New Diastereoselective Synthesis of 3-Alkylidene-1-methyloxindoles

Pilar López-Alvarado, Carmen Avendaño*

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain
Fax +34(91)3941822; E-mail: avendano@eucmax.sim.ucm.es

Received 12 June 2001; revised 26 September 2001

Abstract: Addition of alkyl or aryl α-substituted acetophenones to *N*-methylisatin in basic media gives diastereomeric mixtures of the corresponding α-substituted 3-benzoylmethyl-3-hydroxy-1-methyloxindole in good yields. Under anhydrous conditions (concentrated sulfuric acid at 0 °C) these adducts eliminate benzoic acid, instead of water, to give pure (*E*)-3-alkylidene derivatives in quantitative yield. Applying the same treatment to the α-unsubstituted analogue, dehydration took place to give pure (*Z*)-3-benzoylmethylen-1-methyloxindole.

Key words: indoles, addition reactions, eliminations, rearrangements, isatinylidenes

Some 3-alkylidenoxindole derivatives have recently attracted pharmacological interest in preventing, treating and relieving proliferative vascular lesions such as vascular reconstriction after percutaneous transluminal coronary recanalization, arterial sclerosis, peripheral embolism and angiitis.[1] Their synthesis by base-catalyzed condensation of aldehydes[2] or ketones[3] with oxindoles, or by Wittig reaction of aldehydes with 3-indolyltriphenylphosphoranylidene derivatives[4] usually requires rather drastic conditions and gives mixtures of *E*/*Z*-diastereomers. The same mixtures are normally formed in the alternative condensations of isatin derivatives and methylene active reagents, either in the presence of base or in Wittig reactions.[5]

Addition of acetophenone (**1a**) to *N*-methylisatin in basic medium to give 3-benzoylmethyl-3-hydroxy-1-methyloxindole (**2**), followed by dehydration in acid to the (*E*)-olefin **3** (Table 1 and Scheme 1), was first described in 1932.[6] However, we have not found any literature precedent of this protocol involving α-substituted acetophenones. This work comprises some of these adducts and their subsequent acid treatment.

With the exception of compound **12** (Tables 1 and 2), which precipitated in ethanol as a single diastereoisomer, addition of phenones **1b**–**e** to *N*-methylisatin gave diastereomeric mixtures in which the *erythro* isomers were the major products (Tables 1 and 2).

Assignment of the relative configuration of the two stereocenters by extensive NMR experiments (HETCOR, COSY and NOE) was possible thanks to the conformational restriction imposed by a hydrogen-bonded six-membered pseudocyclic structure involving the C(3β)=O

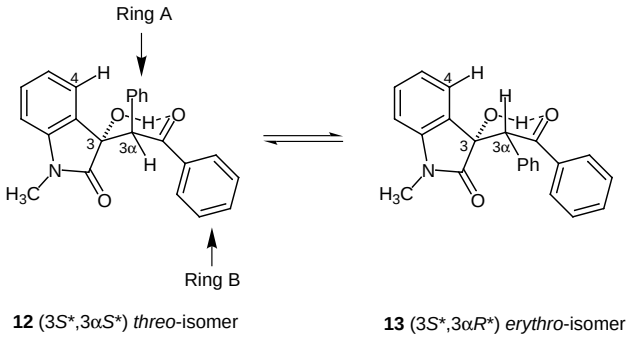
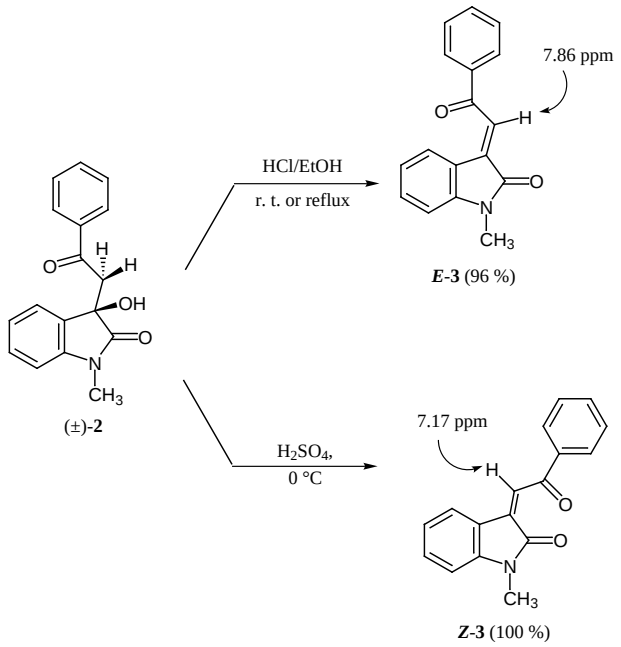


Figure Conformations of *threo*-isomer **12** and *erythro*-isomer **13**

carbonyl and the C(3)-OH groups (Figure). Thus, spectroscopic data of *threo*-isomers **12** and **15** (Tables 3 and 4) showed the indole H-4 signal more shielded (Δδ > 1 ppm) than their diastereomers **13** and **14**, indicating that the H-4 proton is close to the benzene ring A in the first case. In fact, irradiation of the H-4 proton in compounds **12** and **15** produced a NOE enhancement of the protons H-2'', 6'' (ring A). On the other hand, compounds **13** and **14** showed NOEs between H-2', 6' (ring B) and H-2'', 6''-protons, indicating the proximity of rings A and B. In a model where the benzene indole ring is located in the pseudocy-

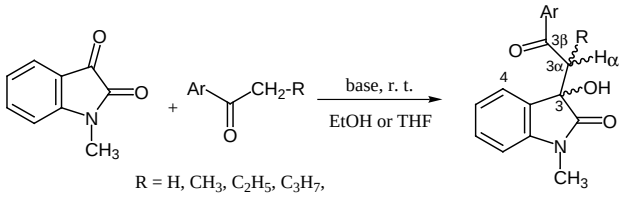


Scheme 1

Synthesis 2002, No. 1, 28 12 2001. Article Identifier:
1437-210X,E;2002,0,01,0104,0110,ftx,en;T04501SS.pdf.

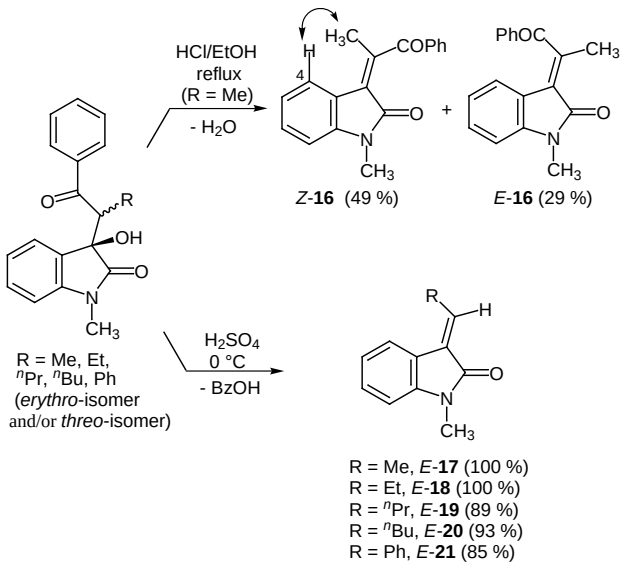
ISSN 0039-7881

Table 1 Addition of Acetophenones to *N*-Methylisatin



Compound	Ar	R	Base	Configuration	Diasteromeric Ratio	Isolation	Yield (%)
(±)-**2**[a]	Ph	H	piperidine	3*S* + 3*R*	–	precipitation	84
(±)-**4**	Ph	Me	KOH	*erythro*	**4**:**5** = 3:1	chromatography	71
(±)-**5**	Ph	Me	KOH	*threo*		chromatography	24
(±)-**6**	Ph	Et	KOH	*erythro*	**6**:**7** = 2:1	chromatography	60[b]
(±)-**7**	Ph	Et	KOH	*threo*		chromatography	30[b]
(±)-**8**	Ph	Pr	piperidine	*erythro*	**8**:**9** = 4:1	chromatography	65[b]
(±)-**9**	Ph	Pr	piperidine	*threo*		chromatography	17[b]
(±)-**10**	Ph	Bu	piperidine	*erythro*	**10**:**11** = 7:2	chromatography	73[b]
(±)-**11**	Ph	Bu	piperidine	*threo*		chromatography	21[b]
(±)-**12**	Ph	Ph	piperidine	*threo*	–[c]	precipitation	80
(±)-**13**	Ph	Ph	piperidine	*erythro*	–[d]	–	–
(±)-**14**	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	piperidine	*erythro*	**14**:**15** = 3:1	chromatography	65[b]
(±)-**15**	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	piperidine	*threo*		chromatography	22[b]

[a] Ref.[6]
[b] Overall yield calculated for converted starting material.
[c] Isolated as a single diastereomer.
[d] Formed by epimerization of (±)-**12** in DMSO-d_6 and observed by ^{1}H NMR.



Scheme 2

cle equatorially, the (3*S**, 3α*R**)-*erythro*-isomers **13** and **14** have ring A also equatorial and far away from the H-4-proton, while the (3*S**, 3α*S**)-*threo*-isomers **12** and **15** have this ring upon the H(4)-proton in an axial position.[7] Because of the acidity of benzylic 3α-protons, both isomers of compounds with R = aryl are soon equilibrated in solution and decompose in a retroaldol reaction.

^{1}H NMR data of adducts where R is Me, Et, Pr or Bu, did not allow a conclusive assignment and the stereochemisty of both diastereomers was proposed by assuming that their relative stability was also in favor of the *erythro*-isomers. Because of the lower reactivity of the H-3α proton, these adducts are stable in deuterated chloroform. The addition reaction failed with isobutyrophenone, indicating that the active mehylene must not be disubstituted.

According to the literature,[6] compound **2** was dehydrated in HCl/EtOH at room temperature to give (*E*)-**3** as the only product, but when we treated **2** with concentrated sulfuric acid at 0 °C for 5 minutes (*Z*)-**3**[8] was quantitatively obtained (Scheme 1).[9] This unprecedented result must be a consequence of the anhydrous conditions.[10]

When we studied the α-substituted adducts, we observed that dehydration of the mixture of isomers **4** and **5** (derived from propiophenone) with HCl/EtOH required their treatment under reflux and gave a 5:3 mixture of (*Z*)-**16**/(*E*)-**16** together with a considerable amount of 1-methylisatin, which is formed in a retroaldol reaction.[11] However, treatment of the same mixture with sulfuric acid at 0 °C gave quantitatively (*E*)-**17** by elimination of benzoic acid. The same behavior was observed in compounds **6**–**12**, which gave (*E*)-**18**–(*E*)-**21** as products (Scheme 2).

The elimination of benzoic acid does not occur during the quenching with water, since the treatment of adducts with dilute sulfuric acid reverted them near quantitatively to the starting materials.

It can be concluded that, since most of the methods so far described for the synthesis of 3-alkylidenoxindole derivatives gave mixtures of *E/Z*-isomers, the debenzoylation in sulfuric acid of adducts of *N*-methylisatin and α-substituted acetophenones here described, can be proposed as an alternative method for the synthesis of pure (*E*)-isomers.

IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrophotometer, for solids as KBr pellets and liquids as films between NaCl paltes. NMR spectra were obtained on Bruker AC-250 (250 MHz for ^{1}H, 63 MHz for ^{13}C) and Bruker AC-200 spectrometers (Servicio de Espectroscopía, Universidad Complutense). The solvents used were $CDCl_3$ and DMSO-d_6. Interchangeable chemical shifts are marked with the symbol *.

Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense. Melting points were measured on a 'Reichert' hot stage microscope model 723, and are uncorrected. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (Scharlau Cf 530), which were visualized with a UV lamp (Camag UV-II, 254 and 366 nm). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230–400 mesh). All reagents were of commercial quality (Aldrich, Merck, SDS, Probus, Panreac, Scharlau, Fluka) and were used as received. Petroleum ether refers to the fraction boiling at 40–60 °C.

Table 2 Melting Points and IR Data of Compounds **2**,**4**–**15**

Compound[a]	IR (cm^{-1})	Mp (°C) (solvent)
(±)-**2**	3370 (OH), 1686 (C=O)	166–167[b] (EtOH)
(±)-**4**	3388 (OH), 1693 (C=O)	128–130 (EtOH)
(±)-**5**	3328 (OH), 1700, 1677 (C=O)	134–136 (EtOH)
(±)-**6**	3592, 3519, 3294 (OH), 1697, 1665 (C=O)	103–105 (EtOH)
(±)-**7**	3334 (OH), 1698, 1663 (C=O)	156–158 (EtOH)
(±)-**8**	3379 (OH), 1715, 1681 (C=O)	110–111 (Et_2O)
(±)-**9**	3380 (OH), 1703, 1680 (C=O)	152–154 (Et_2O)
(±)-**10**	3380 (OH), 1715, 1682 (C=O)	107–109 (Et_2O)
(±)-**11**	3378 (OH), 1704, 1679 (C=O)	135–137 (Et_2O)
(±)-**12**	3338 (OH), 1682 (C=O)	127–129 (EtOH)
(±)-**14**	3326 (OH), 1719, 1648 (C=O)	160–162 (Et_2O)
(±)-**15**	3378 (OH), 1717, 1673 (C=O)	Oil

[a] Satisfactory microanalyses obtained: C ±0.37, H ±0.33, N ±0.21.
[b] Lit.[6] mp 168–170 °C.

Addition of Acetophenones 1a–e to *N*-Methylisatin; General Procedure

Compounds **2**, **8**–**15**: *N*-Methylisatin (10 g, 6.21 mmol) and an equimolecular amount of the corresponding acetophenone were dissolved in absolute ethanol (200 mL) (or THF for compounds **14** and **15**) and piperidine (2 mL) was added. The mixture was allowed to stand overnight at r.t. In the case of compounds **2** and **12**, the off-white precipitates formed were separated by filtration and for compounds **8**–**11**, **14** and **15**, the mixture was concentrated under reduced pressure to give an orange oil which was purified by flash chromatography on silica gel ($CHCl_3$ to 90% $CHCl_3$–Et_2O).

Compounds **4**-**7**: Equimolecular amounts of *N*-methylisatin and the corresponding acetophenone were dissolved in 60% aq EtOH (15 mL) containing 0.16% of KOH per gram of isatin. The mixture was allowed to stand overnight at r.t. and then isolated following the method for compounds **8**–**11**, **14** and **15**.

Dehydration of Compounds 4 and/or 5

A solution of **4** and/or **5** (2.5 g, 8.47 mmol) in a mixture of HCl–EtOH (15/8 mL) was refluxed for 14 h. Then, the mixture was quenched with H_2O (50 mL), extracted with Et_2O (2 × 100 mL), washed with aq $NaHCO_3$ solution (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give an orange oil. Flash chromatography (80% petroleum ether–Et_2O) yielded 1.150 g (49%) of (*Z*)-3-(1-benzoylethylidene)-1-methyloxindole [(*Z*)-**16**], 0.680 g (29%) of (*E*)-3-(1-benzoylethylidene)-1-methyloxindole [(*E*)-**16**], and 0.286 g (21%) of isatin.

(*Z*)-16

Yellow solid; mp 169–171 °C.

IR (KBr): 1699, 1665 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.93 (dd, 2 H, *J* = 7.0, 1.5 Hz, H-2',6'), 7.63 (d, 1 H, *J* = 7.6 Hz, H-4), 7.55 (tt, 1 H, *J* = 7.1, 1.2 Hz, H-4'), 7.46 (tt, 2 H, *J* = 7.0, 1.2 Hz, H-3',5'), 7.34 (td, 1 H, *J* = 7.8, 1.1 Hz, H-6), 7.09 (td, 1 H, *J* = 7.6, 0.9 Hz, H-5), 6.83 (d, 1 H, *J* = 7.8 Hz, H-7), 3.10 (s, 3 H, NCH_3), 2.48 (s, 3 H, C_{3a}-CH_3).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 198.77 (C-3β), 165.82 (C-2), 147.46 (C-3a), 144.40 (C-7a), 134.59 (C-1'), 134.57 (C-4'), 129.55 (C-6), 128.75 (C-3',5'), 128.57 (C-2',6'), 125.54* (C-3α), 123.74 (C-4), 122.17 (C-5), 121.50* (C-3), 108.30 (C-7), 25.75 (NCH_3) 18.62 (C_{3a}-CH_3).

Anal. Calcd for $C_{18}H_{15}NO_2$: C 77.96; H 5.45; N 5.05. Found: C 77.77; H 5.13; N 5.00.

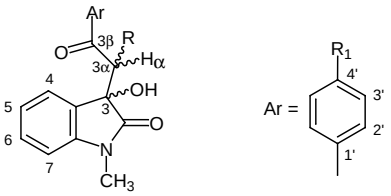
(*E*)-16

Yellow solid; mp 179–181 °C.

IR (KBr): 1703, 1670 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.96 (d, 2 H, *J* = 7.5 Hz, H-2'6'), 7.60 (t, 1 H, *J* = 7.0 Hz, H-4'), 7.46 (t, 2 H, *J* = 7.7, 1.2 Hz, H-3',5'), 7.14 (t, 1 H, *J* = 7.7 Hz, H-6), 6.84 (d, 1 H, *J* = 7.6 Hz, H-4), 6.76–6.68 (m, 2 H, H-5 and H-7), 3.23 (s, 3 H, NCH_3), 2.68 (s, 3 H, C_{3a}-CH_3).

Table 3a ^{1}H NMR Data of Compounds **2**, **4**–**15** [$CDCl_3$, δ, *J* (Hz)]



Compound	R	NCH_3	H_4	H_5	H_6	H_7	Hα
(±)-**2**	3.51 (d, 1 H, *J* = 17.4)	3.22 (s, 3 H)	7.42 (d, 1 H, *J* = 7.4)	7.01 (td, 1 H, *J* = 7.4, 0.8)	7.30 (td, 1 H, *J* = 7.8, 1.2)	6.84 (d, 1 H, *J* = 7.8)	3.80 (d, 1 H, *J* = 17.4)
(±)-**4**	1.24 (d, 3 H, *J* = 7.2, CH_3)	3.17 (s, 3 H)	7.56 (d, 1 H, *J* = 7.4)	7.06 (td, 1 H, *J* = 7.4, 0.7)	7.32 (td, 1 H, *J* = 7.8, 1.2)	6.82 (d, 1 H, *J* = 7.8)	3.99 (q, 1 H, *J* = 7.2)
(±)-**5**	1.54 (d, 3 H, *J* = 7.2, CH_3)	2.95 (s, 3 H)	7.30 (d, 1 H, *J* = 7.5)	6.95 (t, 1 H, *J* = 7.5)	7.24 (t, 1 H, *J* = 7.7)	6.74 (d, 1 H, *J* = 7.7)	4.06 (q, 1 H, *J* = 7.2)
(±)-**6**	0.67 (t, 3 H, *J* = 7.4, CH_3), 1.55–1.40 (m, 1 H, CH_2), 1.78–1.62 (m, 1 H, CH_2)	3.03 (s, 3 H)	7.50 (d, 1 H, *J* = 7.5)	6.98 (t, 1 H, *J* = 7.5)	7.32 (td, 1 H, *J* = 7.7, 0.9)	6.73 (d, 1 H, *J* = 7.7)	4.02 (dd, 1 H, *J* = 4.0, 10.5)
(±)-**7**	0.83 (t, 3 H, *J* = 7.4, CH_3), 2.14–2.00 (m, 1H, CH_2), 2.44–2.31 (m, 1 H, CH_2)	2.98 (s, 3 H)	7.30 (d, 1 H, *J* = 7.5)	6.94 (td, 1 H, *J* = 7.5, 0.8)	7.32 (td, 1 H, *J* = 7.8, 1.2)	6.74 (d, 1 H, *J* = 7.7)	3.84 (dd, 1 H, *J* = 3.3, 10.5)
(±)-**8**	0.70 (t, 3 H, *J* = 7.4, CH_3), 1.14–0.99 (m, 2 H, C*H*$_2$$CH_3$), 1.42–1.29 (m, 1 H, C*H*$_2$$CH_2CH_3$), 1.75–1.63 (m, 1 H, C*H*$_2$$CH_2CH_3$)	3.05 (s, 3 H)	7.51 (d, 1 H, *J* = 7.4)	7.02 (td, 1 H, *J* = 7.4, 0.8)	7.25 (td, 1 H, *J* = 7.7, 1.2)	6.74 (d, 1 H, *J* = 7.7)	4.15 (dd, 1 H, *J* = 3.5, 10.8)
(±)-**9**	0.88 (t, 3 H, *J* = 7.1, CH_3), 1.34–1.13 (m, 2 H, C*H*$_2$$CH_3$), 2.18–2.00 (m, 1 H, C*H*$_2$$CH_2CH_3$), 2.42–2.28 (m, 1 H, C*H*$_2$$CH_2CH_3$)	2.75 (s, 3 H)	7.57–7.51 (overlapped m)	6.96 (t, 1 H, *J* = 7.5)	7.28 (td, 1 H, *J* = 7.7, 1.2)	6.78 (d, 1 H, *J* = 7.7)	3.91 (dd, 1 H, *J* = 3.3, 10.7)
(±)-**10**	0.69 (t, 3 H, *J* = 7.1, CH_3), 1.18–1.08 [m, 4 H, (C*H*$_2$)$_2$$CH_3$] 1.50–1.37 [m, 1 H, C*H*$_2$$(CH_2)_2CH_3$], 1.83–1.68 [m, 1 H, C*H*$_2$$(CH_2)_2CH_3$]	3.09 (s, 3 H)	7.55–7.49 (overlapped m)	7.03 (t, 1 H, *J* = 7.6)	7.28 (t, 1 H, *J* = 7.7)	6.77 (d, 1 H, *J* = 7.8)	4.11 (dd, 1 H, *J* = 3.3, 10.7)
(±)-**11**	0.81 (t, 3 H, *J* = 7.3, CH_3), 1.25–1.02 [m, 4 H, (C*H*$_2$)$_2$$CH_3$], 2.19–2.00 [m, 1 H, C*H*$_2$$(CH_2)_2CH_3$], 2.42–2.25 [m, 1 H, C*H*$_2$$(CH_2)_2CH_3$]	2.80 (s, 3 H)	7.54 (d, 1 H, *J* = 7.4)	6.98 (td, 1 H, *J* = 7.5, 0.8)	7.28 (td, 1 H, *J* = 7.7, 1.3)	6.76 (d, 1 H, *J* = 7.7)	3.95 (dd, 1 H, *J* = 3.3, 10.7)
(±)-**12**	7.29–7.23 (m, 5 H, C_6H_5)	3.15 (s, 3 H)	6.43 (d, 1 H, *J* = 7.4)	6.87 (t, 1 H, *J* = 7.4)	7.29 (t, 1 H, *J* = 7.7)	6.83 (d, 1 H, *J* = 7.7)	5.32 (s, 1 H)
(±)-**12**[a]	7.24 (m, 2 H, H-2'',6''), 7.41–7.29 (m, 3 H, C_6H_5)	3.10 (s, 3 H)	5.92 (d, 1 H, *J* = 7.4)	6.75 (t, 1 H, *J* = 7.4)	7.25 (t, 1 H, *J* = 7.7)	7.02 (d, 1 H, *J* = 7.7)	5.51 (s, 1 H)
(±)-**13**[a]	7.70–7.10 (m, 5 H, C_6H_5)	2.87 (s, 3 H)	7.83 (d, 1 H, *J* = 7.3)	7.70–7.10 (overlapped m)	7.70–7.10 (overlapped m)	7.70–7.10 (overlapped m)	5.48 (s, 1 H)
(±)-**14**	3.58 (s, 3 H, OCH_3), 6.93 (d, 2 H, *J* = 8.5, H-2'',6''), 6.56–6.51 (m, 2 H, H-3'',5'')	2.95 (s, 3 H)	7.89 (d, 1 H, *J* = 7.2)	6.99 (t, 1 H, *J* = 7.5)	7.13 (t, 1 H, *J* = 7.5)	6.56–6.51 (m, 1 H)	5.11 (s, 1 H)
(±)-**15**	3.74 (s, 3 H, OCH_3), 7.16 (d, 2 H, *J* = 8.5, H-2'',6''), 6.90–6.70 (overlapped m)	3.21 (s, 3 H)	6.40 (d, 1 H, *J* = 7.3)	6.90–6.70 (overlapped m)	7.27 (t, 1 H, *J* = 7.7)	6.90–6.70 (overlapped m)	5.02 (s, 1 H)

[a] Recorded in DMSO

Table 3b ^{1}H NMR Data of Compounds **2**, **4**–**15** [$CDCl_3$, δ, *J* (Hz)] (continued)

Compound	H-2',6'	H-3',5'	H-4'	OH	R (4-CH_3OC_6H_4)
(±)-**2**	7.85 (dd, 2 H, *J* = 7.2, 1.3)	7.41 (t, 2 H, *J* = 7.4)	7.54 (tt, 1 H, *J* = 7.4, 1.3)	4.55 (s, 1 H)	–
(±)-**4**	7.93 (dd, 2 H, *J* = 7.2, 1.3)	7.42 (t, 2 H, *J* = 7.7)	7.54 (tt, 1 H, *J* = 7.3, 1.3)	4.33 (s, 1 H)	–
(±)-**5**	7.73 (d, 2 H, *J* = 7.3)	7.32 (t, 2 H, *J* = 7.3)	7.45 (t, 1 H, *J* = 7.5)	4.80 (s, 1 H)	–
(±)-**6**	7.96 (d, 2 H, *J* = 7.3)	7.36 (t, 2 H, *J* = 7.2)	7.48 (t, 1 H, *J* = 7.5)	4.25 (br s, 1 H)	–
(±)-**7**	7.75 (d, 2 H, *J* = 7.3)	7.37 (t, 2 H, *J* = 7.3)	7.51 (tt, 1 H, *J* = 7.3, 1.4)	4.09 (br s, 1 H)	–
(±)-**8**	8.01 (dd, 2 H, *J* = 7.2, 1.3)	7.37 (t, 2 H, *J* = 7.7)	7.49 (tt, 1 H, *J* = 7.3, 1.2)	4.50 (br s, 1 H)	–
(±)-**9**	7.76 (d, 2 H, *J* = 7.4)	7.40 (t, 2 H, *J* = 7.8)	7.57–7.51 (overlapped m)	4.74 (br s, 1 H)	–
(±)-**10**	8.00 (d, 2 H, *J* = 7.8)	7.40 (t, 2 H, *J* = 7.8)	7.55–7.49 (overlapped m)	4.32 (br s, 1 H)	–
(±)-**11**	7.75 (dd, 2 H, *J* = 7.2, 1.4)	7.38 (t, 2 H, *J* = 7.8)	7.59–7.53 (overlapped m)	4.56 (br s, 1 H)	–
(±)-**12**	7.76 (d, 2 H, *J* = 7.9)	7.25 (t, 2 H, *J* = 7.3)	7.39 (t, 1 H, *J* = 7.2)	3.43 (s, 1 H)	–
(±)-**12**[a]	7.76 (dd, 2 H, *J* = 7.2, 1.0)	7.41–7.29 (m, 2 H)	7.51 (t, 1 H, *J* = 7.3)	6.27(s, 1 H)	–
(±)-**13**[a]	7.95 (d, 2 H, *J* = 7.2)	7.70–7.10 (m, 2 H)	7.70–7.10 (m, 1 H)	6.31 (s, 1 H)	–
(±)-**14**	7.85 (d, 2 H, *J* = 8.0)	6.73 (d, 2 H, *J* = 8.0)	–	2.13 (br s,1 H)	3.70 (s, 3 H, OCH_3)
(±)-**15**	7.72 (d, 2 H, *J* = 8.9)	6.72 (d, 2 H, *J* = 8.9)	–	n. o.	3.78 (s, 3 H, OCH_3)

[a] Recorded in DMSO

Table 4a ^{13}C NMR Data of Compounds **2**, **4**–**15** ($CDCl_3$, δ)[a]

Compound	NCH_3	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	C-3α	C-3β
(±)-**2**	26.48	176.28	74.61	130.13	124.14	123.20	130.08	108.49	143.79	44.55	198.60
(±)-**4**	26.17	176.79	77.64	128.19	125.74	122.85	129.85	108.32	143.69	45.19	203.37
(±)-**5**	26.00	176.74	76.53	129.68	124.53	122.72	129.48	108.38	143.39	47.60	202.33
(±)-**6**	26.11	177.08	77.77	128.14	126.03	122.77	129.76	108.23	143.43	51.92	203.10
(±)-**7**	26.21	176.16	77.06	129.39	124.51	122.76	129.56	108.47	142.81	53.74	203.04
(±)-**8**	26.62	177.62	78.20	128.66	126.50	123.26	130.22	108.73	143.88	50.92	203.50
(±)-**9**	26.55	176.53	77.60	129.84	124.97	123.24	130.08	108.77	143.10	52.24	203.37
(±)-**10**	26.63	177.58	78.26	128.59	126.51	123.28	130.26	108.73	143.92	50.87	203.60
(±)-**11**	26.46	176.86	77.57	128.74	125.08	123.25	130.05	108.75	143.28	52.62	203.32
(±)-**12**[b]	27.75	179.15	76.94	131.28	126.86	122.93	129.54	110.09	146.50	61.51	199.54
(±)-**14**	25.85	178.21	63.92	126.38	125.41	122.41	128.70	107.67	143.33	60.03	196.42
(±)-**15**	26.38	176.87	76.86	125.90	125.15	122.30	129.66	108.01	144.52	59.53	196.88

Table 4b ^{13}C NMR Data of Compounds **2**, **4**–**15** ($CDCl_3$, δ) (continued)

Compound	R	Ar				
		C-1'	C-2',6'	C-3',5'	C-4'	R
(±)-**2**	-	136.44	128.28	128.82	133.97	–
(±)-**4**	12.85 (CH_3)	136.50	128.41	128.61	133.39	–
(±)-**5**	12.26 (CH_3)	136.06	128.33	128.48	133.24	–
(±)-**6**	21.28 (CH_2), 12.01(CH_3)	138.95	128.44	128.44	133.08	–
(±)-**7**	20.40 (CH_2), 12.76(CH_3)	138.05	128.25	128.45	133.38	–
(±)-**8**	30.62 (CH_2), 21.33 (CH_2), 14.61 (CH_3)	139.36	128.92*	128.95*	133.54	–
(±)-**9**	29.54 (CH_2), 21.83 (CH_2), 14.69 (CH_3)	138.37	128.74*	128.97*	133.92	–
(±)-**10**	30.15 (CH_2), 28.24 (CH_2), 23.16 (CH_2), 14.15 (CH_3)	139.32	128.92*	128.94*	133.57	–
(±)-**11**	30.67 (CH_2), 27.10 (CH_2), 23.30 (CH_2), 14.26 (CH_3)	138.38	129.02*	129.76*	133.84	–
(±)-**12**[b]	135.79 (C-4''), 132.52 (C-3'',5''), 130.65 (C-2'',6''), 129.82 (C-1)	137.35	130.27	130.54	135.06	–
(±)-**14**	54.98 (OCH_3), 130.74 (C-2'',6''), 113.27 (C-3'',5''), 158.77 (C-4'')	129.52	131.03	113.52	163.16	55.25 (OCH_3)
(±)-**15**	55.45 (OCH), 113.68 (C-3'',5''), 128.93 (C-1''), 131.43 (C-2'',6''), 159.40 (C-4'')	129.47	131.82	113.91	163.42	55.28 (OCH_3)

[a] The chemical shifts marked with an * are interchangeable.
[b] Recorded in DMSO

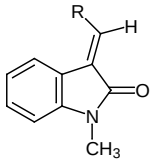
^{13}C NMR ($CDCl_3$, 63 MHz): δ = 198.17 (C-3b), 167.31 (C-2), 148.80 (C-3a), 142.54 (C-7a), 134.57 (C-4'), 133.40 (C-1'), 129.43 (C-3',5'), 129.19 (C-2'6'), 129.12 (C-6), 123.43* (C-3a), 122.90 (C-4), 121.94 (C-5), 120.36* (C-3), 107.85 (C-7), 25.71 (NCH_3), 17.19 (C_{3a}-CH_3).

Anal. Calcd for $C_{18}H_{15}NO_2$: C 77.96; H 5.45; N 5.05. Found: C 77.68; H 5.29; N 4.89.

Treatment of 3-Benzoylmethyl-3-hydroxy-1-methyloxindole Derivatives 2, 4–12 with Sulfuric Acid; (*Z*)-3-Benzoylmethylen-1-methyloxindole [(*Z*)-3] and (*E*)-3-Alkyliden-1-methyloxindole Derivatives 17–21; General Procedure

A solution of the corresponding 3-benzoylmethyl-3-hydroxy-1-methyloxindole **2**, **4**–**12** (0.100–0.050 g, 0.356–0.140 mmol) in 96% H_2SO_4 (2–3 mL) was stirred at r.t. for 5–10 min, and was then quenched with ice and extracted with $CHCl_3$ (3 × 25–50 mL). The combined organic layers were washed with aq $NaHCO_3$ solution (25–50 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give **3** (~100% from **2**), **17** (~100% from **4** or **5**), **18** (~100% from **6** or **7**), **19** (89% from **8** or **9**), **20** (93% from **10** or **11**), and **21** (85% from **12**) as yellow compounds (Table 5).

Table 5 ^{1}H NMR [$CDCl_3$, δ, *J* (Hz)] of Compounds *Z*-**3** and *E*-**17–21**



Z-**3** (R = PhCO)
E-**17** (R = Me)
E-**18** (R = Et)
E-**19** (R = ^{n}Pr)
E-**20** (R = ^{n}Bu)
E-**21** (R = Ph)

Compound[a]	NCH_3	H-4	H-5	H-6	H-7	Hα	R
(Z)-**3**	3.11 (s, 3 H)	7.49 (d, 1 H, *J* = 7.7)	7.07 (td, 1 H, *J* = 7.5, 0.6)	7.34 (td, 1 H, *J* = 7.8, 1.1)	6.79 (d, 1 H, *J* = 7.8)	7.17 (s, 1 H)	7.99 (dd, 2 H, *J* = 7.1, 1.5, H-2',6'), 7.45 (tt, 2 H, *J* = 7.1, 1.3, H-3',5'), 7.57 (tt, 1 H, *J* = 7.3, 1.3, H-4')
(*E*)-**17**	3.21 (s, 3 H)	7.54 (d, 1 H, *J* = 7.5)	7.02 (t, 1 H, *J* = 7.5)	7.26 (t, 1 H, *J* = 7.8)	6.80 (d, 1 H, *J* = 7.8)	7.09 (q, 1 H, *J* = 7.6)	2.25 (d, 3 H, *J* = 7.6, CH_3)
(*E*)-**18**	3.20 (s, 3 H)	7.49 (d, 1 H, *J* = 7.5)	7.01 (t, 1 H, *J* = 7.5)	7.24 (t, 1 H, *J* = 7.8)	6.79 (d, 1 H, *J* = 7.8)	7.00 (t, 1 H, *J* = 7.5)	2.67 (m, 2 H, CH_2), 1.22 (t, 3 H, *J* = 7.5, CH_3)
(*E*)-**19**[b]	3.23 (s, 3 H)	7.54 (d, 1 H, *J* = 7.5)	7.04 (t, 1 H, *J* = 7.5)	7.26 (t, 1 H, *J* = 7.8)	6.81 (d, 1 H, *J* = 7.8)	7.03 (t, 1 H, *J* = 7.5)	2.64 (q, 2 H, *J* = 7.4, CH_2), 1.67 (m, 2 H, CH_2), 1.03 (t, 3 H, *J* = 7.4, CH_3)
(*E*)-**20**[b]	3.24 (s, 3 H)	7.55 (d, 1 H, *J* = 7.5)	7.04 (t, 1 H, *J* = 7.5)	7.26 (t, 1 H, *J* = 7.8)	6.82 (d, 1 H, *J* = 7.8)	7.03 (t, 1 H, *J* = 7.5)	2.68 (q, 2 H, *J* = 7.4, CH_2), 1.68–1.52 (m, 2 H, CH_2), 1.50–1.38 (m, 2 H, CH_2), 0.95 (t, 3 H, *J* = 7.3, CH_3)
(*E*)-**21**[b]	3.25 (s, 3 H)	7.63–7.36 (overlapped m)	6.86 (td, 1 H, *J* = 7.6, 0.8)	7.25 (td, 1 H, *J* = 7.8, 1.0)	6.82 (d, 1 H, *J* = 7.8)	7.83 (s, 1 H)	7.63–7.36 (overlapped m, 5 H, C_6H_5)

[a] Compounds (*E*)-**20** and (*E*)-**21** are yellow oils. (*E*)-**3**: mp 155–156 °C (EtOH) (Lit.[5c] mp 156–158 °C); (*E*)-**17**: mp 76–78 °C (Lit.[2a] mp 78–79 °C); (*E*)-**18** mp 55–57 °C (Lit.[2a] mp 53–54 °C); (*E*)-**19** mp 36–38 °C.
[b] Satisfactory microanalyses obtained: C ±0.25, H ±0.33, N ±0.20.

Acknowledgement

We thank CICYT for financial support of this research through grant SAF-2000-0130.

References

(1) (a) Sato, A.; Asao, T.; Hagiwara, Y.; Kitade, M.; Yamazaki, Y. PCT Int. Appl. WO 9726242 A1., **1997**; *Chem. Abstr.* **1997**, *127*, 161696. (b) Sato, A.; Asao, T.; Hagiwara, Y.; Kitade, M.; Yamazaki, Y. PCT Int. Appl. WO 9725986A1, **1997**; *Chem. Abstr*. **1997**, *127*, 190643.
(2) (a) Tacconi, G.; Maggi, L. D.; Righetti, P.; Desimoni, G.; Azzolina, O.; Ghislandi, V. *J. Chem. Soc., Perkin Trans. 2* **1976**, 150. (b) Sumpter, W. E.; Miller, F. M. *Heterocyclic Compounds with Indole and Carbazole Systems*; Interscience: New York, **1954**.
(3) (a) Wahl, A.; Livovschi, V. *Bull. Soc. Chim. Fr.* **1938**, *5*, 653. (b) Anthony, W. C. *J. Org. Chem.* **1966**, *31*, 77.
(4) Lathourakis, G. E.; Litinas, K. E. *J. Chem. Soc., Perkin Trans. 1* **1996**, 491.
(5) (a) Pietra, S.; Tacconi, G. *Il Farmaco* **1958**, *13*, 893. (b) Tacconi, G.; Gamba, A.; Marinone, F.; Desimoni, G. *Tetrahedron* **1971**, *27*, 561. (c) Tacconi, G.; Marinone, F.; Gamba, A.; Desimoni, G. *Tetrahedron* **1972**, *28*, 1517. (d) Fahmy, A. M.; Badr, M. Z. A.; Mohamed, Y. S.; Abdel-Latif, F. F. *J. Heterocycl. Chem.* **1984**, *22*, 1233. (e) Faita, G.; Mella, M.; Righetti, P. P.; Tacconi, G. *Tetrahedron* **1994**, *50*, 10955. (f) Kozminykh, E. N.; Berezina, E. S.; Kozminykh, V. O. *Zh. Obshch. Khim.* **1996**, *66*, 1128; Chem. Abstr. 1996, 126, 7942.
(6) Lindwall, H. G.; Maclennan, J. S. *J. Am. Chem. Soc.* **1932**, *54*, 4739.
(7) In the case of compounds **9**, **11**, and **15** we observed slight variations in the positions of the NMe, C(2)=O and C(3)NMR signals, which may be a new example of the known concentration dependence of NMR data that has been found in other indole derivatives. For other examples, see: (a) Jardine, R. V.; Brown, R. K. *Can. J. Chem.* **1963**, *41*, 2067. (b) Reinecke, M. G.; Johnson, H. W.; Sebastian, J. F. *J. Am. Chem. Soc.* **1969**, *91*, 3817. (c) Avendaño, C.; De Diego, C.; Elguero, J. *Bull. Soc. Chim. Belg.* **1989**, *98*, 73.
(8) Compound (*Z*)-**3** has been obtained in Ref.[5e] by isomerization of (*E*)-**3** in the presence of $AlCl_3$.
(9) Both isomers are clearly distinguished by the chemical shift of their H(3α)-protons.
(10) For other acid-catalyzed dehydrations of 3-hydroxy analogues, see: (a) Autrey, R. L.; Tahk, F. C. *Tetrahedron* **1967**, *23*, 901. (b) Beccalli, E. M.; Marchesini, A.; Pilati, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 579.
(11) A mutual NOE between H-4 and (3α)-methyl protons characterized the *Z*-isomer.