in 3-position *via* Wittig or Horner-Wadsworth-Emmons reactions. These 2-methoxyketones were employed in a synthesis of carbazole alkaloid Hyellazole.[17] The tetracyclic framework of Mitomycin C was also formed from substituted 2-hydroxyindol-3-one.[8] (Figure 1).

Even more recently, oxazole derivatives were synthetised from 2-hydroxyketones and found to inhibit ADP-induced aggregation of human platelets[18].



Mitomycin C



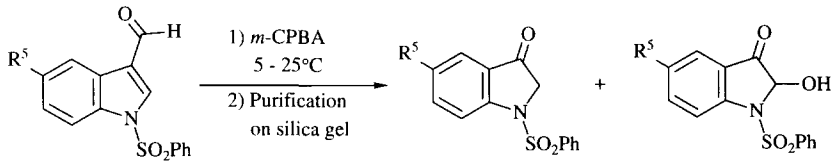
Hyellazole

Figure 1

Most of the reported synthesis of these hydroxyketones start from indolic compounds with simultaneous generation of the ketone and the hydroxy groups; we wish to report here another approach with the α-hydroxylation of ketones **2** by *m*-CPBA oxidation.

Our aim was to obtain new oxazoles possessing an indolic moiety and with potential antithrombic activity. We have recently reported the formation of 2-hydroxyketones **3b,c** by Baeyer-Villiger oxidation of 5-substituted-1-(phenylsulfonyl)-1*H*-indole-3-carboxaldehyde **1**[19] (Scheme 1). The formation of 2-hydroxyketones **3** is not observed if the 2-position of the compound **1** is substituted by a methyl or a phenyl group and, more surprisingly, by the unsubstituted compound **1a** (R^5 = H).

In these reactions, the first step is the Baeyer-Villiger rearrangement followed by hydroxylation in 2-position. With an α,β-ethylenic aldehyde, Bose[20] has shown that *m*-CPBA epoxidation is the first step of the reaction followed by the Baeyer-Villiger rearrangement. The formation of 2-hydroxyketones **3b** (R^5 = Br) or **3c** (R^5 = CH_3O) seems to be due to an *m*-CPBA oxidation of the enolic form of ketone compounds **2b,c**.

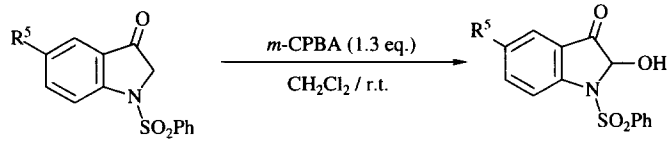


1a-c **2a-c** **3b-c**

R^5 = H, CH_3O, Br

Scheme 1

The 2-hydroxy group may be the result of the opening of the intermediate epoxide. In order to test this hypothesis, we performed directly the *m*-CPBA oxidation of the ketones **2** (Scheme 2). We did not observe the formation of lactones as expected for a normal Baeyer-Villiger rearrangement and described for five membered ketones,[21] but rather the formation of hydroxy ketones **3**.



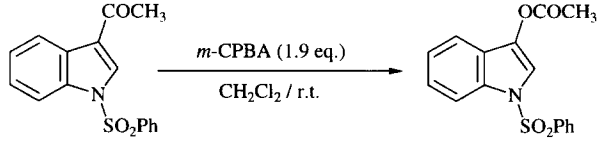
2a-c **3a-c**

2	R^5	Yield of 3
a	H	60%
b	Br	50%
c	CH_3O	40%

Scheme 2

2-Hydroxyketones **3a-c** were obtained from ketones **2a-c** after oxidation with 1.3 eq. of *m*-CPBA at room temperature in dichloromethane (Scheme 2). On the other hand, during oxidation of [1-(phenylsulfonyl)indol-3-yl] ethanone **4** using 1.9 eq. of *m*-CPBA,[19] only [1-(phenylsulfonyl)indol-2-yl] acetate **5** was observed; hydroxyketone **3a** was not detected (Scheme 3). These attempts seem to prove that formation of compounds **3** occured under the free enolic form of ketones **2** since, in the case of oxidation of ketone **4**, hydroxylation did not occur under the stable form of acetate **5**. All attempts to obtain **3a** directly from **1a** (increase in number of equivalent (2.5 to 4.2 eq.) of *m*-CPBA at room temperature) gave only a mixture of **1a**, 2-phenylsulfonamidophenol and degradation products.

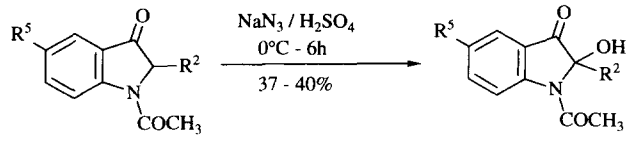
The protecting group on the nitrogen atom greatly influences the reactivity of the 1,2-dihydro-3*H*-indol-3-ones **2** since compound **2d**, treated with *m*-CPBA, did not lead to the corresponding 2-hydroxyketone **3d**. It is new evidence for the tremendous role on reactivity played by the protecting group in the 1-position of indole.



4 **5**

Scheme 3

Nevertheless it was possible to obtain the 1-acetyl-2-hydroxy-1,2-dihydro-3*H*-indol-3-one **3d**,[22] from 1-acetyl-1,2-dihydro-3*H*-indol-3-one **2d**, in 37% yield, using Schmidt rearrangement conditions (NaN_3/ H_2SO_4) under argon. Only 1-acetyl-5-chloro-1,2-dihydro-3*H*-indol-3-one **2e** gave the corresponding 2-hydroxyketone **3e** in 40% yield, 1-acetyl-5-methoxy-1,2-dihydro-3*H*-indol-3-one **2f** or 1-acetyl-2-methyl-1,2-dihydro-3*H*-indol-3-one **2g** did not work (Scheme 4). Various experimental conditions were used in order to better understand this reaction; 2 eq. of sodium azide and H_2SO_4 conc. were absolutely necessary. The use of HBr in acetic acid instead of sulfuric acid afforded brominated compounds but not the hydroxyketones **3d** or **3e**.

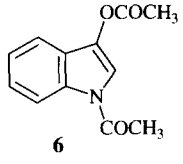


2d-g **3d-e**

2	R^5	R^2	Yield of 3
d	H	H	37%
e	Cl	H	40%
f	CH_3O	H	degradation
g	H	CH_3	degradation

Scheme 4

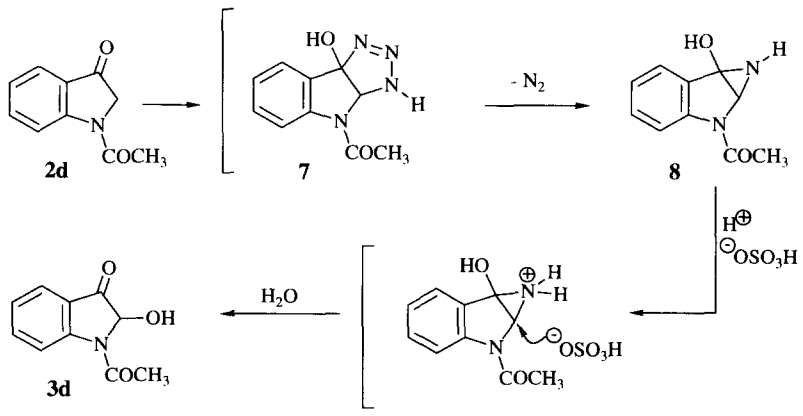
The 2-hydroxyketone **3d** was also obtained in 47% yield from (1-acetylindol-3-yl) ethanoate **6** under the same Schmidt conditions but the 1-(phenylsulfonyl)-1,2-dihydro-3*H*-indol-3-one **2a** did not give compound **3a** (Figure 2).



6

Figure 2

A plausible explanation for the formation of compounds **3d,e** is first, formation of a triazine ring **7** which gives aziridine ring **8** by nitrogen evolution and then, nucleophilic attack by the hydrosulfate anion which leads to the 2-hydroxyketones **3d,e**. The addition of sodium azide on the ethylenic bond, which then forms an aziridine has been reported in the literature[23](Scheme 5).



2d **7** **8** **3d**

Scheme 5

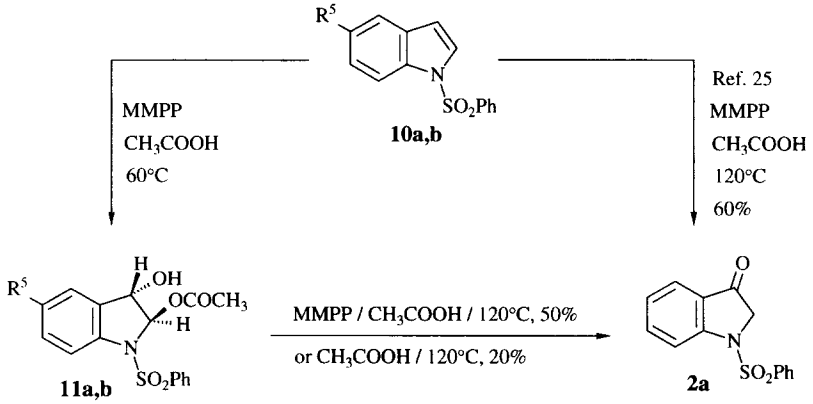
Recently, Foote[3] reported *inter alia* the synthesis of 1-acetyl-2-hydroxy-2-methyl-3*H*-indol-3-one **3g** (Figure 3) in low yield by oxidation of 1-acetyl-2-methylindole with dimethyldioxirane in acetone / CH_2Cl_2 at -78°C (the major product being the 1-acetyl-2-methyl-1,2-dihydro-3*H*-indol-3-one **2g**) *via* an isolated 2,3-epoxide intermediate which leads to rearrangement products **2g** and **3g**.

3g **9**

Figure 3

So, the same postulated mechanism which involves the formation either of an epoxide or an aziridine ring may explain the formation of the reported hydroxyketones **3**.

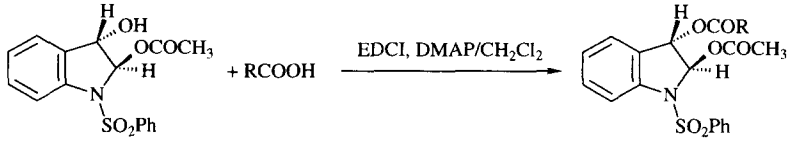
After examining the reactivity of 1,2-dihydro-3*H*-indol-3-ones, we turned our attention towards the oxidation of indole itself since Foote[24] has also reported the formation of *cis* and *trans* 2-methoxy-3-hydroxyindoline **9** (Figure 3). Recently, Gribble[25] has reported the magnesium monoperphtalate (MMPP) oxidation of 1-(phenylsulfonyl)indole **10a** in acetic acid at 120°C which gave **2a** as major product. In order to trap intermediates, we have performed this oxidation at 60°C and obtained [3-hydroxy-1-(phenylsulfonyl)-2,3-dihydro-indol-2-yl] acetate **11a**, which was the result of the opening of the intermediate epoxide, together with other unidentified products rather than **2a** (Scheme 6). The relative stereochemistry at C_2 and C_3 of compound **11a** is *trans* since the vicinal coupling constant is $J_{2,3}$ # 0 Hz (2D NMR experiments clearly show a very small coupling constant $J_{2,3}$) instead of the expected 5 Hz for the *cis* isomer as reported for 5,6-dimethoxy-2-methyl-3[2-(4-phenylpiperazinyl)ethyl] indoline.[26] The similar compound **11b** has been obtained from 5-bromo-1-phenylsulfonylindole **10b.**



10	R^5	Yield of 11
a	H	20%
b	Br	40%

Scheme 6

Compound **11a** gives ketone **2a** by elimation of acetic acid (unusual *syn* elimination) under Gribble's conditions or simply by refluxing in acetic acid; the selective oxidation of the alcohol of compound **11a** was unproductive using Swern conditions or CrO_3 / *tert*-BuOOH[27].



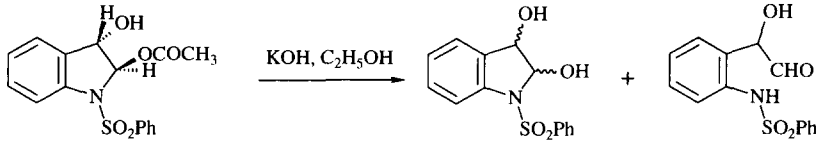
11a **12h-j**

12	R	Yield
h	CH_3	84%
i	C_2H_5	96%
j	CH_2-NHCOCH$_3$	60%

Scheme 7

Nevertheless, it was possible to react the benzylic alcohol in 3-position of compound **11a** in presence of carboxylic acids in dichloromethane with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and dimethylaminopyridine (DMAP) to lead to esters **12h-j** (Scheme 7).

The 2,3-dihydroxy-2,3-dihydro-1-phenylsulfonylindole **13** can be obtained by careful hydrolysis of compound **11a** (Boyd tried unsuccessfully to obtain 2,3-dihydro-2,3-dihydroxyindole by metabolite oxydation of indole with *Pseudomonas putida*).[28] The formation of the open compound **14** is also observed and the ratio of isolated cyclic diol **13** and the form **14** depends on the basic experimental conditions used. A mixture of two diastereoisomeric forms of compound **13** is the result of the likely equilibrium between the open ring form **14** and the ring closure form **13** in the basic mixture as reported for structurally related compounds by Sakamoto[29a] and Buchardt[29b] and postulated by Jimenez[8] (Scheme 8).

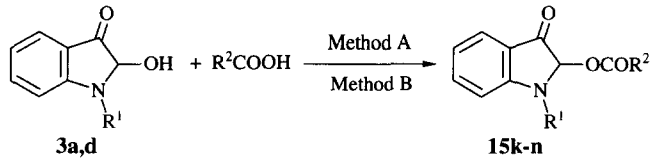


11a **13** **14**

Conditions	Time	Yield of **13**	Yield of **14**
1 eq. KOH in C_2H_5OH, 20°C	12 h	10%	7%
1 eq. KOH in C2H5OH, 50°C	1 h	-	16%
2 eq. KOH in C_2H_5OH, 20°C	0.5h	22%	12%
4 eq. KOH in C_2H_5OH, 20°C	0.5h	-	20%

Scheme 8

Since the reactivity of the hydroxy group in 3-position of compound **11a** has been examined, we have also examined the behavior of the 2-hydroxy ketones **3a** and **3d**. Acetylation of compounds **3a,d** is carried out in acetic anhydride at room temperature to give compounds **15k,l**.



3a,d **15k-n**

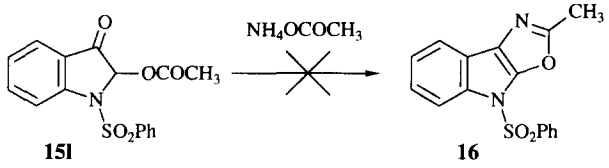
Method A: $(CH_3CO)_2O$. Method B: EDCI-DMAP, CH_2Cl_2, r.t.

3	15	R^1	R^2	Method	Yield
d	**k**	$COCH_3$	CH_3	A	35%
a	**l**	SO_2Ph	CH_3	A	89%
a	**m**	SO_2Ph	CH_2-Cl	B	96%
a	**n**	SO_2Ph	$(CH_2)_4$-Br	B	82%

Scheme 9

The hydroxy group of **3a** can also be esterified by reaction of the required carboxylic acid in dichloromethane with EDCI and DMAP at room temperature to give compounds **15m-n** (Scheme 9).

Till now, all attempts to cyclize keto ester **15l** to oxazole **16**[18] with ammonium acetate (mixture heated at the reflux temperature of acetic acid), have failed (Scheme 10).



15l **16**

Scheme 10

Nevertheless, compounds **15k,l** may be useful for selective monoalkylation in 2-position followed by removing of the acetate group.

Hydroxylation of C_2 position of dihydroindol-3-ones **2** was performed either by oxidation with m-CPBA or by reaction with NaN_3 / H_2SO_4 depending on the protecting group of the nitrogen atom. Our oxidation of 3-formylindoles in two separate steps is a new and flexible approach to the synthesis of hydroxyketones providing indole derivatives which are suitable for subsequent transformations. We were also able to obtain selectively (*trans*) dihydroxyderivatives **13**. Experiments are underway to extend the scope of these process to the 7-azaindole derivatives .

Experimental conditions:

Melting points were measured using a Kofler apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer, ^{1}H-NMR on a Bruker AM 300 spectrometer and MS on a Nermag R-10-10C spectrometer (ionization with ammonia). All reagents were purchased from Aldrich Chemical Co. and used without further purification. Dry solvents were prepared according to standard procedures reported in the literature. Chromatography was carried out with Merck silica gel (230-400 mesh) and TLC with Merck silica gel 60 F_{254} TLC plates (200 µ).
Compounds (**1a-e**),[19] (**2a**),[25] (**2b,c**),[19] (**2d**),[30] (**2e**),[31] (**4**),[32] (**5**),[19] (**6**),[30] (**10a**),[25] (**10b**),[33] were prepared according to reported procedures.

General procedure for compounds (3a-c):

A solution of 1-(phenylsulfonyl)-2,3-dihydro-3*H*-indol-3-one (**2**) (1 mmol) in CH_2Cl_2 (10 mL) and *m*-CPBA (1.3 mmol) was stirred 24 hours at room temperature. Water (10 mL) was added and the aqueous layer was neutralized with an aqueous solution of Na_2SO_3 5%. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was chromatographed on a silica gel column with CH_2Cl_2/MeOH (99/1: v/v) as eluent to give compound (**3**).

2-Hydroxy-1-(phenylsulfonyl)-1,2-dihydro-3*H*-indol-3-one (3a).
Yield: 60%; mp 196-198°C (Toluene). IR (KBr), ν: 3400-3300 (OH), 1720 (CO) cm^{-1}. ^{1}H-NMR (300MHz; $CDCl_3$+D_2O), δ: 5.41 (1H, s, CH), 7.17 (1H, t, J=6.3Hz, Harom), 7.46-7.76 (6H, m, Harom), 7.96 (2H, d, J=6.3Hz, Harom). MS, m/z= 307 (M^++18).
5-Bromo-2-hydroxy-1-phenylsulfonyl-1,2-dihydro-3*H*-indol-3-one (3b)[19].
Yield: 50%; mp 158-160°C (Ethanol). IR (KBr), ν: 3480 (OH), 1720 (CO) cm^{-1}. ^{1}H-NMR (300MHz; $CDCl_3$ + D_2O), δ: 5.45 (1H, s, CHOH), 7.50-7.77 (7H, m, Harom), 7.94 (1H, dd, J<1.0Hz, J=7.3Hz, Harom). MS, m/z= 369 (M^+ +1), 371 (M^++3).
2-Hydroxy-5-methoxy-1-phenylsulfonyl-1,2-dihydro-3H-indol-3-one (3c)[19].
Yield: 40%; mp 144-146°C (Ethanol). IR (KBr), ν: 3460 (OH), 1700 (CO) cm^{-1}. ^{1}H-NMR, (300MHz; $CDCl_3$ + D_2O), δ: 3.74 (3H, s, OCH_3), 5.35 (1H, s, CHOH), 7.05 (1H, d, J=2.9Hz, H_4), 7.22 (1H, dd, J= 2.9Hz, 8.8Hz, H_6), 7.40-7.60 (3H, m, Harom), 7.67 (1H, d, J=8.8Hz, H_7), 7.86(2H, dd, J<1.0Hz, J=7.3Hz, Harom). MS, m/z= 320 (M^+ +1).

General procedure for compounds (3d), (3e).

To a stirred solution of concentrated sulfuric acid (5 mL) cooled at 0°C, a solution of 1-acetyl-5-substituted-2,3-dihydroindol-3-one (**2d,e**) (2.86 mmol), dissolved in chloroform (10 mL), was added dropwise in 10 min. Sodium azide (5.72 mmol) was carefully added (T<0°C). The mixture was stirred for 6 hours at 0°C and 2 hours at room temperature, then quenched with ice (100 g). The mixture was neutralized with an aqueous

solution of NaOH 10 % (T<0°C) and filtered on Celite. CH_2Cl_2 (2 x 100 ml) was then added and organic layers were separated and dried ($MgSO_4$). The solvent was evaporated, leaving a solid.

1-Acetyl-2-hydroxy-1,2-dihydro-3*H*-indol-3-one (3d).
Yield: 37 %; mp 145-147°C (Toluene). IR (KBr), ν: 3300-3200 (OH), 1735 (CO), 1650 (NCO) cm^{-1}. ^{1}H-NMR (300MHz; DMSO-d_6+D_2O), δ: 2.32 (3H, s, $COCH_3$), 5.43 (1H, s, H_2), 7.20 (1H, dd, J=1.4Hz, J=10.9Hz, Harom), 7.67 (1H, fd, J<1.0Hz, Harom), 7.72 (1H, ft, J=10.9Hz, Harom), 8.34 (1H, fd, J<1.0Hz, Harom). MS FAB/Xe, m/z= 192.0688 (M^++1).
1-Acetyl-5-chloro-2-hydroxy-1,2-dihydro-3*H*-indol-3-one (3e).
Yield: 40 %; mp 165-167°C (Toluene). IR (KBr), ν: 3300-3200 (OH), 1735 (CO), 1650 (NCO) cm^{-1}. ^{1}H-NMR (300MHz; DMSO-d_6+D_2O), δ: 2.31 (3H, s, $COCH_3$), 5.50 (1H, s, H_2), 7.69 (1H, d, J=2.4Hz, Harom), 7.77 (1H, q, J=9.0Hz, J=2.4Hz, Harom), 8.35 (1H, d, J=9.0Hz, Harom).

(*trans*)-Ethanoic acid [3-hydroxy-1-phenylsulfonyl-2,3-dihydro-1*H*-indol-2-yl] ester (11a).
To a solution of 1-(phenylsulfonyl)indole (**10a**) (7.00 g, 27 mmol) in acetic acid (140 mL), MMPP (16.87 g, 27 mmol) was added and the mixture was stirred for 2h30 at 60°C. The solvent was evaporated in *vacuo* and water (100 mL) was added. The aqueous layer was neutralized with solid Na_2CO_3 and extracted with CH_2Cl_2 (3 x 75 mL). Organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was treated with ether and the white precipitate was filtered to give **11a** (1.80 g, 20 %); mp 142-144°C (Ether). IR (KBr), ν: 3300-3200 (OH), 1700 (CO) cm^{-1}. ^{1}H-NMR (500MHz; $CDCl_3$+D_2O), δ: 1.84 (3H, s, $COCH_3$), 5.66 (1H, s, H_3), 5.76 (1H, s, H_2), 7.09 (1H, t, J=7.2Hz, Harom), 7.37 (2H, t, J=8.2Hz, Harom), 7.42-7,58 (4H, m, Harom), 7.84 (2H, d, J=8.2Hz, Harom). ^{13}C-NMR (125MHz; $CDCl_3$) δ: 20.64 (CH_3), 77.64 (C2), 90.23 (C3), 114.94 (Carom), 124.56 (Carom), 127.09 (2 x Carom), 127.23 (Carom), 127.61 (Carom), 129.04 (2 x Carom), 131.08 (Carom), 133.34 (Carom), 138.26 (Carom), 141.59 (Carom), 169.90 (CO). MS, m/z= 316 (M^+-17), 333 (M^+).

(*trans*)-Ethanoic acid [5-bromo-3-hydroxy-1-phenylsulfonyl-2,3-dihydro-1*H*-indol-2-yl] ester (11b).
Similarly prepared as for compound **11a** using 5-bromo-1-phenylsulfonylindole.[33]
Yield: 40 %; oil. IR (KBr), ν: 3450-3250 (OH), 1710 (CO) cm^{-1}. ^{1}H-NMR (300MHz; $CDCl_3$+D_2O), δ: 1.82 (3H, s, $COCH_3$), 5.67 (1H, s, H_3), 5.70 (1H, s, H_2), 7.35 -7.65 (6H, m, Harom), 7.80 (2H, d, J=8.2Hz, Harom).

General procedure for compounds (12h-j).
To a cooled (0°C) solution of (*trans*)-ethanoic acid [3-hydroxy-1-phenylsulfonyl-2,3-dihydro-1*H*-indol-2-yl] ester (**11a**) (0.330 g, 1 mmol) in CH_2Cl_2 (9 mL), DMAP (0.06 g, 0.05 mmol), EDCI (0.210 g, 1.10 mmol) and the corresponding carboxylic acid (1.1 mmol) were added. The mixture was stirred 1 hour at 0°C and 30 minutes at room temperature. Water (10 mL) was added and the aqueous layer was neutralized with a saturated aqueous solution of $NaHCO_3$ and extracted twice with CH_2Cl_2 (2 x 10 mL). Organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*.
(*trans*)-Ethanoic acid [2-acetoxy-1-(phenylsulfonyl)-2,3-dihydro-1*H*-indol-3-yl] diester (12h).
Yield: 84%; mp 166-168°C (Ether). IR (KBr), ν: 1750 (CO) cm^{-1}. ^{1}H-NMR (300MHz; $CDCl_3$), δ: 1.83 (3H, s, $COCH_3$), 2.09 (3H, s, $COCH_3$), 5.76 (1H, s, H_2), 6.64 (1H, s, H_3), 7.10 (1H, t, J=7.3Hz, Harom), 7.35-7.45

(2H, m, Harom), 7.46 (2H, t, J=8.2Hz, Harom), 7.54-7.61 (1H, m, Harom), 7.67 (1H, d, J=7.3Hz, Harom), 7.85 (2H, d, J=8.2Hz, Harom).

(*trans*)-Propionic acid [2-acetoxy-1-phenylsulfonyl-2,3-dihydro-1*H*-indol-3-yl] ester (12i).

Yield: 96%; mp 140-142°C (Ether). IR (KBr), ν: 1765-1750 (CO) cm^{-1}. ^{1}H-NMR (300MHz; $CDCl_3$), δ: 1.15 (3H, t, J=6.3Hz, CH_3), 1.83 (3H, s, $COCH_3$), 2.27-2.37 (2H, m, CH_2), 5.73 (1H, s, H_2), 6.66 (1H, s, H_3), 7.15 (1H, t, J=7.3Hz, Harom), 7.38-7.45 (2H, m, Harom), 7.47 (2H, t, J=8.2Hz, Harom), 7.58 (1H, m, Harom), 7.67 (1H, d, J=7.3Hz, Harom), 7.85 (2H, d, J=8.2Hz, Harom).

(*trans*)-(Acetyl)amino acetic acid [2-acetoxy-1-phenylsulfonyl-2,3-dihydro-1*H*-indol-3-yl] ester (12j).

Yield: 60%; mp 60-62°C (Ether). IR (KBr) ν: 3500 (NH), 1765-1740 (CO) cm^{-1}. ^{1}H-NMR (300MHz; $CDCl_3$+D_2O), δ: 1.84 (3H, s, $OCOCH_3$), 2.04 (3H, s, $NCOCH_3$), 3.92-4.14 (2H, m, CH_2), 5.77 (1H, s, H_2), 6.70 (1H, s, H_3), 7.15 (1H, t, J=7.3Hz, Harom), 7.38-7.45 (2H, m, Harom), 7.49 (2H, t, J=8.2Hz, Harom), 7.55-7.70 (2H, m, Harom) 7.85 (2H, d, J=8.2Hz, Harom).

1-Phenylsulfonyl-2,3-dihydro-1*H*-indol-2,3-diol (13) and *N*-[2-(1-hydroxy-2-oxo-ethyl)phenyl]phenyl sulfonamide (14).

A solution of indole (**11a**) (0.330 g, 1 mmol) in ethanol (5 mL) and potassium hydroxide (0.110 g, 2 mmol) was stirred for 30 min. at room temperature. Water was added (2 mL), the mixture was neutralized with HCl 10% and extracted with CH_2Cl_2 (3 x 15 mL). Organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was chromatographed on a silica gel column with CH_2Cl_2/MeOH (99/1: v/v) as eluent to give compounds (**13**) (0.060 g; 22%) and (**14**) (0.032 g; 12%).

(*cis*, *trans*)-1-Phenylsulfonyl-2,3-dihydro-1*H*-indol-2,3-diol (13).

Yield: 22%; oil. IR (film), ν: 3600-3200 (OH) cm^{-1}. ^{1}H-NMR (300MHz; $CDCl_3$+D_2O), δ: 4.90 (1H, s, H_{2trans}), 5.06 (1H, d, J=6.3Hz, H_{2cis}), 5.61 (1H, s, H_{3trans}), 5.77 (1H, d, J=6.3Hz, H_{3cis}), 7.04-7.14 (2H, m, Harom), 7.29-7.62 (12H, m, Harom), 7.88-7.95 (4H, m, Harom). MS, m/z= 309 (M^++18).

***N*-[2-(1-Hydroxy-2-oxo-ethyl)phenyl] phenylsulfonamide (14).**

Yield: 12%; mp 114-116°C (Ether). IR (KBr), ν: 3400-3100 (NH, OH), 1690 (CO) cm^{-1}. ^{1}H-NMR (300MHz; $CDCl_3$+D_2O), δ: 3.88 (1H, s, CH), 7.14 (1H, t, J=8.6Hz, Harom), 7.40-7.54 (2H, m, Harom), 7.58 (2H, d, J=10.3Hz, Harom), 7.73 (2H, d, J=7.7Hz, Harom), 7.90 (2H, d, J=7.7Hz, Harom), 9.85 (1H, s, CHO). MS, m/z= 292 (M^++1).

Ethanoic acid [3-oxo-1-acetyl-2,3-dihydro-1*H*-indol-2-yl] ester (15k).

In acetic anhydride (4 mL), compound (**3d**) (0.140 g, 0.74 mmol) was stirred for 48 hours at room temperature. $(CH_3CO)_2O$ was evaporated *in vacuo* and the residue was chromatographed on a silica gel column with CH_2Cl_2 as eluent. Yield: 35%; mp, IR, ^{1}H-NMR and MS were identical to the already described product.[29a]

Ethanoic acid [3-oxo-1-phenylsulfonyl-2,3-dihydro-1*H*-indol-2-yl] ester (15l).

In acetic anhydride (2 mL), compound (**3a**) (0.080 g, 0.277 mmol) was heated at 50°C for 30 min. $(CH_3CO)_2O$ was evaporated *in vacuo* and the residue was chromatographed on a silica gel column with CH_2Cl_2 as eluent.

Yield: 89%; mp 148-150°C (Ether). IR (KBr), ν: 1755 (OCO), 1730 (CO) cm^{-1}. ^{1}H-NMR (300MHz; $CDCl_3$), δ : 2.17 (1H, s, CH_3), 6.23 (1H, s, H_2), 7.21 (1H, t, J=7.2Hz, Harom), 7.51 (2H, t, J=8.2Hz, Harom), 7.59-7.73 (3H, m, Harom), 7.81 (2H, d, J=8.2Hz, Harom), 7.98 (1H, d, J=7.2Hz, Harom). MS, m/z= 349 (M^++18).

Compounds (**15m,n**) were obtained by the same procedure used for compounds (**12h-j**).

Chloroethanoic acid [3-oxo-1-phenylsulfonyl-2,3-dihydro-1*H*-indol-2-yl] ester (15m).
Yield: 96%; mp 135-137°C (Ether). IR (KBr), ν: 1770 (OCO), 1730 (CO) cm^{-1}. ^{1}H-NMR (300MHz; $CDCl_3$), δ: 4.15-4.25 (2H, m, CH_2Cl), 6.28 (1H, s, H_2), 7.24 (1H, t, J=7.2Hz, Harom), 7.53 (2H, t, J=8.2Hz, Harom), 7.61-7.75 (3H, m, Harom), 7.92 (2H, d, J=8.2Hz, Harom), 8.00 (1H, d, J=7.2Hz, Harom).

5-Bromopentanoic acid [3-oxo-1-phenylsulfonyl-2,3-dihydro-1*H*-indol-2-yl] ester (15n).
Yield: 82%; oil. IR (film), ν: 1770 (OCO), 1730 (CO) cm^{-1}. ^{1}H-NMR (300MHz; $CDCl_3$), δ: 1.75-2.00 (4H, m, $(CH_2)_2$), 2.42-2.52 (2H, m, CH_2), 3.42 (2H, t, J=6.6Hz, CH_2Br), 6.21 (1H, s, H_2), 7.22 (1H, t, J=7.2Hz, Harom), 7.51 (2H, t, J=8.2Hz, Harom), 7.58-7.73 (3H, m, Harom), 7.90 (2H, d, J=8.2Hz, Harom), 7.99 (1H, d, J=7.2Hz, Harom).

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