A stereochemical investigation of the nucleophilic addition of methyl ethyl ketone to (*E*)-alkyloxindolylideneacetates

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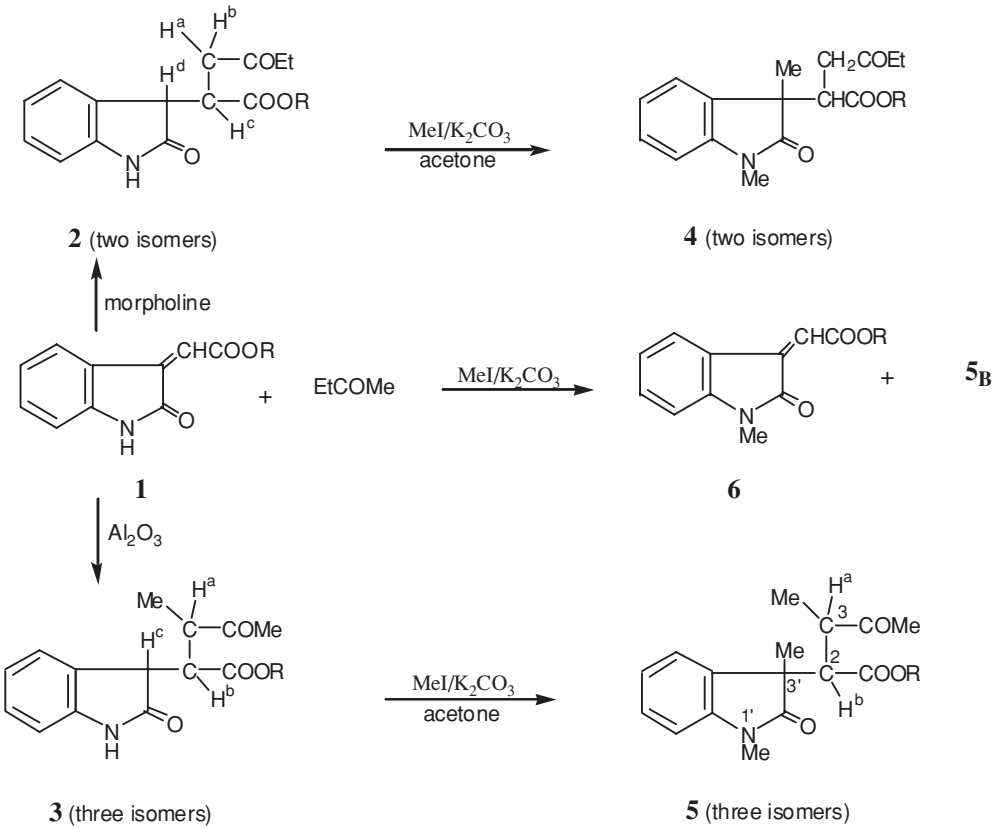
The reaction of (*E*)-(2-oxo-1,2-dihydroindol-3-ylidene)acetic acid esters (**1**) with methyl ethyl ketone in the presence of morpholine as a catalyst gave 4-oxo-2-(2-oxo-2,3-dihydro-1*H*-indole-3-yl)hexanoic acid esters, a diastereomeric mixture of two isomers ($\mathbf{2_A}$ and $\mathbf{2_B}$). Using aluminium oxide as a catalyst for the above reaction led to the formation of 4-oxo-3-methyl-2-(2-oxo-2,3-dihydro–1*H*-indole-3-yl)-pentanoic acid esters as a mixture of three isomers $\mathbf{3_A}$, $\mathbf{3_B}$ and $\mathbf{3_C}$, which upon methylation with methyl iodide in acetone and in the presence of anhydrous potassium carbonate yield the corresponding methylated products. The structural assignments of the new compounds are based on their chemical and spectroscopic properties. The stereochemical structures of $\mathbf{5a_A}$, $\mathbf{5b_B}$ and $\mathbf{5a_C}$ are identified by X-ray analysis.

Keywords: oxindolylideneacetate, methyl ethyl ketone, hexanoic acid esters, pentanoic acid esters, Michael reaction

Considerable interest was developed some time ago in the chemistry of 2-oxo-1*H*-indole containing compounds due to their wide application in various fields. Thus, many 2-oxo-1*H*-indoles have been reported to exhibit various biological activities as antitumor,[1] antimicrobial,[2,3] antiviral,[4-7] antifungal,[8-10] antibacterial,[11-13] and anticancer agents[14] and also as an orally active potent growth hormone.[15] In the light of previous reports, a number of publications have appeared dealing with synthesis of different 3-substituted 2-oxo-1*H*-indoles.[16–18]

In the present work, it is intended to study the reaction of methyl ethyl ketone with oxindolylideneacetates not only to construct novel 2-oxo-1*H*-indolyl heterocyclic compounds but also to investigate the stereochemical configuration of the isolated product.

Reaction of (*E*)-(2-oxo-1,2-dihydroindol-3-ylidene) acetic acid esters (**1**) with dry methyl ethyl ketone at 80 °C in the presence of a catalytic amount of morpholine led to the formation of 4-oxo-2-(2-oxo-2,3-dihydro-1*H*-indole-3-yl)hexanoic acid esters, a diastereomeric mixture of two isomers $\mathbf{2_A}$ and $\mathbf{2_B}$ (Scheme 1) through Michael addition of the carbanion of methyl ethyl ketone to the α,β-unsaturated carbonyl compounds[19]. The pure isomers $\mathbf{2a_A}$ and $\mathbf{2b_B}$ were isolated by fractional recrystallisation of the isomeric mixture from benzene.



a, R = Me
b, R = Et

Scheme 1

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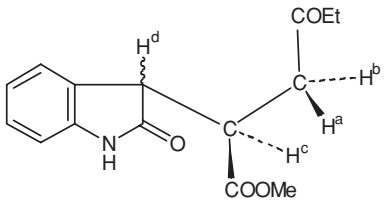
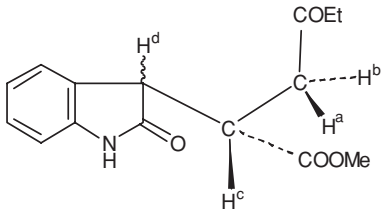


2a$_A$



2a$_B$

The constitutions of **2$_A$** and **2$_B$** were established from their spectroscopic properties. ^{1}H NMR spectra of the two isomers **2a$_A$** and **2a$_B$** show the chemical shift of H^a as a doublet of doublets downfield (δ = 2.47) in **2a$_A$** by about 0.3 ppm from that of **2a$_B$** (δ = 2.17). On the other hand H^b in **2a$_A$** (δ = 2.77) is shielded compared with H^b in **2a$_B$** (δ = 3.05). This could be attributed to the anisotropic properties of the carbonyl ester residue.[20]

Replacement of morpholine by aluminium oxide led to the abstraction of a hydrogen ion from the CH_2 of the ethyl group in methyl ethyl ketone thus generating a carbanion which attacked the α,β-unsaturated centre in **1** and caused the formation of 4-oxo-3-methyl-2-(2-oxo-2,3-dihydro-1*H*-indole-3-yl) pentanoic acid esters as a mixture of three isomers **3$_A$**, **3$_B$** and **3$_C$**. These isomers were separated by careful column chromatography and elemental analyses, molecular weight determination (MS) and spectroscopic results elucidated their structures. Their IR spectra exhibit absorption bands in the region 3130–3194 (NH) and 1709–1736 cm^{-1} (C=O). The ^{1}H NMR spectra of **3a$_A$** and **3a$_B$** and **3a$_C$** showed the characteristic signals at δ = 1.12, 1.01 and 1.21 (d, J = 7 Hz), corresponding to methyl groups. Also, it showed signals corresponding to the acetyl methyl groups at δ = 2.22, 2.14 and 2.32 for the three isomers, respectively. The ester methyl groups appeared as singlets at δ = 3.44 (**3a$_A$**), 3.64 (**3a$_B$**) and 3.38 (**3a$_C$**) and the signals at δ = 3.51 (dd, J_Hb_Ha = 11 Hz, J_Hb_Hc = 5 Hz), 3.66 (dd, J_Hb_Ha = 10 Hz, J_Hb_Hc = 2.6 Hz) and 3.78 (dd, J_Hb_Ha = 10 Hz, J_Hb_Hc = 2.6 Hz) were ascribed to H^b for each isomer. Moreover, the proton H^a appeared as a multiplets at different chemical shifts for the three isomers and the signals at δ = 3.67 (d, J_Hc_Hb = 4.6 Hz), 3.87 (d, J_Hc_Hb = 2.4 Hz) and 3.75 (d, J_Hc_Hb = 2.6 Hz) were attributed to H^c. The aromatic protons (4H) appeared as two doublets (H-4, H-7) and two triplets (H-5, H-6). The broad singlet at downfield is due to an exchangeable proton (NH).

Methylation of a mixture of the two isomers **2$_A$** and **2$_B$** with methyl iodide in acetone in the presence of anhydrous potassium carbonate led to the formation of the relative stable 4-oxo-2-(2-oxo-2,3-dihydro-1,3-dimethyl-1*H*-indole-3-yl)hexanoic acid esters as the diastereomers **4$_A$** and **4$_B$**, which were separated by column chromatography.

The structures of **4$_A$** and **4$_B$** were deduced from satisfactory elemental analyses and spectroscopic data. The IR spectra of **4a** exhibit strong absorption bands in the region 1695–1735 cm^{-1} (C=O), but lacked a characteristic NH band. Analysis of the ^{1}H NMR spectra of the two isomers **4$_A$** and **4$_B$** reveals that the most significant difference is found in the chemical shift and coupling constant of the protons H^a, H^b and H^c (*cf.* experimental).

Treatment of **3** (as three isomers) with methyl iodide and potassium carbonate anhydrous in boiling acetone yielded 4-oxo-3-methyl-2-(2-oxo-2,3-dihydro-1,3-dimethyl-1*H*-indole-3-yl)pentanoic acid esters (**5**).The three isomers **5$_A$**, **5$_B$** and **5$_C$** can be isolated by careful column chromatography and their structures were established by elemental analyses and spectroscopic data.

The IR spectra of **5** display bands due to carbonyl groups at 1716 (**5a$_A$**), 1728 and 1697 (**5a$_B$**) and 1732 and 1712 cm^{-1} (**5a$_C$**), but lacked a characteristic NH band. The ^{1}H NMR spectra of **5a** showed three multiplets for H^a at δ = 3.20 (**5a$_A$**), 2.61–2.78 (**5a$_B$**) and 3.15–3.24 (**5a$_C$**) along with three doublets of H^b with coupling constant J = 9.8 Hz at 3.58 (**5a$_A$**), 3.38 (**5a$_B$**) and overlapped with H^a in **5a$_C$**.

Single crystal X-ray data of **5a$_A$**, **5b$_B$** (the crystal of **5a$_B$** could not be obtained) and **5a$_C$** (Figs 1, 2, 3) show that the isolated products are 2*R*, 3*S*, 3'*R* (isomer A), 2*R*, 3*R*, 3'*R* (isomer B), 2*S*, 3*S*, 3'*R* (isomer C). The ^{1}H NMR shielding effect of CH**Me** (δ = 0.74) in isomer B compared with isomer A (δ = 0.92) could now be attributed to the anisotropic properties of the indolyl heterocycle affecting the neighbouring methyl function.

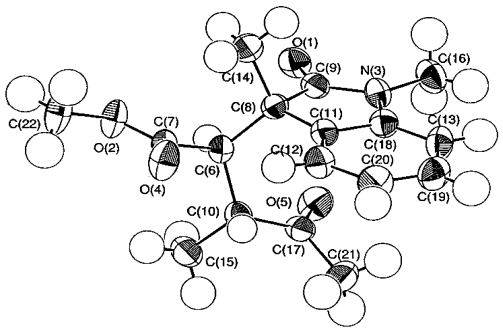


Fig. 1 ORTEP perspective view of isomer **5a$_A$**.

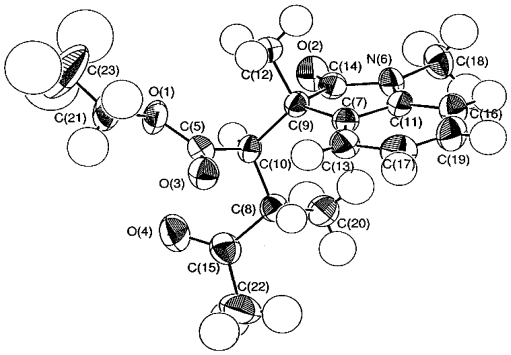


Fig. 2 ORTEP perspective view of isomer **5b$_B$**.

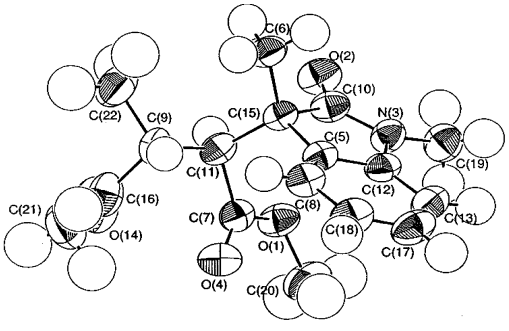


Fig. 3 ORTEP perspective view of isomer **5a$_C$**.

Treatment of **1** with methyl iodide in dry methyl ethyl ketone in presence of potassium carbonate gave a mixture of (2-oxo-1,2-dihydro-1-methylindole-3-ylidene)-acetic acid esters (**6**) as orange red crystals (42%) and **5_B** as colourless crystals (15%).

In conclusion, Michael addition of carbon nucleophiles to conjugated enones **1** under different catalytic conditions gave different products **2**, **3**. This observation may be attributed to thermodynamic effects. Aluminium oxide may stabilise the thermodynamically less stable form of the products, probably *via* complexation prior to work-up, giving **3**. However, using morpholine as a basic catalysis in the reaction gives rise to the thermodynamically were stable products **2**.

X-ray structure determination

The crystal data were measured at $T = 298$ °k on a Kappa CCD Enraf Nonius FR 590 diffractometer. The crystal structure was solved and refind, using maXus (Bruker Nonius, Delft and MacScience, Japan). Mo–Kα radiation (λ = 0.71073 Å) and a graphite monochromator were used for data collection.

Isomer **$5a_A$**: $C_{17}H_{21}NO_4$, $M_r = 303.358$, triclinic, crystallises in space group *P*-1, $a = 8.4589$ (3), $b = 9.5205$ (3), $c = 10.0483$ (4) Å, Cell angles "α= 84.776(2), β = 79.529(2), γ = 90.011(2)", $V = 792.32$ (5) Å^3, $Z = 2$, $D_c = 1.33$ g cm^{-1}, θ values 2.91–27.48°, absorption coefficient μ (Mo–Kα) = 0.09 mm^{-1}, $F(000) = 342$. The unique reflections measured 3945, of which 2074 reflections with threshold expression $I > 3\sigma(I)$ were used in the structural analysis. Convergence for 199 variable parameters by least-squares refinement on F^2 with $w = 1/[\sigma^2(F_o^2) + 0.10000\,F_o^2]$. The final agreement factors were $R = 0.061$ and $wR = 0.120$ with a goodness-of-fit of 1.509.

Isomer **$5b_B$**: $C_{18}H_{23}NO_4$, $M_r = 317.385$, monoclinic, crystallises in space group $P\,2_1/c$, $a = 14.3080$ (8), $b = 8.8873$ (4), $c = 14.0542$ (7) Å, Cell angles "α= 90.00, β = 105.023(2), γ = 90.00",$V = 1726.0$ (2) Å^3, $Z = 4$, $D_c = 1.22$ g cm^{-1}, θ values 2.91–23.82°, absorption coefficient μ (Mo–Kα) = 0.09 mm^{-1}, $F(000) = 648$. The unique reflections measured 2908, of which 1556 reflections with threshold expression $I > 3\sigma(I)$ were used in the structural analysis. Convergence for 208 variable parameters by least-squares refinement on F^2 with $w = 1/[\sigma^2(F_o^2) + 0.10000\,F_o^2]$. The final agreement factors were $R = 0.051$ and $wR = 0.094$ with a goodness-of-fit of 1.909.

Isomer **$5a_C$**: $C_{17}H_{21}NO_4$, $M_r = 303.358$, monoclinic, crystallises in space group $P\,2_1/c$, $a = 7.5796(3)$, $b = 11.6388$ (4), $c = 18.2150$ (9) Å, Cell angles "α= 90.00, β = 91.199(2), γ = 90.00",$V = 1606.53$ (12) Å^3, $Z = 4$, $D_c = 1.25$ g cm^{-1}, θ values 2.91–27.48°, absorption coefficient μ (Mo–Kα) = 0.09 mm^{-1}, $F(000) = 648$. The unique reflections measured 4460, of which 1242 reflections with threshold expression $I > 3\sigma(I)$ were used in the structural analysis. Convergence for 256 variable parameters by least-squares refinement on F^2 with $w = 1/[\sigma^2(F_o^2) + 0.10000\,F_o^2]$. The final agreement factors were $R = 0.046$ and $wR = 0.094$ with a goodness-of-fit of 1.651.

Further details of the structure determination (complete bond lengths and angles, H atom coordinates, structure factors, temperature factors) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IEZ, United Kingdom. Any request should be accompanied by the full literature citation and the CCDC reference numbers 216176 (**$5a_A$**), 216177 (**$5b_B$**) and 216178 (**$5a_C$**).

Experimental

Melting points were determined on an Electrothermal 9100 melting point apparatus and are uncorrected. The IR spectra were recorded (KBr) on a Jasco FT-IR spectrophotometer, model FT/IR-3000E. The NMR spectra were recorded ($CDCl_3$) on a Varian GEMINI 200 (200 MHz) spectrometer. Chemical shifts are given from internal *TMS*. Mass spectra were determined on a Finnigan MAT SSQ 7000 spectrometer (EI 70 eV). Al_2O_3 S, basic super active for column chromatography from Riedel-De Haen AG Seelze Hannover was used. Compounds **$2a_B$**, **$2b_A$** and **$3a_C$** were not isolated in a pure form and so elemental analysis was not possible. Characterisation is less rigorous than for the other compounds depending on spectroscopic data from mixtures.

4-Oxo-2-(2-oxo-2,3-dihydro-1H-indole-3-yl)hexanoic acid methyl ester (**$2a_A$, $2a_B$**) : To the orange solution of **1a** (0.5 g, 2.5 mmol) in dry methyl ethyl ketone (15 ml), morpholine (1 ml) was added and the mixture was heated under reflux at 80 °C for about 10 h. The solution was evaporated and the residue was purified on silica gel using pet. ether (60–80 °C)/acetone (4 : 1) to give a diastereomeric mixture of two isomers **$2a_A$** and **$2a_B$** total, 0.49 g (72%). Fractional recrystallisation of the isomeric mixture from benzene gave colourless crystals of **$2a_A$** in a pure form, m.p. 133–134 °C. IR: ν = 3348 (NH), 1713, 1687 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 0.98 (t, $J = 7.2$ Hz, 3H, $COCH_2CH_3$), 2.35 (q, $J = 7.2$ Hz, 2H, $COCH_2$), 2.44 (dd, J_Ha_Hb = 17.8 Hz, J_Ha_Hc = 4.8 Hz, 1H, H^a), 2.74 (dd, J_Hb_Ha = 17.8 Hz, J_Hb_Hc = 8.8 Hz, 1H, H^b), 3.72 (s, 3H, ester CH_3), 3.79–3.87 (m, 2H, H^c & H^d), 6.92, 7.21 (2d, $J = 7.6$ Hz, 2H, arom. H-7, H-4), 7.0, 7.08 (2t, $J = 7.6$ Hz, 2H, arom. H-5, H-6), 9.18 (s, NH). MS: *m/z* (%) = 275 [M$^+$]. $C_{15}H_{17}NO_4$ (275.304): calcd. C 65.4, H 6.2, N 5.1; found C 65.35, H 6.2, N 5.15.

$2a_B$: ^{1}H NMR ($CDCl_3$): δ = 0.98 (t, $J = 7.2$ Hz, 3H, $COCH_2CH_3$), 2.12 (dd, J_Ha_Hb = 17.2 Hz, J_Ha_Hc = 3.8 Hz, 1H, H^a), 2.39 (q, $J = 7.2$ Hz, 2H, $COCH_2$), 3.01 (dd, J_Hb_Ha = 17.2 Hz, J_Hb_Hc = 10.2 Hz, 1H, H^b), 3.70 (s, 3H, ester CH_3), 3.79–3.85 (m, 1H, H^c), 4.0 (d, J_Hd_Hc = 4.2 Hz, 1H, H^d), 6.95, 7.21 (2d, $J = 7.6$ Hz, 2H, arom. H-7, H-4), 7.0, 7.08 (2t, $J = 7.6$ Hz, 2H, arom. H-5, H-6), 9.18 (s, NH) (the data were taken from the spectrum of mixture).

4-Oxo-2-(2-oxo-2,3-dihydro-1H-indole-3-yl)hexanoic acid ethyl ester (**$2b_A$, $2b_B$**): Following the typical procedure, **1b** (0.54 g, 2.5 mmol) reacted with methyl ethyl ketone (15 ml) in presence of morpholine (1ml) to yield a diastereomeric mixture of **$2b_A$** and **$2b_B$** (0.51 g, 71%). Fractional recrystallisation of the isomeric mixture from benzene gave colourless crystals of **$2b_B$** in a pure form.

$2b_A$: ^{1}H NMR ($CDCl_3$,): δ = 1.01 (t, $J = 7.2$ Hz, 3H, $COCH_2CH_3$), 1.20 (t, $J = 7.2$ Hz, 3H, ester CH_3), 2.39 (m, 2H, $COCH_2$), 2.56 (dd, J_Ha_Hb = 18 Hz, J_Ha_Hc = 5.4 Hz, 1H, H^a), 2.78 (dd, J_Hb_Ha = 17.8 Hz, J_Hb_Hc = 8.4 Hz, 1H, H^b), 3.77 (dt, J_Hc_Hb = 10 Hz, J_Hc_Hd = 4 Hz, 1H, H^c), 3.87 (d, J_Hd_Hc = 3.4 Hz, 1H, H^d), 4.14 (m, 2H, ester CH_2), 6.88, 7.14 (2d, $J = 7.6$ Hz, 2H, arom. H-7, H-4), 7.02, 7.23 (2t, $J = 7.2$ Hz, 2H, arom. H-5, H-6), 7.98(s, NH) (the data were taken from the spectrum of mixture).

$2b_B$: m.p. 110–111 °C. IR: ν = 3183 (NH), 1707 cm^{-1}(C=O). ^{1}H NMR ($CDCl_3$,): δ = 1.0 (t, $J = 7.2$ Hz, 3H, $COCH_2CH_3$), 1.16 (t, $J = 7.2$ Hz, 3H, ester CH_3), 2.16 (dd, J_Ha_Hb = 17.2 Hz, J_Ha_Hc = 3.6 Hz, 1H, H^a), 2.29–2.56 (m, 2H, $COCH_2$), 3.05 (dd, J_Hb_Ha = 17.2 Hz, J_Hb_Hc = 10 Hz, 1H, H^b), 3.78 (dt, J_Hc_Hb = 10 Hz, J_Hc_Hd = 4 Hz, 1H, H^c), 3.97 (d, J_Hd_Hc = 4 Hz, 1H, H^d), 4.06–4.22 (m, 2H, ester CH_2), 6.89, 7.23 (2d, $J = 7.6$ Hz, 2H, arom. H-7, H-4), 7.01, 7.23 (2t, $J = 7.2$ Hz, 2H, arom. H-5, H-6), 9.02 (s, NH). MS: *m/z* (%) = 289 [M$^+$]. $C_{16}H_{19}NO_4$ (289.331): calcd. C 66.4, H 6.6, N 4.8; found C 66.55, H 6.6, N 4.75.

4-Oxo-3-methyl-2-(2-oxo-2,3-dihydro-1H-indole-3-yl)pentanoic acid methyl ester (**$3a_A$, $3a_B$** and **$3a_C$**): A mixture of **1a** (2.03 g, 10 mmol) and aluminium oxide (10 g) in dry methyl ethyl ketone (30 ml) was heated under reflux at 80 °C for 20 h. The inorganic material was removed by filtration. The remaining solution was evaporated under reduced pressure to afford **3a** as a mixture of three isomers **$3a_A$**, **$3a_B$** and **$3a_C$**, which separated, by column chromatography using silica gel and *n*-hexane/acetone as eluent.

(2R,3S,3'R)-4-Oxo-3-methyl-2-(2-oxo-2,3-dihydro-1H-indole-3-yl)pentanoic acid methyl ester (**$3a_A$**): The first fraction (83% *n*-hexane) gave colourless crystals of **$3a_A$**, recrystallised from chloroform/ *n*-hexane, yield 0.45 g (16%), m.p.128–129 °C. IR: ν = 3130 (NH), 1736, 1713 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$,): δ = 1.12 (d, $J = 7$ Hz, 3H, CH_3), 2.22 (s, 3H, $COCH_3$), 3.44 (s, 3H, ester CH_3), 3.51 (dd, J_Hb_Ha = 11 Hz, J_Hb_Hc = 5 Hz, 1H, H^b), 3.67 (d overlapped, J_Hc_Hb = 4.6 Hz, 1H, H^c), 3.65–3.75 (m overlapped, 1H, H^a), 6.81, 7.28 (2d, $J = 7.2$ Hz, 2H, arom. H-7, H-4), 6.79, 7.18 (2t, $J = 7.6$ Hz, 2H, arom. H-6, H-5), 8.83 (s, NH). MS: *m/z* (%) = 275 [M$^+$]. $C_{15}H_{17}NO_4$ (275.304): calcd. C 65.4, H 6.2, N 5.1; found C 65.5, H 6.3, N 5.0.

(2R,3R,3'R)-4-Oxo-3-methyl-2-(2-oxo-2,3-dihydro-1H-indole-3-yl) pentanoic acid methyl ester (**$3a_B$**): The second fraction (82% *n*-hexane) gave the isomeric mixture **$3a_B$** and **$3a_C$** (1.55 g, 55%). Fractional

recrystallisation of the isomeric mixture from chloroform/*n*-hexane gave **3a$_B$**, m.p. 200–201 °C. IR: ν = 3194 (NH), 1728, 1709 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.01(d, *J* = 7.2 Hz, 3H, CH_3), 2.14 (s, 3H, $COCH_3$), 3.08–3.25 (m, 1H, H^a), 3.64 (s, 3H, ester CH_3), 3.66 (dd, J_Hb_Ha = 10 Hz, J_Hb_Hc = 2.6 Hz, 1H, H^b), 3.87 (d, J_Hc_Hb = 2.4 Hz, 1H, H^c), 6.91, 7.24 (2d, *J* = 7.6 Hz, 2H, arom. H-7, H- 4), 7.04, 7.25 (2t, *J* = 7.6 Hz, 2H, arom. H-6, H-5), 8.37 (s, NH). MS: *m/z* (%) = 275 [M$^+$]. $C_{15}H_{17}NO_4$ (275.304): calcd. C 65.4, H 6.2, N 5.1; found C 65.5, H 6.3, N 5.0.

(2S,3S,3′R)-4-Oxo-3-methyl-2-(2-oxo-2,3-dihydro-1H-indole-3-yl)pentanoic acid methyl ester (**3a$_C$**): The third isomer **3a$_C$** could not be isolated in the pure form, and its ^{1}H NMR data was taken from the isomeric mixture. ^{1}H NMR ($CDCl_3$): δ = 1.21 (d, *J* = 7.2 Hz, 3H, CH_3), 2.32 (s, 3H, $COCH_3$), 3.22–3.35 (m, 1H, H^a), 3.38 (s, 3H, ester CH_3), 3.75 (d, J_Hc_Hb = 2.6 Hz, 1H, H^c), 3.78 (dd, J_Hb_Ha = 10 Hz, J_Hb_Hc = 2.6 Hz, 1H, H^b), 6.90, 7.23 (2d, *J* = 7.6 Hz, 2H, arom. H-7, H-4), 7.04, 7.22 (2t, *J* = 7.6 Hz, 2H, arom. H-6, H-5), 8.44 (s, NH).

By the same manner, **3b$_A$**, **3b$_B$** and **3b$_C$** were obtained from the reaction of **1b** (2.17 g, 10 mmol) with methyl ethyl ketone (30 ml) and aluminium oxide (10 g)

(2R,3S,3′R)-4-Oxo-3-methyl-2-(2-oxo-2,3-dihydro-1H-indole-3-yl)pentanoic acid ethyl ester (**3b$_A$**): The first fraction (85% *n*-hexane) gave colourless crystals of isomer **3b$_A$**, recrystallised from benzene/*n*-hexane, yield: 0.42 g (15%), m.p. 105–106 °C. IR: ν = 3178 (NH), 1737, 1714 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 0.94 (t, *J* = 7.2 Hz, 3H, ester CH_3), 1.14 (d, *J* = 7.2 Hz, 3H, CH_3), 2.26 (s, 3H, $COCH_3$), 3.47 (dd, J_Hb_Ha = 10.8 Hz, J_Hb_Hc = 5.2 Hz, 1H, H^b), 3.68 (d, J_Hc_Hb = 5 Hz, 1H, H^c), 3.67–3.80 (m, 1H, H^a), 3.90 (q, *J* = 7.2 Hz, 2H, ester CH_2), 6.80, 7.29 (2d, *J* = 7.8 Hz, 2H, arom. H-7, H-4), 7.0, 7.18 (2t, *J* = 7.6 Hz, 2H, arom. H-6, H-5), 8.22 (s, NH). MS: *m/z* (%) = 289 [M$^+$]. $C_{16}H_{19}NO_4$ (289.331): calcd. C 66.4, H 6.6, N 4.8; found C 66.3, H 6.7, N 4.8.

(2R,3R,3′R)-4-Oxo-3-methyl-2-(2-oxo-2,3-dihydro-1H-indole-3-yl)pentanoic acid ethyl ester (**3b$_B$**): The second fraction (83% *n*-hexane) afforded colourless crystals of **3b$_B$**, recrystallised from chloroform/*n*-hexane, yield: 0.61 g (21%), m.p. 154–155 °C. IR: ν = 3196 (NH), 1707 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.01 (d, *J* = 7.2 Hz, 3H, CH_3), 1.13 (t, *J* = 7.2 Hz, 3H, ester CH_3), 2.16 (s, 3H, $COCH_3$), 3.12–3.29 (m, 1H, H^a), 3.64 (dd, J_Hb_Ha = 10.4 Hz, J_Hb_Hc = 2.8 Hz, 1H, H^b), 3.88 (d, J_Hc_Hb = 2.8 Hz, 1H, H^c), 4.08 (dq, *J* = 7.2, 1.2 Hz, 2H, ester CH_2), 6.93, 7.24 (2d, *J* = 7.6 Hz, 2H, arom. H-7, H-4), 7.04, 7.25 (2t, *J* = 7.4 Hz, 2H, arom. H-6, H-5), 8.77 (s, NH). MS: *m/z* (%) = 289 [M$^+$]. $C_{16}H_{19}NO_4$ (289.331): calcd. C 66.4, H 6.6, N 4.8; found C 66.5, H 6.7, N 4.7.

(2S,3S,3′R)-4-Oxo-3-methyl-2-(2-oxo-2,3-dihydro-1H-indole-3-yl)pentanoic acid ethyl ester (**3b$_C$**): The third fraction (83% *n*-hexane) yielded colourless crystals of **3b$_C$**, recrystallised from benzene/pet. ether (b.p. 60–80 °C), yield: 0.7 g (24%), m.p. 124–125 °C. IR: ν = 3174 (NH), 1732, 1701 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 0.86 (t, *J* = 7.2 Hz, 3H, ester CH_3), 1.24 (d, *J* = 7.4 Hz, 3H, CH_3), 2.34 (s, 3H, $COCH_3$), 3.27–3.45 (m, 1H, H^a), 3.69–3.95 (m, 4H, "H^b, H^c, ester CH_2"), 6.91, 7.19 (2d, *J* = 7.6 Hz, 2H, arom. H-7, H-4), 7.0, 7.23 (2t, *J* = 7.6 Hz, 2H, arom. H-6, H-5), 8.67 (s, NH). MS: *m/z* (%) = 290 [$(M_+ 1)^+$]. $C_{16}H_{19}NO_4$ (289.331): calcd. C 66.4, H 6.6, N 4.8; found C 66.5, H 6.55, N 4.8.

4-Oxo-2-(2-oxo-2,3-dihydro-1,3-dimethyl-1H-indole-3-yl) hexanoic acid methyl ester (**4a$_A$, 4a$_B$**): A mixture of **2a** (0.7 g, 2.5 mmol), freshly distilled methyl iodide (7 ml) and anhydrous potassium carbonate (3 g) in dry acetone (20 ml) was gently heated under reflux for 15 h. After removal of the inorganic material, the solution was evaporated under reduced pressure. The residue was chromatographed on silica gel using *n*-hexane/ethyl acetate as eluent to give colourless crystals of **4a.** The first fraction (83% *n*-hexane) gave **4a$_A$**, yield: 0.2 g (26%), m.p. 50–51 °C (pet. ether b.p. 40–60 °C). IR: ν = 1735, 1712, 1695 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 0.94 (t, *J* = 7.4 Hz, 3H, $COCH_2CH_3$), 1.37 (s, 3H, CH_3 at C-3), 2.28 (q, *J* = 7.2 Hz, 2H, $COCH_2$), 2.30 (dd, J_Ha_Hb = 18 Hz, J_Ha_Hc = 3.4 Hz, 1H, H^a), 2.64 (dd, J_Hb_Ha = 18 Hz, J_Hb_Hc = 11 Hz, 1H, H^b), 3.21 (s, 3H, NCH_3), 3.41 (dd, J_Hc_Ha = 3.4 Hz, J_Hc_Hb = 11 Hz, 1H, H^c), 3.63 (s, 3H, ester CH_3), 6.85, 7.24 (2d, *J* = 7.6 Hz, 2H, arom. H-7, H-4), 7.05, 7.29 (2t, *J* = 7.6 Hz, 2H, arom. H-5, H-6). MS: *m/z* (%) = 303 [M$^+$]. $C_{17}H_{21}NO_4$ (303.358): calcd. C 67.3, H 7.0, N 4.6; found C 67.4, H 6.9, N 4.7.

The second fraction (82% *n*-hexane) afforded colourless crystalline product of isomer **4a$_B$**, recrystallised from chloroform/*n*-hexane, yield: 0.12 g (16%), m.p. 91–92 °C. IR: ν = 1732, 1716 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.00 (t, *J* = 7.4 Hz, 3H, $COCH_2CH_3$), 1.44 (s, 3H, CH_3 at C-3), 2.39 (dq, *J* = 7.4, 3 Hz, 3H, $COCH_2$), 2.54 (dd, J_Ha_Hb = 17.4 Hz, J_Ha_Hc = 3 Hz, 1H, H^a), 2.99 (dd, J_Hb_Ha = 17.4 Hz, J_Hb_Hc = 11.2 Hz, 1H, H^b), 3.21 (s, 3H, NCH_3), 3.38 (dd, J_Hc_Ha = 3 Hz, J_Hc_Hb = 11.2 Hz, 1H, H^c), 3.55 (s, 3H, ester CH_3), 6.85, 7.05 (2d, *J* = 7.6 Hz, 2H, arom. H-7, H-4), 7.11, 7.29 (2t, *J* = 7.2 Hz, 2H, arom. H-5, H-6). MS: *m/z* (%) = 303 [M$^+$]. $C_{17}H_{21}NO_4$ (303.358): calcd. C 67.3, H 7.0, N 4.6; found C 67.2, H 6.95, N 4.75.

4-Oxo-2-(2-oxo-2,3-dihydro-1,3-dimethyl-1H-indole-3-yl)hexanoic acid ethyl ester (**4b$_A$, 4b$_B$**): By using the same previous experimental procedure, the diastereomers mixture of **2b$_A$** and **2b$_B$** (0.7 g, 2.4 mmol) reacted with methyl iodide to give **4b$_A$** and **4b$_B$**. The first fraction (85% *n*-hexane) gave **4b$_A$** as colourless crystals, recrystallised from *n*-hexane, yield 0.24 g (32%), m.p. 76–77 °C. IR: ν = 1714 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 0.96 (t, *J* = 7.4 Hz, 3H, $COCH_2CH_3$), 1.35 (t, *J* = 7.2 Hz, 3H, ester CH_3), 1.39 (s, 3H, CH_3 at C-3), 2.30 (q, *J* = 7.4 Hz, 2H, $COCH_2$), 2.38 (dd, J_Ha_Hb = 17.8 Hz, J_Ha_Hc = 3.4 Hz, 1H, H^a), 2.70 (dd, J_Hb_Ha = 17.8 Hz, J_Hb_Hc = 10.8 Hz, 1H, H^b), 3.22 (s, 3H, NCH_3), 3.41 (dd, J_Hc_Ha = 3.4 Hz, J_Hc_Hb = 10.8 Hz, 1H, H^c), 4.07 (q, *J* = 7.2 Hz, 2H, ester CH_2), 6.85, 7.27 (2d, *J* = 7.4 Hz, 2H, arom. H-7, H-4), 7.06, 7.29 (2t, *J* = 7.4 Hz, 2H, arom. H-5, H-6). MS: *m/z* (%) = 317 [M$^+$]. $C_{18}H_{23}NO_4$ (317.385): calcd. C 68.2, H 7.3, N 4.4; found C 68.3, H 7.25, N 4.4.

The second fraction (84% *n*-hexane) gave **4b$_B$** as colourless crystals, recrystallised from benzene/*n*-hexane, yield: 0.09 g (12%), m.p. 94–95 °C. IR: 1718 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.01 (t, *J* = 7.4 Hz, 3H, $COCH_2CH_3$), 1.06 (t, *J* = 7 Hz, 3H, ester CH_3), 1.42 (s, 3H, CH_3 at C-3), 2.42 (dq, *J* = 7.4 Hz, 2H, $COCH_2$), 2.53 (dd, J_Ha_Hb = 17.4 Hz, J_Ha_Hc = 3 Hz, 1H, H^a), 3.02 (dd, J_Hb_Ha = 17.4 Hz, J_Hb_Hc = 11.2 Hz, 1H, H^b), 3.21 (s, 3H, NCH_3), 3.43 (dd, J_Hc_Ha = 3 Hz, J_Hc_Hb = 11.2 Hz, 1H, H^c), 3.97 (q, *J* = 7 Hz, 2H, ester CH_2), 6.84, 7.14 (2d, *J* = 7.4 Hz, 2H, arom. H-7, H-4), 7.03, 7.28 (2t, *J* = 7.6 Hz, 2H, arom. H-5, H-6). MS: *m/z* (%) = 317 [M$^+$]. $C_{18}H_{23}NO_4$ (317.385): calcd. C 68.2, H 7.3, N 4.4; found C 68.3, H 7.4, N 4.35.

(2R,3S,3′R)-4-Oxo-3-methyl-2-(2-oxo-2,3-dihydro-1,3-dimethyl-1H-indole-3-yl)pentanoic acid methyl ester (**5a$_A$**): A mixture of **3a$_A$** (0.14 g, 0.5 mmol) in dry acetone (10 ml), anhydrous potassium carbonate (2 g) and freshly distilled methyl iodide (2 ml) were added, the mixture was heated under reflux for 7 h. Then, the inorganic material was filtered off and the solution evaporated under reduced pressure. The residue triturated with chloroform and crystallised from chloroform/pet. ether (b.p. 40–60 °C) to yield **5a$_A$** as colourless crystals, yield 0.13 g (87%), m.p. 66–67 °C. IR: ν = 1716 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 0.92 (d, *J* = 7 Hz, 3H, CH_3), 1.26 (s, 3H, CH_3 at C-3), 1.90 (s, 3H, $COCH_3$), 3.19 (s, 3H, NCH_3), 3.20 (m overlapped, 1H, H^a), 3.57(s, 3H, ester CH_3), 3.58 (d overlapped, J_Hb_Ha = 9.8 Hz, 1H, H^b), 6.80, 7.53 (2d, *J* = 7.8 Hz, 2H, arom. H-7, H-4), 7.08, 7.28 (2t, *J* = 7.8 Hz, 2H, arom. H-5, H-6). MS: *m/z* (%) = 303 [M$^+$]. $C_{17}H_{21}NO_4$ (303.358): calcd. C 67.3, H 7.0, N 4.6; found C 67.4, H 7.05, N 4.55.

(2R,3S,3′R)-4-Oxo-3-methyl-2-(2-oxo-2,3-dihydro-1,3-dimethyl-1H-indole-3-yl)pentanoic acid ethyl ester (**5b$_A$**): Under the same experimental condition described above **3b$_A$** (0.29 g, 1 mmol) reacts with methyl iodide (3 ml) in acetone (15 ml) and presence of anhydrous potassium carbonate (2 g) to give **5b$_A$**, as colourless oil, yield: 0.27 g (84%). IR: ν = 1716 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 0.95 (d, *J* = 7.2 Hz, 3H, CH_3), 1.13 (t, *J* = 7.2 Hz, 3H, ester CH_3), 1.27 (s, 3H, CH_3 at C-3), 1.94 (s, 3H, $COCH_3$), 3.20 (s, 3H, NCH_3), 3.18–3.32 (m, 1H, H^a), 3.48 (d, J_Hb_Ha = 9.2 Hz, 1H, H^b), 3.95 (q, *J* = 7.2 Hz, 2H, ester CH_2), 6.76, 7.44 (2d, *J* = 7.6 Hz, 2H, arom. H-7, H-4), 7.08, 7.29 (2t, *J* = 7.6 Hz, 2H, arom. H-5, H-6). MS: *m/z* (%) = 317 (M$^+$). $C_{18}H_{23}NO_4$ (317.385): calcd. C 68.1, H 7.3, N 4.4; found C 68.2, H 7.4, N 4.3.

(2R,3R,3′R)-4-Oxo-3-methyl-2-(2-oxo-2,3-dihydro-1,3-dimethyl-1H-indole-3-yl)pentanoic acid methyl ester (**5a$_B$**): The mixture of two isomers **3a$_B$** and **3a$_C$** (6 mmol) reacts with methyl iodide (10 ml) in dry acetone (50 ml) in the presence of anhydrous potassium carbonate (5 g). After heating under reflux for 10 h, the inorganic material was filtered off and the solution was evaporated. The residue was chromatographed on silica gel using acetone/pet. ether (b.p. 60–80 °C) to give **5a$_B$** and **5a$_C$**. The first fraction (85% pet. ether b.p. 60–80 °C) gave **5a$_B$** as a colourless crystals, recrystallisation from benzene/*n*-hexane, yield: 35%, m.p. 140–141 °C. IR: ν = 1728, 1697 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 0.74 (d, *J* = 7.4 Hz, 3H, CH_3), 1.32 (s, 3H, CH_3 at C-3), 1.94 (s, 3H, $COCH_3$), 2.61–2.78 (m, 1H, H^a), 3.22 (s, 3H, NCH_3), 3.38 (d, J_Ha_Hb = 9.8 Hz, 1H, H^b), 3.74 (s, 3H, ester CH_3), 6.88, 7.58 (2d, *J* = 7.6 Hz, 2H, arom. H-7, H-4), 7.10, 7.33 (2dt, *J* = 7.8, 1.4 Hz, 2H, arom. H-5, H-6). MS: *m/z* (%) = 303 [M$^+$]. $C_{17}H_{21}NO_4$ (303.358): calcd. C 67.3, H 7.0, N 4.6; found C 67.4, H 6.9, N 4.5.

(2S,3S,3′R)-4-Oxo-3-methyl-2-(2-oxo-2,3-dihydro-1,3-dimethyl-1H-indole-3-yl)pentanoic acid methyl ester (**5a$_C$**): The second fraction

(84% pet. ether b.p. 60–80 °C) gave colourless crystals of **5a$_C$**, recrystallised from benzene/*n*-hexane, yield: 0.58 g (32%), m.p. 73–74 °C. IR: ν = 1732, 1712 cm^{-1}(C=O). ^{1}H NMR ($CDCl_3$): δ = 0.71 (d, *J* = 5.8 Hz, 3H, CH_3), 1.41 (s, 3H, CH_3 at C-3), 2.12 (s, 3H, $COCH_3$), 3.15–3.24 (m, 2H overlapped, H^a, H^b), 3.23 (s, 3H, NCH_3), 3.63 (s, 3H, ester CH_3), 6.83, 7.22 (2d, *J* = 7.6 Hz, 2H, arom. H-7, H-4), 7.05, 7.27 (2t, *J* = 7.4 Hz, 2H, arom. H-5, H-6). MS: *m*/*z* (%) = 303 [M$^+$]. $C_{17}H_{21}NO_4$ (303.358): calcd. C 67.3, H 7.0, N 4.6; found C 67.4, H 7.1, N 4.65.

(2R,3R,3'R)-4-Oxo-3-methyl-2-(2-oxo-2,3-dihydro-1,3-dimethyl-1H-indole-3-yl)pentanoic acid ethyl ester (**5b$_B$**): Similarly, **3b$_B$** and **3b$_C$** (1.45 g, 5 mmol) were reacted with methyl iodide (6 ml) to yield two fractions. The first fraction (88% pet. ether b.p. 60–80 °C) yielded colourless crystals of **5b$_B$**, recrystallised from benzene/*n*-hexane, yield 0.54 g (34%), m.p. 114–115 °C. IR: ν = 1722, 1707 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 0.74 (d, *J* = 7.4 Hz, 3H, CH_3), 1.30 (t, *J* = 7.2 Hz, 3H, ester CH_3), 1.34 (s, 3H, CH_3 at C-3), 1.95 (s, 3H, $COCH_3$), 2.62–2.79 (m, 1H, H^a), 3.22 (s, 3H, NCH_3), 3.35 (d, $J_{H^bH^a}$ = 10 Hz, 1H, H^b), 4.19 (q, *J* = 7.2 Hz, 2H, ester CH_2), 6.88, 7.58 (2d, *J* = 7.6 Hz, 2H, arom. H-7, H-4), 7.09, 7.33 (2t, *J* = 7.6 Hz, 2H, arom. H-5, H-6). MS: *m*/*z* (%) = 317 [M$^+$]. $C_{18}H_{23}NO_4$ (317.385): calcd. C 68.1, H 7.3, N 4.4; found C 68.2, H 7.4, N 4.3.

(2S,3S,3'R)-4-Oxo-3-methyl-2-(2-oxo-2,3-dihydro-1,3-dimethyl-1H-indole-3-yl)pentanoic acid ethyl ester (**5b$_C$**): The second fraction, (87% pet. ether b.p. 60–80 °C) gave colourless crystals of **5b$_C$**, recrystallised from *n*-hexane, yield: 0.48 g (30%), m.p. 72–73 °C. IR: ν = 1732, 1710 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 0.74 (d, *J* = 7 Hz, 3H, CH_3), 1.20 (t, *J* = 7.2 Hz, 3H, ester CH_3), 1.43 (s, 3H, CH_3 at C-3), 2.14 (s, 3H, $COCH_3$), 3.19–3.23 (m, 2H, H^a, H^b), 3.24 (s, 3H, NCH_3), 4.09 (q, *J* = 7.2 Hz, 2H, ester CH_2), 6.83, 7.25 (2d, *J* = 7.6 Hz, 2H, arom. H-7, H-4), 7.06, 7.28 (2t, *J* = 7.6 Hz, 2H, arom. H-5, H-6). MS: *m*/*z* (%) = 317 (M$^+$). $C_{18}H_{23}NO_4$ (317.385): calcd. C 68.1, H 7.3, N 4.4; found C 68.2, H 7.4, N 4.4.

Reaction of **1a** with methyl iodide in methyl ethyl ketone: To a solution of **1a** (0.6 g, 3 mmol) in dry methyl ethyl ketone (15 ml), anhydrous potassium carbonate (2 g) and freshly distilled methyl iodide (5 ml) were added. The mixture was gently heated under reflux for 25 h, then the inorganic materials was filtered and the solution evaporated under reduced pressure. The residue was chromatographed on silica gel using *n*-hexane/acetone to give orange red crystals of **6a** and **5a$_B$**.

(2-Oxo-1,2-dihydro-1-methylindol-3-ylidene)acetic acid methyl ester (**6a**): Yield 0.33 g (42%), m.p. 137–138 °C. IR: ν = 1709 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 3.22 (s, 3H, NCH_3), 3.87 (s, 3H, ester CH_3), 6.79 (d, *J* = 7.6 Hz, 1H, arom. H-7), 6.90 (s, 1H, ylidene CH), 7.06, 7.37 (2t, *J* = 7.6 Hz, 2H, arom. H-5, H-6), 8.54 (d, *J* = 7.6 Hz, 1H, arom. H-4). MS: *m*/*z* (%) = 217 [M$^+$]. $C_{12}H_{11}NO_3$ (217.224): calcd. C 66.35, H 5.1, N 6.45; found C 66.4, H 5.0, N 6.5.

5a$_B$: Yield 0.12 g (15%) which identified by its m.p., mixed m.p. and comparative ^{1}H NMR spectrum with an authentic sample previously obtained.

By the same manner, **Ib** reacted with methyl iodide in boiling methyl ethyl ketone to yield **6b** and **5b$_B$**

(2-Oxo-1,2-dihydro-1-methyl-indol-3-ylidene)acetic acid ethyl ester (6b): Yield 0.24 g (37%), m.p. 83–85 °C. IR: ν = 1710 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.35 (t, *J* = 7.2 Hz, 3H, ester CH_3), 3.23 (s, 3H, NCH_3), 4.30 (q, *J* = 7.2 Hz, 2H, ester CH_2), 6.78 (d, *J* =7.6 Hz, 1H, arom. H-7), 6.90 (s. 1H, ylidene H), 7.05, 7.35 (2dt, *J* = 7.6, 1.6 Hz, 2H, arom. H-5, H-6), 8.55 (d, *J* = 7.6 Hz, 1H, arom. H-4). MS *m*/*z* (%) = 231 [M$^+$]. $C_{13}H_{13}NO_3$ (231.251): calcd. C 67.5, H 5.7, N 6.1; found C 67.9, H 5.6, N 6.1.

5b$_B$: Yield 0.11 g (17%), which identified by its m.p., mixed m.p. and comparative ^{1}H NMR spectrum with an authentic sample previously obtained.

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