SYNTHESIS OF INDOLO[1,2-*b*]ISOQUINOLINEDIONES; REDUCTION OF 2-[(SUBSTITUTED PHENYL)METHYLIDENE]-3-OXO-2,3-DIHYDROINDOLE

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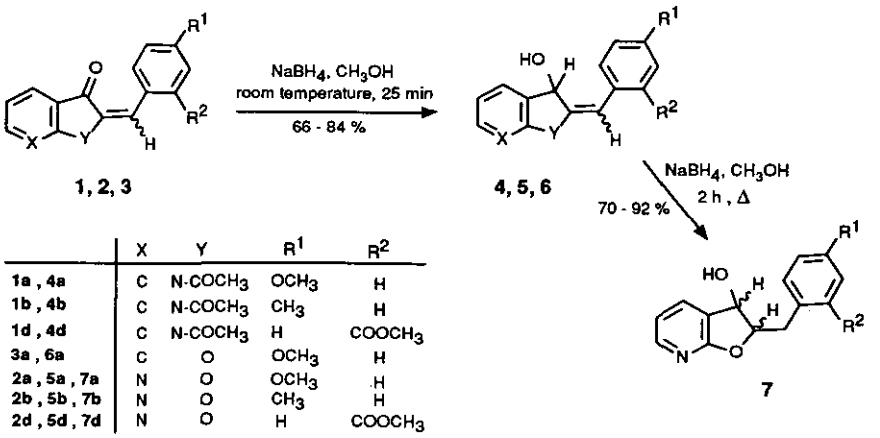
Abstract - *Indolo[1,2-b]isoquinoline-5,12-dione and the isomeric 6,12-dione have been prepared respectively from 1-sulfonylindole and 1-acetyl-2-[(2-methoxycarbonyl phenyl)methylidene]-3-oxo-2,3-dihydroindole; the reduction of 1-acetyl-2-[(substituted phenyl)methylidene]-3-oxo-2,3-dihydroindole and their oxygen analogs with sodium borohydride have been studied.*

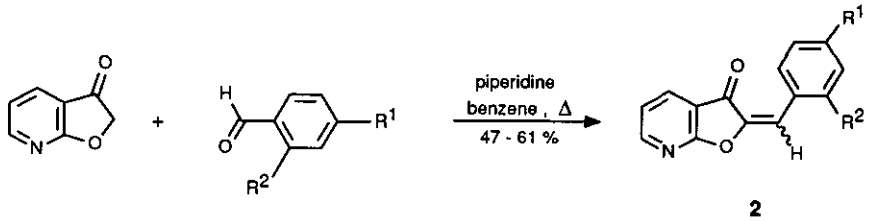
1,2 or 1,4 addition of a nucleophilic reagent over an α,β-ethylenic ketone is still an old challenge where most of the parameters are known;[1] nevertheless, some improvements regularly appear in the literature in order to obtain best synthetic results; 1,2 reduction with a complex hydride like sodium borohydride[2-5] affords allylic alcohols which are useful starting materials for [3,3] sigmatropic rearrangement like the Claisen rearrangement or its Eschenmoser modification. We report here our results in the field of the heterocyclic α,β-ethylenic ketones (**1**, **2**, **3**).

Two aspects of the sodium borohydride reduction were examined: the influence of the heteroatoms which modify the electronic density of the π system and the role played by the substituent R^2 in 2-position on the phenyl ring of the benzylidene moiety.



	X	Y	R^1	R^2
1a , 4a	C	N-$COCH_3$	OCH_3	H
1b , 4b	C	N-$COCH_3$	CH_3	H
1d , 4d	C	N-$COCH_3$	H	$COOCH_3$
3a , 6a	C	O	OCH_3	H
2a , 5a , 7a	N	O	OCH_3	H
2b , 5b , 7b	N	O	CH_3	H
2d , 5d , 7d	N	O	H	$COOCH_3$

Some years ago, we started a program based on the use of 1-acetyl-3-oxo-2,3-dihydroindole[6-9] as a tool for the synthesis of biologically active compounds and we have reported[6] the synthesis of 1-acetyl-2-[(substituted phenyl)methylidene]-3-oxo-2,3-dihydroindoles (**1**) and their uses, after selective reduction (hydrogenation over palladium), as starting materials for the synthesis of 2-substituted 3-(2-aminoethyl)indole (tryptamines). In a similar fashion, aza-aurones (**2**) were obtained from 3-oxo-7-aza-2,3-dihydrobenzofuran[10] and the appropriate benzaldehyde in the presence of a few drops of piperidine in refluxing benzene or toluene; compouds (**2**) were obtained as a mixture of E + Z isomers.

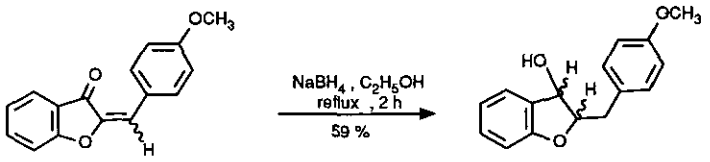


2

2	R^1	R^2
a	OCH_3	H
b	CH_3	H
c	Cl	H
d	H	$COOCH_3$
e	H	NO_2

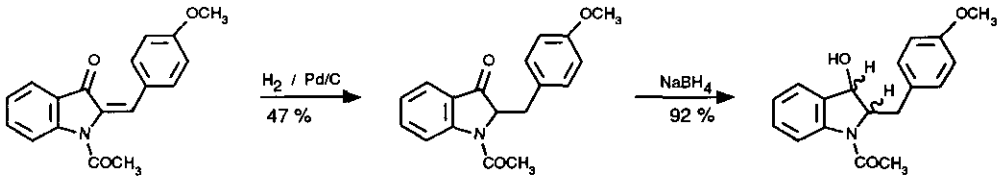
Sodium borohydride reduction[11,12] of ketones (**1a,b, 2a,b, 3a**) was undertaken first at room temperature with 3 molar equivalents of $NaBH_4$ in methanol. In all cases the secondary allylic alcohols (**4a,b, 5a,b, 6a**) were obtained in 66-84% yield after 25 min of reaction. In refluxing methanol (2 h), the results of the reduction were more contrasted. Indolic compounds (**1a,b**) afforded only degradation products ; the aza-aurone compound (**2a**) gave the fully reduced alcohol (**7a**) as a mixture of diastereomers ($7a_1$) and ($7a_2$); similarly (**2b**) afforded

(**7b**) as a mixture of diastereomers (**7b**$_1$) and (**7b**$_2$); compound (**3a**) furnished the fully reduced alcohol (**9a**) (as a mixture of diastereomers) only if methanol is replaced by ethanol; this alcohol (**9a**) has been reported by Holy.[11]



3a **9a**

Despite the fact that degradation products were obtained in the reduction of (**1a**), *the expected fully reduced* indolic alcohol (**8a**) could be prepared by an independent two step-procedure: a catalytic hydrogenation of (**1a**) *over palladium first afforded* (**10a**),[6] then a sodium borohydride reduction of compound (**10a**) at room temperature gave (**8a**) in 92% yield; (only one diastereomer by nmr).

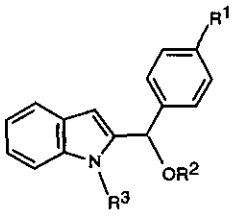


1a **10a** **8a**

The behaviour of compounds (**1a,b**) (where the nitrogen atom is acetylated), towards $NaBH_4$ reduction was different from that of 2-[(substituted phenyl)methylidene]-3-oxo-2,3-dihydroindoles (unsubstituted on the nitrogen atom); in the latter case, the only isolated products[12,13] at room temperature were 2-substituted benzylindoles (95% yields).

These results were in good agreement with our previous findings about the influence on the reactivity of the substitution on the nitrogen atom in such compounds.

The reactivity of the indolic allylic alcohols (**4**) has been examined; they did not react with phthalimide under Mitsunobu conditions ; their also failed to react with trimethyl orthoacetate or *N,N*-dimethylacetamide dimethyl acetal preventing any study of the [3,3] sigmatropic rearrangement. Alcohols (**4a,b**), which are stable at room temperature, immediately decomposed in presence of a catalytic amount of BF_3 etherate; the reaction with acetyl chloride or acetic anhydride afforded a mixture of products from which the rearranged allylic alcohols (**15a,b**) could be isolated and in some cases (use of an excess of acetic anhydride) the O-acetyl derivatives (**16b**).

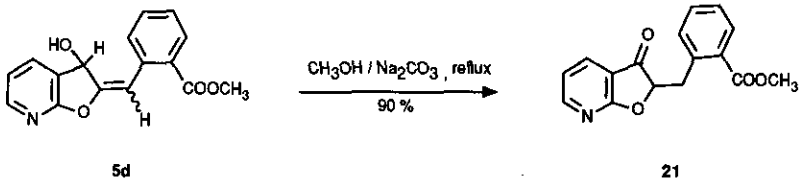


	R^1	R^2	R^3
15a	OCH_3	H	$COCH_3$
15b	CH_3	H	$COCH_3$
15f	CH_3	H	$SO_2C_6H_5$
16b	CH_3	$COCH_3$	$COCH_3$
16f	CH_3	$COCH_3$	$SO_2C_6H_5$

The structures of compounds (**15**) and (**16**) have been determined by comparison of the nmr data of 1-sulfonyl-2-[(4-methylphenyl)hydroxymethyl]indole (**15f**) prepared from 1-sulfonyl-2-lithioindole and 4-methylbenzaldehyde.

The reduction of compounds (**1d**) and (**2d**) substituted by a methoxycarbonyl group in 2-position of the phenyl ring was undertaken. In the aza series the allylic alcohol (**5d**) was obtained at room temperature from the aza-aurone (**2d**); in refluxing methanol the fully reduced alcohol (**7d**) was obtained from (**2d**) but this reduction followed an other course since a ketonic intermediate (**21**) was formed and isolated when 3 equivalents of $NaBH_4$ were used for this reduction; the net result seemed to be a 1,4 addition and not a 1,2 addition as for the other compounds of the series; (**21**) was reduced to compound (**7d**) by adding 1.5 equivalents of $NaBH_4$ to the refluxing mixture. Compound (**5d**) gave also the benzyl ketone (**21**) by heating in methanol with Na_2CO_3 which implied that the initial addition of $NaBH_4$ on compound (**2d**) was a 1,2 addition and not a 1,4 addition, followed by an isomerisation to the ketone (**21**).

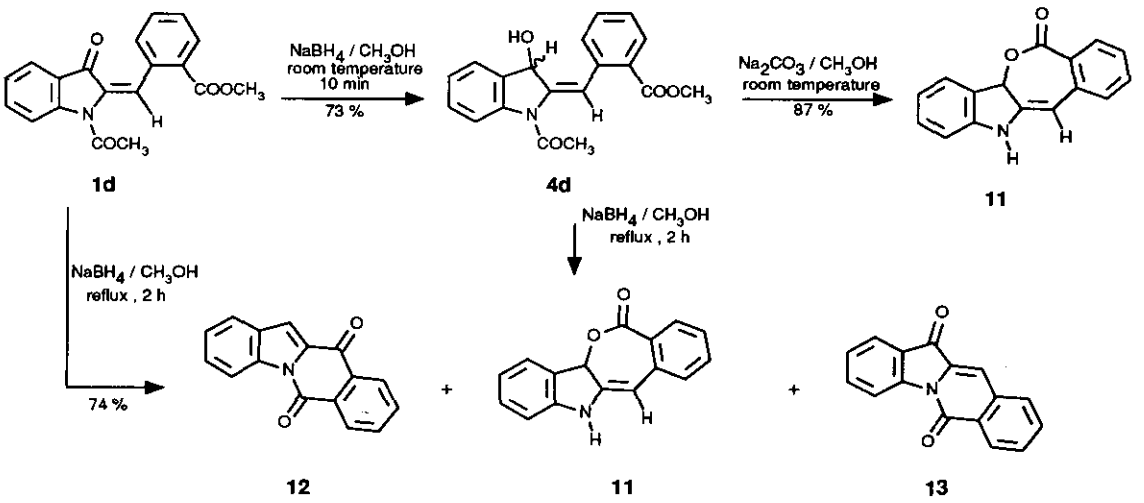
Whatever is the α,β-ethylenic ketone (**1, 2, 3**) an 1,2-addition of $NaBH_4$ is always observed.



5d **21**

In the indole series the reduction of compound (**1d**) (E isomer) with 3 molar equivalents of sodium borohydride in methanol at room temperature afforded 1-acetyl-2-[(2-methoxycarbonylphenyl)methylidene]-3-hydroxy-2,3-dihydroindole (**4d**)(E isomer). If this reaction was performed in refluxing methanol, a mixture of lactone (**11**)(54% yield), cyclized indolo[1,2-*b*]isoquinoline-5,12-dione (**12**)(15% yield) and indolo[1,2-*b*]-isoquinoline-6,12-dione (**13**)(5% yield) was obtained. Compounds (**12, 13**) were present even if a large excess of

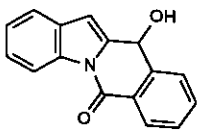
sodium borohydride was used. Compound (**4d**) at room temperature with sodium carbonate in methanol afforded only lactone (**11**) in good yield (87%), which involved that the cyclized products (**11, 12, 13**) were due to the basic media resulting of the decomposition of sodium borohydride in refluxing methanol. Compound (**4d**) gave the same mixture of compounds (**11, 12, 13**) if treated with $NaBH_4$ in refluxing methanol. Tlc monitoring of the reduction of **1d** in refluxing methanol indicates that **4d** is first formed and then, compounds (**11, 12, 13**).



Compound (**12**) may result from an isomerisation of the alcohol (**4d**), the E isomer affording directly compound (**11**), to a rearranged benzyl alcohol structurally related to (**15a,b**) (the same allylic transposition has been observed in the $NaBH_4$ reduction of related compounds in the sulfur series)[15] followed by a cyclization to compound (**17**) which in the basic media afforded the ketone (**12**). We have observed (*vide infra*) that the reduction of compound (**12**) or (**13**) affords respectively the allylic alcohol in 5-position (compound **17**) or 6-position (compound **18**); these alcohols give back to the ketone (**12**) or (**13**) rapidly in the solid state.

The formation of **13** implies a Z configuration of the ethylenic bond in compound (**4d**), but as compound (**13**) is also directly obtained (84% yield) from **1d** by heating in basic media, the very low yield (5%) obtained for compound (**13**) in this reduction may be attributed either to a direct cyclization of **1d** before reduction or to the presence in a low ratio (<5/95) of the Z isomer in compound (**4d**) which gives **13** *via* the alcohol (**18**) ; the synthesis of compound (**11**) involves a E configuration for compound (**4d**); these results indicate that the sodium borohydride reduction at reflux of methanol begins with a 1,2 addition followed by an isomerization

as indicated for compound (**2a**) in the aza series. The lactonic structure of **11** has been established by ^{1}H, ^{13}C nmr ; the presence of the N-H bond has been confirmed by heteronuclear multiple-quantum correlation (HMQC δ^{1}_{H}-δ^{15}_{N}, δ_{N}= - 247±5 ppm, $^{1}J_{H\text{-}N}$ = 90 Hz).



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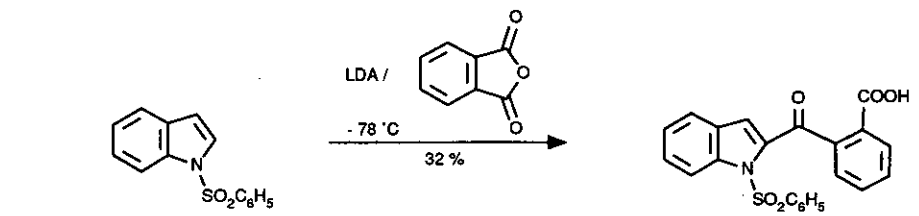
In order to establish the structure of the indolo[1,2-*b*]isoquinoline-5,12-dione (**12**), 1-sulfonylindole was lithiated in 2-position with lithium diisopropylamide and reacted with phthalic anhydride, using a similar procedure as for the synthesis of ellipticine.[16-22] The keto acid (**19**) was deprotected into compound (**20**) and then cyclized in acetic anhydride to compound (**12**).



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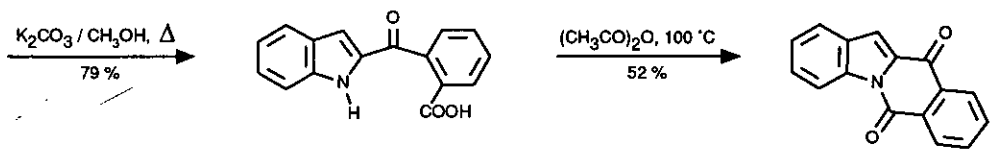
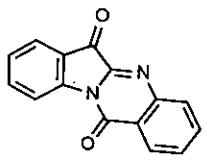


20 **12**

We also prepared the isomeric indolo[1,2-*b*]isoquinoline-6,12-dione (**13**)[12] in good yield (84%) by heating compound (**1d**) with potassium hydroxide or potassium carbonate in refluxing methanol (1 h).

Compound (**13**) has a structure similar to indolo[2,1-*b*]quinazoline-6,12-dione (**14**), whose $NaBH_4$ reduction has been studied by Bergman;[14] recently[22] the related indolo[1,2-*b*][2,7]naphthyridine-5,12-quinone (**25**) has been reacted with other nucleophiles, like cyanide, for leading to a dimer.



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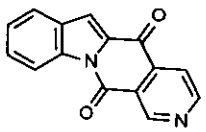

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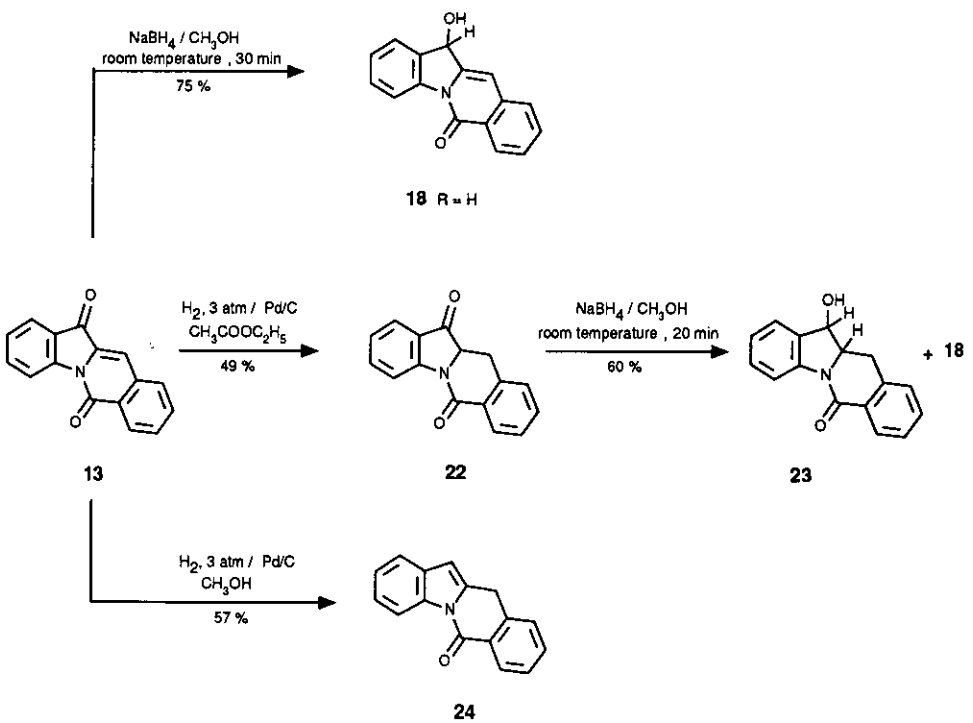
The reduction of ketones (**12**) and (**13**) has been investigated; at room temperature, the allylic alcohols (**17**) and (**18**) were obtained respectively from **12** and **13** . The fully reduced alcohol (**23**) was obtained by a two step-reduction starting from (**13**); a catalytic hydrogenation in ethyl acetate over palladium first afforded the ketone (**22**) which was then reduced by $NaBH_4$. The use of methanol instead of ethyl acetate in the catalytic hydrogenation afforded the indolic compound (**24**). When exposed to the air alcohol (**18**) oxidized back to ketone (**13**) and more generally all these cyclic alcohols were of limited stability at room temperature and showed the same behaviour as alcohols obtained by reduction of indolo[2,1-*b*]quinazoline-6,12-dione (**14**).



EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. The ^1H nmr spectra of all products were recorded on a Bruker AM 300 WB (300 MHz) spectrometer in $CDCl_3$ solutions containing Me_4Si as internal standard ; fd false doublet, ft false triplet, dd doublet of doublet, J (Hz). Mass spectra were recorded on a Nermag R10-10C spectrometer. Infrared spectra were recorded on a Perkin Elmer 257 spectrophotometer.

1-Acetyl-2-[(2-methoxycarbonylphenyl)methylidene]-3-oxo-2,3-dihydroindole (1d) :

This compound was prepared according our described method;[6] yield: (71%); mp 162°C (benzene); ir (KBr): ν = 1705 (COO), 1670 (CO), 1665 (NCO) cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 2.73 (s, 3H, $COCH_3$), 3.85 (s, 3H, OCH_3), 7.20 (ft, J= 7.7, 1H, H_{arom}), 7.45-7.70 (m, 6H, H_{arom}), 8.08 (s, 1H, =CH), 8.20 (fd, J=7.7, 1H, H_{arom}); ms (m/z): 321 (M^+). Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.37; H, 4.47; N, 4.25.

2-Arylmethylidene-3-oxo-7-aza-2,3-dihydrobenzofuran (2) : general procedure:

3-Oxo-7-aza-2,3-dihydrobenzofuran[10] (1 g, 7.4 mmol), appropriate substituted benzaldehyde (8 mmol) and piperidine (5 drops) in benzene (30 ml) were stirred and heated under reflux. The reaction monitored by tlc was complete after 4 h. The resulting hot dark solution was filtered and the filtrate was cooled to 10 °C. The resulting precipitate was collected and dried. Recrystallization from benzene or benzene/diisopropyl ether gave analytically pure product.

Compound (2a): ratio isomers Z/E (79/21); yield: 61%; mp 190°C (benzene); ir (KBr): ν = 1705, 1650 cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 3.89(s, 3H, OCH_3), 6.95-7.09(m, 2H, H_{arom}), 7.01(s, 1H, $=CH)^Z$, 7.09(s, 1H, $=CH)^E$, 7.12-7.28(m, 1H, H_{arom}), 7.95(d, J=8, 2H, H_{arom}), 8.12-8.26(m, 1H, H_{arom}), 8.59(dd, J= 5, 1.8, 1H, H_{arom}). Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.02; H, 4.53; N, 5.70.

Compound (2b): ratio isomers Z/E (82/18); yield: 55%; mp 168°C (benzene); ir (KBr): ν = 1710, 1650 cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 2.42(s, 3H, CH_3), 7.00(s, 1H, $=CH)^Z$, 7.09(s, 1H, $=CH)^E$, 7.18-7.32(m, 3H, H_{arom}), 7.89(d, J=8, 2H, H_{arom}, 8.07-8.20(m, 1H, H_{arom}), 8.60(dd, J=7.1, 1.2, 1H, H_{arom}). Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 76.02; H, 4.53; N, 5.74.

Compound (2c): ratio isomers Z/E (85/15); yield 47%; mp 188°C (benzene); ir (KBr): ν = 1715, 1660 cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 6.95(s, 1H, $=CH)^Z$, 7.05(s, 1H, $=CH)^E$, 7.20-7.47(m, 3H, H_{arom}), 7.92(d, J=8, 2H, H_{arom}), 8.10-8.20(m, 1H, H_{arom}), 8.61(dd, J=5, 1.5, 1H, H_{arom}). Anal. Calcd for $C_{14}H_8NO_2Cl$: C, 65.26; H, 3.13; N, 5.44. Found: C, 65.02; H, 3.32; N, 5.67.

Compound (2d): ratio isomers Z/E (75/25); yield: 45%; mp 159°C (benzene/diisopropyl ether); ir (KBr): ν = 1720, 1715, 1650 cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 3.90(s, 3H, $OCH_3)^E$, 3.96(s, 3H, $OCH_3)^Z$, 7.17-7.22(m, 1H, $H_{arom})^E$, 7.25-7.30(m, 1H, $H_{arom})^Z$, 7.44-7.67(m, 2H, H_{arom}), 7.72(s, 1H, =CH)^E, 7.90(s, 1H, =CH)^Z, 7.98-8.11(m, 1H, H_{arom}), 8.19(dd, J=7.1, 1.5, 1H, H_{arom}), 8.36(fd, J=7.9, 1H, Harom), 8.59(dd, J=5, 1.5, 1H, H_{arom}). Anal. Calcd for $C_{16}H_{11}NO_4$: C, 68.33; H, 3.94; N, 4.98. Found: C, 68.15; H, 3.99; N, 5.17.

Compound (2e): ratio isomers Z/E (80/20); yield: 53%; mp 198°C (benzene); ir (KBr): ν = 1720, 1660 cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 7.20-7.26(m, 1H, $H_{arom})^E$, 7.28-7.34(m, 1H, $H_{arom})^Z$, 7.35(s, 1H, =CH)^E, 7.44(s, 1H, =CH)^Z, 7.35-7.86(m, 2H, H_{arom}), 8.06(fd, J=7.9, 1H, H_{arom}), 8.20(dd, J=7.9, 1.5, 1H, H_{arom}), 8.35(fd, J=7.9, 1H, H_{arom}), 8.61(dd, J=5.6, 1.5, 1H, H_{arom}). Anal. Calcd for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.01; N, 10.44. Found: C, 62.87; H, 3.14; N, 10.23.

1-Acetyl-2-[(substituted phenyl)methylidene]-3-hydroxy-2,3-dihydroindole (4) ; general procedure :

1-Acetyl-2-[(substituted phenyl)methylidene]-3-oxo-2,3-dihydroindole (1.5 mmol) was added to a stirred suspension of sodium borohydride (0.19 g, 5 mmol) in methanol (25 ml) at room temperature. In few minutes the mixture became hot . The reaction was complete after 10 min. Water (20 ml) was added to the cooled mixture from which a solid precipitated. (Except compound (**4a**) which separated as an oily product which was extracted with CH_2Cl_2 (2 x 20 ml) and isolated by evaporation in vacuo). Recrystallization gave a light yellow solid.

Compound (4a) : yield 84% ; mp 81°C (petroleum ether/benzene); ir (KBr): ν = 3360, 1650 cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 1.87(s, 3H, $COCH_3$), 2.46(br s, 1H, OH), 3.82(s, 3H, OCH_3), 5.54(br s, 1H, CHOH), 6.47(s, 1H, =CH), 6.89(fd, J=7.7, 2H, H_{arom}), 7.14-7.50(m, 5H, H_{arom}), 8.04(fd, J=7.7, 1H, H_{arom}); ms (m/z): 295(M^+). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.02; H, 5.93; N, 4.89.

Compound (4b): yield 66% ; mp 185°C(methanol/water); ir (KBr): ν = 3360, 1660 cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 1.86(s, 3H, $COCH_3$), 2.28(br s, 1H, OH), 2.35(s, 3H, CH_3), 5.55(br s, 1H, CHOH), 6.48(s, 1H, =CH), 7.12-7.29(m, 5H, H_{arom}), 7.35(ft, J=8.8, 1H, H_{arom}), 7.47(fd, J=8.8, 1H, H_{arom}), 8.02(fd, J=8.8, 1H, H_{arom}); ms (m/z): 279 (M^+). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.52; H, 5.95; N, 5.17.

Compound (4d): 1-Acetyl-2-[(2-methoxycarbonylphenyl)methylidene]-3-oxo-2,3-dihydroindole (**1d**) (0.5 g, 1.5 mmol) was added to a stirred suspension of sodium borohydride (0.2 g, 5 mmol) in methanol (25 ml) at room temperature ; the mixture became homogeneous, followed quickly by the precipitation of the white reduction product. The reaction was complete after 10 min. Water (20 ml) was added to the cooled mixture (ice bath) and the solid was collected and washed with water ; yield : 0.37 g (73 %) ; mp 182 °C (methanol/water); ir (KBr) : ν

= 3320 (OH), 1710 (COO), 1645 (NCO) cm^{-1}; ^1H nmr ($CDCl_3$/TMS) : δ = 2.35 (s, 3H, $COCH_3$), 3.36 (d, J=7.9, 1H, OH), 3.84 (s, 3H, OCH_3), 5.12 (d, J=7.9, 1H, CH), 7.13 (ft, J=7.2, 1H, H_{arom}), 7.27-7.43 (m + s, 4H, H_{arom}, =CH), 7.60 (ft, J=7.2, 1H, H_{arom}), 7.96-8.04 (m, 3H, H_{arom}); ms (DCI/NH_3) (m/z): 324 (M^++1). Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.82; H, 5.12; N, 4.28.

2-[(Substituted phenyl)methylidene]-3-hydroxy-7-aza-2,3-dihydrobenzofuran (5) :

Prepared from 2-[(substituted phenyl)methylidene]-3-oxo-7-aza-2,3-dihydrobenzofuran (**2**) in a similar way as for compounds (**4**). The reaction was complete after 30 min at room temperature ; the compounds precipitated as light yellow solids.

Compound (5a): yield: 83% ; mp 152°C (methanol/water); ir (KBr): ν = 3340, 1690, 1605 cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 3.20(br s, 1H, OH), 3.82(s, 3H, OCH_3), 5.74(br s, 1H, CHOH), 5.97(s, 1H, =CH)*, 6.88(d, J=9, 2H, H_{arom}), 6.96(dd, J=7.5, 5, 1H, H_{arom}), 7.65(fd, J=9, 2H, H_{arom}), 7.81(fd, J=7.5, 1H, H_{arom}), 8.13(fd, J=5, 1H, H_{arom}), (*after exchange with D_2O, d, J=1.5); ms (m/z): 255(M^+). Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.31; N, 5.49. Found: C, 70.64; H, 5.26; N, 5.62.

Compound (5b): yield: 75% ; mp 202°C (methanol/water); ir (KBr): ν = 3340, 1685, 1600 cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 2.36(s, 3H, CH_3), 2.48(d, J=9.5, 1H, OH), 5.77(d, J=9.5, 1H, CHOH), 6.03(d, J=1.2, 1H, =CH), 7.02(dd, J=7, 5, 1H, H_{arom}), 7.17(fd, J=8.3, 2H, H_{arom}), 7.66(fd, J=8.3, 2H, H_{arom}), 7.83(fd, J=7, 1H, H_{arom}), 8.21(dd, J=5, 1.2, 1H, H_{arom}). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.52; H, 5.29; N, 5.62.

Compound (5d): yield: 77% ; mp 170°C (methanol/water); ir (KBr): ν = 3320, 1705, 1605 cm^{-1}; ^1H nmr($CDCl_3$/TMS): δ = 2.00(s, 1H, OH), 3.87(s, 3H, OCH_3), 5.85(s, 1H, CHOH), 6.90(s, 1H, =CH), 7.01(dd, J=7, 5, 1H, H_{arom}), 7.24-7.31(m, 2H, H_{arom}), 7.50(ft, J=7, 1H, H_{arom}), 7.81(d, J=7, 1H, H_{arom}), 7.86(d, J=7, 1H, H_{arom}), 8.15(m, 1H, H_{arom}); ms (m/z): 283 (M^+). Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.89; H, 4.75; N, 5.12.

2-[(4-Methoxyphenyl)methylidene]-3-hydroxy-2,3-dihydrobenzofuran (6a) :

2-[(4-Methoxyphenyl)methylidene]-3-oxo-2,3-dihydrobenzofuran (**3a**) (0.49 g, 1.9 mmol) was reacted with $NaBH_4$ (0.1 g, 2.6 mmol) at room temperature in methanol (20 ml) ; The reaction was complete after 30 min ; after addition of water, product (**6a**) precipitated as a light yellow solid ; yield: 0.4 g (81 %) ; mp 115 °C (methanol); ir (KBr): ν = 3300, 1610 cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 2.26(d, J=9.5, 1H, OH), 3.84(s, 3H, OCH_3), 5.74(d, J=9.5, 1H, CHO), 5.95(s, 1H, =CH), 6.92(fd, J=9, 2H, H_{arom}), 7.03-7.10(m, 2H, H_{arom}), 7.33(ft, J=7.6, 1H,

H_{arom}), 7.48(fd, J=7.6, 1H, H_{arom}), 7.66(fd, J=9, 2H, H_{arom}); ms (m/z): 254 (M^+). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.58 ; H, 5.55 . Found: C, 75.43 ; H, 5.68.

2-[(4-Methoxyphenyl)methyl]-3-hydroxy-7-aza-2,3-dihydrobenzofuran (7a) :

2-[(4-Methoxyphenyl)methylidene]-3-oxo-7-aza-2,3-dihydrobenzofuran (**2a**) (0.30 g, 1.2 mmol) was added to a stirred suspension of $NaBH_4$ (0.30 g, 8 mmol) in methanol (25 ml) at room temperature and the mixture was heated under reflux. The reaction was complete after 3 h. The reaction mixture was cooled and poured into water and extracted with CH_2Cl_2 (2 x 20 ml). The organic extracts were washed with water (20 ml) and dried over $MgSO_4$. Evaporation in vacuo left the crude product as a foam which was purified by preparative tlc on silica gel (CH_2Cl_2/methanol 95/5 v/v). Two diastereomers (**7a$_1$**)(Rf = 0.37; yield: 46%) and (**7a$_2$**)(Rf = 0.32 yield: 39%) enriched (90%) in each of the two diastereomers were thus obtained for analytical controls. Compounds (**7a**); yield: 0.28 g (92%); ir (KBr): ν = 3220, 1610 cm^{-1}; ms (m/z): 257 (M^+). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.87; H, 5.94; N, 5.73.

Diastereomer (7a$_1$): ^{1}H Nmr ($CDCl_3$/TMS): δ = 2.86-3.07(m, 2H, CH_2), 3.20(br s, 1H, OH), 3.53(s, 3H, OCH_3), 4.33-4.44(m, 1H, CHO), 4.80-4.88(m, 1H, CHOH), 6.49-6.62(m, 1H, H_{arom}), 6.58(fd, J=7, 2H, H_{arom}), 7.02, (fd, J=7, 2H, H_{arom}), 7.43(fd, J=7, 1H, H_{arom}), 7.70(fd, J=4, 1H, H_{arom}).

Diastereomer (7a$_2$): ^{1}H Nmr ($CDCl_3$/TMS): δ = 2.54(dd, J=14, 7, 1H, CH_2), 2.76(dd, J=14, 7, 1H, CH_2), 3.30(br s, 1H, OH), 3.50(s, 3H, OCH_3), 4.46-4.51(m, 1H, CHO), 4.80-4.88(m, 1H, CHOH), 6.49-6.62(m, 1H, H_{arom}), 6.54(fd, J=7, 2H, H_{arom}), 6.90(fd, J=7, 2H, H_{arom}),7.38(fd, J=7, 1H, H_{arom}), 7.70(fd, J=4, 1H, H_{arom}).

2-[(4-Methylphenyl)methyl]-3-hydroxy-7-aza-2,3-dihydrobenzofuran (7b) :

Compound (**7b**) was obtained as a mixture of diastereomers (**7b$_1$**) (Rf = 0.20 , CH_2Cl_2/methanol 95/5 v/v) and (**7b$_2$**)(Rf = 0.17) in the ratio 76/24; mp 144°C (methanol/water); yield: 62%; ir (KBr): ν = 3220, 1610 cm^{-1}; Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.90; H, 6.12; N, 5.88.

Diastereomer (7b$_1$): ^{1}H Nmr ($CDCl_3$/TMS): δ = 2.33(s, 3H, CH_3), 2.45(br s, 1H, OH), 3.25(m, 2H, CH_2), 4.69(m, 1H, CHO), 5.11(br s*, 1H, CHOH), 6.86(dd, J=8, 6.5, 1H, H_{arom}), 7.13(d, J=8.7, 2H, H_{arom}), 7.28(d, J=8.7, 2H, H_{arom}), 7.70(dd, J=6.5, 1.6, 1H, H_{arom}), 8.09(dd, J=8, 1.6, 1H, H_{arom}); (*d, J= 6.5 after exchange with D_2O).

Diastereomer (7b$_2$): ^{1}H Nmr ($CDCl_3$/TMS): δ = 2.30(s, 3H, CH_3), 2.75(br s, 1H, OH), 2.87(dd, J=14, 7, 1H, CH_2), 3.10(dd, J=14, 7, 1H, CH_2), 4.77(m, 1H, CHO), 5.11(br s*, 1H, CHOH), 6.84(dd, J=8, 6.5, 1H, H_{arom}), 7.13(d, J=8.7, 2H, H_{arom}), 7.28(d, J=8.7, 2H, H_{arom}), 7.65(dd, J=6.5, 1.6, 1H, H_{arom}), 8.07(dd, J=8, 1.6, 1H, H_{arom}); (*d, J= 6.5 after exchange with D_2O).

2[(2-Methoxycarbonylphenyl)methyl]-3-hydroxy-7-aza-2,3-dihydrobenzofuran (7d) :

Compound (**2d**) was reduced as described previously for compound (**2a**) ; compound (**7d**) : yield: 70%; ir (KBr): ν = 3200, 1710, 1605 cm^{-1}; ms (m/z) : 285 (M^+). Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.48; H, 5.39; N, 5.03. Two diastereomers (**7d$_1$**) (Rf = 0.41, yield: 36%) and(**7d$_2$**) (Rf = 0.35, yield: 24%) were obtained by preparative tlc on silica gel (CH_2Cl_2/methanol 95/5 v/v).

Diastereomer (7d$_1$): ^{1}H Nmr ($CDCl_3$/TMS): δ = 3.26-3.36(m, 1H, CH_2), 3.81(dd, J=14, 4, 1H, CH_2), 3.86(s, 3H, CH_3), 4.26(br s, 1H, OH), 4.73-4.80(m, 1H, CHOH), 5.21(ft, J=4, 1H, CHO), 6.78-6.86(m, 1H, H_{arom}), 7.25-7.50(m, 3H, H_{arom}), 7.62-7.72(m, 1H, H_{arom}), 7.90-8.07(m, 2H, H_{arom}).

Diastereomer (7d$_2$): ^{1}H Nmr ($CDCl_3$/TMS): δ = 3.26-3.36(m, 1H, CH_2), 3.48(dd, J=14, 4, 1H, CH_2), 3.86(s, 3H, CH_3), 4.38(br s, 1H, OH), 4.80-4.87(m, 1H, CHO), 5.14(br ft, 1H, CHOH), 6.78-6.86(m, 1H, H_{arom}), 7.25-7.50(m, 3H, H_{arom}), 7.62-7.72(m, 1H, H_{arom}), 7.90-8.07(m, 2H, H_{arom}).

1-Acetyl-2-(4-methoxybenzyl)-3-hydroxy-2,3-dihydroindole (8a) :

Reduction of 1-acetyl-2-(4-methoxybenzyl)-3-oxo-2,3-dihydroindole[6] as described for compounds (**4**) gave after addition of water an oily product. After work up the desired product was obtained as a red foam ; yield 92 %; ir (KBr): ν = 3360, 1630(large), 1600 cm^{-1}; one diastereomer (nmr); ^{1}H nmr (DMSO-d_6/TMS): δ = 1.47(br s, 3H, $COCH_3$), 2.44(dd, J=14, 4.5, 1H, CH_2), 3.03(dd, J=14, 9.5, 1H, CH_2), 3.69(s, 3H, OCH_3), 4.52(br s, 1H, OH), 5.48 (ft, J=6, 1H, CH), 5.95(fd, J=6, 1H, CHOH), 6.81(fd, J=8, 2H, H_{arom}), 7.02(fd, J=8, 2H, H_{arom}), 7.04(fd, J=8, 1H, H_{arom}), 7.07(ft, J=7.6, 1H, H_{arom}), 7.20(ft, J=7.5, 1H, H_{arom}), 7.31(fd, J=7.7, 1H, H_{arom}); ms (m/z): 297 (M^+). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.57; H, 6.28; N, 4.84.

2-(4-Methoxybenzyl)-3-hydroxy-2,3-dihydrobenzofuran (9a) :

2-[(4-Methoxyphenyl)methylidene]-3-oxo-2,3-dihydrobenzofuran (**3a**) (0.25 g, 1mmol) was added to a stirred suspension of $NaBH_4$ (0.13 g, 3mmol) in ethanol (15 ml) at reflux for 1.5 h. Water (15 ml) was added to the cooled mixture. Evaporation in vacuo of the mixture left an oil which was chromatographed on a silica gel column (230/400 mesh) using CH_2Cl_2 as eluent ; yield 0.15g (59%) ; mixture 50/50 of diastereomers (**9a$_1$**) (Rf = 0.52) and (**9a$_2$**) (Rf = 0.47) ; compound (**9a$_1$**) was the more polar by tlc (CH_2Cl_2/methanol, 95/5 v/v); ir (film): ν = 3360 cm^{-1}; ^{1}H nmr ($CDCl_3$/TMS): δ = 1.70(br s, 1H, OH)$^{1 \text{ or } 2}$, 2.00(br s, 1H, OH)$^{1 \text{ or } 2}$, 2.82(dd, J=14, 7, 1H, CH_2)^1, 2.97(dd, J=14, 7.5, 1H, CH_2)^1, 3.18(dd, J= 14, 7, 1H, CH_2)^2, 3.23(dd, J=14, 7.5, 1H, CH_2)^2, 3.78(s, 3H, OCH_3)^1, 3.81(s, 3H, OCH_3)^2, 4.57 (d, J=7, 1H, CHO)^2, 4.70(m, 1H, CHO)^1, 5.00(br s, 1H, CHOH)$^{1 \text{ or } 2}$, 5.06(br s, 1H, CHOH)$^{1 \text{ or } 2}$, 6.83-6.98(m, 3H, H_{arom}), 7.15-7.44(m, 5H, H_{arom}), 1 or 2 refer to (**9a$_1$**) and (**9a$_2$**); ms (m/z): 256 (M^+). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.27; H, 6.11.

8-Oxo-1H-[2](9a,1)-dihydrobenzoxepino[4,3-h]indole (11):

A mixture of compound (**4d**) (0.20 g, 0.6 mmol) and sodium carbonate (0.19 g, 1.8 mmol) in methanol (20 ml) was stirred at room temperature for 0.5 h. Cold water (60 ml) was added ; a precipitate was isolated and washed with water ; yield 0.13g (87%); mp 197°C (methanol/water); ir (KBr): ν = 3280 (NH), 1740 (COO) cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 6.62 (fd, J=2.2, 1H, CH), 6.66 (s, 1H, =CH), 7.12 (ft, J=7.6, 1H, H_{arom}), 7.21 (ft, J=7.6, 1H, H_{arom}), 7.33 (fd, J=8.5, 1H, H_{arom}), 7.53 (fd, J=8.5, 1H, H_{arom}), 7.61 (ft, J=7.6, 2H, H_{arom}), 7.73 (ft, J=7.6, 1H, H_{arom}), 7.98 (fd, J= 7.6, 1H, H_{arom}), 8.32 (br s, 1H, NH); ^{13}C-nmr (DMSO-*d6*): δ = 76.7(CH-O), 102.1(=CH), 111.4, 119.2, 120.4, 122.1, 123.3, 124.9, 129.6, 134.4(CH_{arom}), 125.4(=C), 127.1, 133.3, 137.0, 148.0(C_{arom}), 169.5(C=O); ms (DCI/NH_3) (m/z): 250 (M^++1). Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found : C, 77.18; H, 4.49; N, 5.61.

Formation of compounds (11), (12), (13):

1-Acetyl-2-[(2-methoxycarbonylphenyl)methylidene]-3-oxo-2,3-dihydroindole (**1d**) (0.55 g, 1.7 mmol) was added to a stirred suspension of sodium borohydride (0.2 g, 5 mmol) in methanol (25 ml) at room temperature and the mixture was heated under reflux 2 h. Water (20 ml) was added to the cooled mixture and the product was extracted with CH_2Cl_2 (2 x 20 ml); the organic extracts were washed with water and dried oved $MgSO_4$. Evaporation in vacuo gave the crude product as a brown foam. Recrystallisation in isopropyl ether/methanol (2/1) followed by preparative tlc on silica gel (CH_2Cl_2 as eluent) gave the pure products (**11**) (yellow solid : yield: 0.230 g (54%); mp 209°C (methanol/water)), compound (**12**) (yield : 0.063 g (15%)) and compound (**13**) (yield : 0.021 g (5%)).

Indolo[1,2-b]isoquinoline-5,12-dione (12):

A solution of compound (**20**) (0.5 g, 1.8 mmol) in acetic anhydride (38 ml, 320 mmol) was heated at 85-90 °C with stirring for 22 h. The resulting mixture was concentrated in vacuo and cooled to give a yellow precipitate. This isolated solid was dissolved in dichloromethane (50 ml) and the solution was washed with 5 % Na_2CO_3, water and brine then dried ($MgSO_4$). Evaporation gave pure product (**12**) ; yield : 0.23 g (52 %) ; mp 214 °C (acetone); ir (KBr) : ν = 1690 (CO), 1660 (NCO) cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 7.38 (ft, J= 7.9, 1H, H_{arom}), 7.59 (ft, J= 7.9, 1H, H_{arom}), 7.65 (s, 1H, =CH), 7.75 (fd, J= 7.9, 1H, H_{arom}), 7.79-7.89 (m, 2H, H_{arom}), 8.30 (fd, J= 8.7, 1H, H_{arom}), 8.45 (fd, J= 8.7, 1H, H_{arom}), 8.63 (fd, J= 8.7, 1H, H_{arom}); ms (DCI/NH_3) (m/z): 248 (M^++1). Anal. Calcd for $C_{16}H_9NO_2$: C, 77.72; H, 3.67; N, 5.66. Found: C, 77.68; H, 3.72; N, 5.69.

Indolo[1,2-b]isoquinoline-6,12-dione (13):[12]

Compound (**1d**) (0.35 g, 1.1 mmol) and potassium hydroxide (0.62 g, 11 mmol) were dissolved in methanol (30 ml); the mixture was heated 3 h at 60°C and evaporated on vacuo. The crude solid was suspended in water (25

ml) which was acidified to pH 1 with dilute HCl. The orange solid was collected and recrystallized from acetone; yield: 0.24 g (88%); mp 236°C (lit.,[12] mp 241°C).

1-Acetyl-2-[(4-methylphenyl)hydroxymethyl]indole (15b); 1-acetyl-2[(4-methylphenyl)acetoxymethyl]indole (16b):

Compound (**4b**) (0.279 g, 1 mmol) and acetic anhydride (5 ml, 53 mmol) were heated 2 h at 80°C. After evaporation of the excess of the acetic anhydride water (15 ml) and CH_2Cl_2 (20 ml) were added and the organic layer was washed with water (15 ml); after drying over $MgSO_4$ and evaporation, the oil was chromatographed on a silica gel column (240/400 mesh) using CH_2Cl_2 as eluent. Compound (**16b**), yield 0.064 g (20%), was first obtained as an oil then compound (**15b**): yield 0.042 g (15%), (oil).

Compound (15b): Ir (KBr): ν = 3300 (OH), 1700(CO) cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 2.38(s, 3H, CH_3), 2.83(s, 3H, $OCOCH_3$), 4.66 (d, J= 7.9, 1H, OH), 6.12(d, J= 7.9, 1H , CH), 6.31(s, 1H, =CH), 7.16 (fd, J=7.9, 2H, H_{arom}), 7.25-7.35(m, 3H, H_{arom}), 7.51(fd, J=8.5, 1H, H_{arom}), 7.66(fd, J=8.5, 2H, H_{arom}); ms (DCI/NH_3) (m/z): 262 (M^++1-18). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.52; H, 6.03; N, 4.84.

Compound (16b): Ir (KBr): ν = 1720 (CO) cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 2.14(s, 3H, $OCOCH_3$), 2.36(s, 3H, CH_3), 2.72(s, 3H, $NCOCH_3$), 6.71(s, 1H, CH), 7.16(fd, J=8, 2H, H_{arom}) 7.22-7.38(m, 5H, H_{arom}), 7.68(fd, J=8, 2H, H_{arom}). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.99; H, 5.78; N, 4.17.

1-Sulfonyl-2[(4-methylphenyl)acetoxymethyl]indole (16f):

Acetylation at room temperature of **15f** with a large excess of acetic anhydride during 8 h afforded **16f** as an oil after chromatography on a silica gel column (230/400 mesh) with CH_2Cl_2 as eluent; oil; yield: 65%; ir (KBr): ν = 1720(CO) cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 2.08(s, 3H, $OCOCH_3$), 2.33(s, 3H, CH_3), 6.59(s, 1H, CH), 7.15(fd, J= 8.5, 2H, H_{arom}), 7.16-7.40(m, 8H, H_{arom}), 7.54(s, 1H, =CH), 7.71(fd, J=8.5, 2H, H_{arom}), 8.09(fd, J=8.5, 1H, H_{arom}). Anal. Calcd for $C_{24}H_{21}NO_4S$: C, 68.72; H, 5.05; N, 3.34. Found: C, 68.45; H, 4.93; N, 3.42.

5-Hydroxyindolo[1,2-b]isoquinolin-12-one (17) :

$NaBH_4$ (0.08 g, 2.1 mmol) was added to a stirred suspension of **12** (0.07 g, 0.28 mmol) in methanol (7 ml) under argon. After stirring at room temperature for 20 min ice cold water was added dropwise and the precipitate was isolated and washed with water. Purification by preparative tlc on silica gel (using CH_2Cl_2 as eluent) gave pure product ; yield : 0.04 g (57 %) ; mp 165 °C (methanol/water); ir (KBr) : ν = 3420 (OH), 1670 (CO) cm^{-1}; ^1H nmr ($CDCl_3$/TMS) : δ = 2.44 (br, s, 1H, OH), 5.88 (br, s, 1H, CH), 6.84 (s, 1H, =CH), 7.20-7.55 (m, 4H, H_{arom}), 7.62 (ft, J= 7.5, 1H, H_{arom}), 7.71 (fd, J= 7.5, 1H, H_{arom}), 8.26 (fd, J= 7.9, 1H, H_{arom}), 8.53 (fd, J=

7.9, 1H, H_{arom}); ms (DCI/NH_3) (m/z): 250 (M^++1); Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found C, 76.94; H, 4.58; N, 5.73.

This product was oxidized very easily and gave quickly in air, at room temperature, a mixture of (**12**) and (**17**).

6-Hydroxyindolo[1,2-b]isoquinolin-12-one (18) :

Indolo[1,2-*b*]isoquinoline-6,12-dione (**13**) (0.16 g, 0.64 mmol) was added to a stirred suspension of sodium borohydride (0.15 g, 4 mmol) in methanol (20 ml) at room temperature. In few minutes the mixture became hot and a clear solution occurred followed quickly by the precipitation of the white reduction product. The reaction was complete after 30 min. Water (10 ml) was added to the cooled mixture and the solid was collected and washed with water ; yield : 0.12 g (75 %) ; mp 232 °C (methanol); ir (KBr) : ν = 3310 (OH), 1670 (CO) cm^{-1}; ^1H nmr ($CDCl_3$/TMS) : δ = 3.99 (d, J=11, 1H, OH), 5.75 (d, J=11, 1H, CH-O), 6.89 (s, 1H, =CH), 7.00-7.13 (m, 2H, H_{arom}), 7.40-7.50 (m, 2H, H_{arom}), 7.52-7.62 (m, 3H, H_{arom}), 8.29 (fdd, J=8, 3.5, 1H, H_{arom}); ms (DCI/NH_3) (m/z): 250 (M^++1). Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found C, 76.89; H, 4.62; N, 5.46.

1-(Phenylsulfonyl)indol-2-yl-2-carboxyphenyl ketone (19) :

To a stirred solution of diisopropylamine (1.32 g, 13 mmol) in dry THF (28 ml), under argon at - 78 °C, butyllithium (1.58 M in hexane, 7.8 ml, 12.3 mmol) was dropwise added . The mixture was stirred for 20 min at - 60 °C then cooled at - 78 °C and a solution of 1-phenylsulfonylindole (3 g, 11.6 mmol) in dry THF (30 ml) was added dropwise. The mixture was stirred for 1.5 h at - 78 °C and allowed to warm slowly to + 5 °C over 1 h. The resulting orange solution was cooled at - 78 °C and a solution of phthalic anhydride (3.36 g, 22.7 mmol) in dry THF (20 ml) was added dropwise and stirred for 1 h at - 78 °C. The reaction mixture was then allowed to warm slowly to room temperature overnight then poured into 1 % HCl (350 ml) and extracted with CH_2Cl_2 (3 x 100 ml). The combined extracts were washed with water then extracted with 5 % Na_2CO_3 (4 x 50 ml). The aqueous basic phase was washed with ether then acidified to pH 1 with concentrated hydrochloric acid. The acid aqueous solution was extracted with CH_2Cl_2 (3 x 60 ml), washed with brine, dried ($MgSO_4$) and evaporated. The resulting foam was triturated in chloroform to give a white pure product; yield : 1.50 g (32 %); mp 222 °C (acetone); ir (KBr) : ν = 3310 (OH), 1720 (COOH), 1680 (CO) cm^{-1}; ^1H nmr (DMSO-d_6/TMS) : δ = 7.05(s, 1H, =CH), 7.32(ft, J=6.3, 1H, H_{arom}), 7.53-7.94(m, 10H, H_{arom}), 8.17(ft, 2H, H_{arom}), 13.60(br s, 1H, OH); ms (m/z): 405 (M^+). Anal. Calcd for $C_{22}H_{15}NO_5S$: C, 65.18; H, 3.73; N, 3.45. Found C, 65.32; H, 3.81; N, 3.31.

2-Indolyl-2-carboxyphenyl ketone (20) :

A mixture of compound (**19**) (0.99 g, 2.45 mmol) and potassium carbonate (1.31 g, 9.5 mmol) in methanol (27 ml) and water (10 ml) was refluxed with stirring for 5 h. Methanol was evaporated and ice cold water (100 ml) was added to the yellow solid. The resulting suspension was acidified to pH 1 with concentrated hydrochloric acid. The precipitate was collected and washed with water to give a light yellow product ; yield: 0.51 g (79 %) ; mp 234 °C (acetone); ir (KBr) : ν = 3200 (OH, NH), 1705 (COOH), 1695 (CO), cm^{-1}; ^1H nmr (DMSO-d_6/D_2O) : δ = 6.57 (s, 1H, =CH) , 7.04 (ft, J=7, 1H, H_{arom}) , 7.28 (ft, J=7, 1H, H_{arom}) , 7.38-7.75 (m, 5H, H_{arom}) , 7.94 (fd, J=7, 1H, H_{arom}); ms (m/z): 265 (M^+). Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.34; H, 4.31; N, 5.09.

2-(2-Methoxycarbonylbenzyl)-3-oxo-7aza-2,3-dihydrobenzofuran (21) :

Method A : Compound (**2d**) (0.13 g, 0.4 mmol) was added to a stirred suspension of sodium borohydride (0.05 g, 1.3 mmol) in methanol (6.5 ml) and the mixture was heated under reflux. The reaction monitored by tlc was stopped after 2 h. Water (7 ml) was added to the ice cooled mixture and the product was extracted with CH_2Cl_2 (2 x 10 ml). The combined extracts were washed and dried over $MgSO_4$. Evaporation in vacuo gave a yellow oil which was purified by preparative tlc on silica gel (CH_2Cl_2 as eluent) ; yield : 0.070 g (62%) ; oil; ir (film): ν = 1725, 1715, 1605 cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 3.25(dd, J=14, 9.5, 1H, CH_2), 3.90(dd, J=14, 3.8, 1H, CH_2), 3.95(s, 3H, OCH_3), 5.06(dd, J=9.5, 3.8, 1H, CHO), 7.06-7.12(m, 2H, H_{arom}), 7.25-7.50(m, 2H, H_{arom}), 7.92-8.05(m, 2H, H_{arom}), 8.55(dd, J=4.6, 2, 1H, H_{arom}); ms (m/z): 283(M^+). Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.92; H, 4.72; N, 5.03.

Method B : Sodium carbonate (0.015 g, 0.14 mmol) was added to a stirred solution of compound (**5d**) (0.1 g, 0.3 mmol) in methanol (5ml) and the mixture was heated under reflux for 2 h ; ice cooled water was added to the cooled mixture and the product was extracted with CH_2Cl_2 (2 x 10 ml). The crude product was pure and did not need a preparative tlc; oil; yield: 0.013 g (88 %).

Indolo[1,2-b]-5,5a-dihydroisoquinoline-6,12-dione (22) :

Compound (**22**) was obtained from compound (**13**) using ethyl acetate as solvent for the hydrogenation; yield: 46%; mp 156 °C (methanol); ir (KBr) : ν = 1715 (CO), 1670 (NCO) cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 3.05 (ft, J=18, 1H, CH_2), 3.46 (dd, J=16, 4, 1H, CH_2), 4.55 (dd, J=14, 4, 1H, CHCO), 7.25-7.28 (m, 3H, H_{arom}), 7.65-7.90 (m, 3H, H_{arom}), 8,19 (fd, J=3.2, 1H, H_{arom}), 8.65 (d, J=3.2, 1H, H_{arom}); ms (DCI/NH_3) (m/z): 250 (M^++1). Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.65. Found C, 77.23; H, 4.49; N, 5.48.

6-Hydroxy-5a,6-dihydroindolo[1,2-b]isoquinolin-6(5H)-one (23) :

Sodium borohydride (0.06 g, 1.5 mmol) was added to a stirred suspension of compound (**22**) (0.05 g, 0.2 mmol) in methanol (6 ml). The mixture became hot and a clear solution occurred. The reaction monitored by tlc was complete after 20 min. Water (10 ml) was added dropwise to the cooled mixture and the precipitated solid (mixture of compounds **18** and **23**) was isolated and washed with water ; compound (**18**) and compound (**23**) were obtained after preparative tlc on silica gel using CH_2Cl_2 as eluent; compound (**18**); yield: 0.010 g (19%); compound (**23**); yield: 0.021 g (41 %) ; mp 197 °C (methanol/water). Compound (**23**); ir (KBr) : ν = 3320 (OH), 1640 (NCO) cm^{-1}; ^1H nmr ($CDCl_3$/TMS): δ = 2.57(d, J=10, 1H, OH), 3.10(t, J=14, 1H, CH_2), 3.37(dd, J=14, 1H, CH_2), 4.19(m, 1H, CH), 5.25(t, J=10, 1H, CHOH), 7.00-7.15(m, 2H, H_{arom}), 7.26-7.63(m, 4H, H_{arom}), 8.12 (fd, J=7, 1H, H_{arom}), 8.32(fd, J=7, 1H, H_{arom}); ms (DCI/NH_3) (m/z): 252 (M^++1). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.53; H, 5.37; N, 5.49.

Indolo[1,2-b]isoquinolin-12 (5H)-one (24):[12]

Compound (**13**) (0.21 g, 0.85 mmol) was suspended in methanol (50 ml) in the presence of 10% Pd/C (0.08 g) under hydrogen at room temperature under pressure (3 atm); after stirring for 24 h the mixture was filtered and evaporated. The solid was chromatographed on a silica gel column (230/400 mesh) using CH_2Cl_2 as eluent; yield: 0.11 g (57 %); mp 189 °C (lit.,[12] 201 °C).

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