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A Nucleophilic Addition of Acetone Enolate to (*E*)-Alkyloxindolylideneacetates

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Summary. The reaction of (*E*)-(2-oxo-1,2-dihydroindol-3-ylidene)acetic acid esters with dry acetone at 70°C in presence of aluminum oxide as a catalyst led to the formation of an addition product as a mixture of two isomers. When the same reaction was carried out in presence of morpholine as a base, the unexpected spiro-product was obtained beside the two isomers. Methylation of the latter with methyl iodide in acetone in presence of anhydrous potassium carbonate yielded the corresponding methylated products, whereas methylation of the starting material by the same procedure gave an *N*-methylated product and the unexpected dispiro-compound. The reaction mechanisms are considered and the structural assignments of the new compounds are based on the chemical and spectroscopic evidences. The structure of the dispiro-product was derived by X-ray analysis.

Keywords. Acetone; Oxindolylideneacetates; Condensation; Spirocycles.

Introduction

The oxindole nucleus displays various biological properties and has been exploited as part of antimicrobial [1, 2], antiviral [3–5], antifungal [6], antibacterial [7–9], antihypoxic [10], and anticancer agents [11]. In previous papers [12–14], we have reported the synthesis of (*E*)-(2-oxo-1,2-dihydroindol-3-ylidene)acetic acid esters (**1**) by the reaction of isatin with alkoxycarbonylmethylene(triphenyl)phosphoranes [13]. By heating in acetic anhydride it has been shown to form the dimeric products **2** [14]. Due to the importance of oxindole derivatives and in continuation of previous work, we now investigated the base-catalyzed condensation of acetone, as an example of an aliphatic ketone, with **1**.

Results and Discussion

We found that (*E*)-(2-oxo-1,2-dihydroindol-3-ylidene)acetic acid esters (**1**) react with dry acetone at 70°C in presence of aluminum oxide as the catalyst to yield

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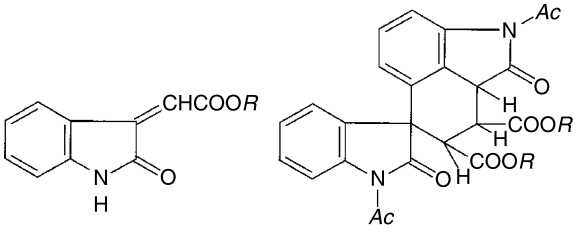


1 2

4-oxo-2-(2-oxo-2,3-dihydro-1*H*-indole-3-yl)pentanoic acid esters diastereomer mixture of $\mathbf{3_A}$ and $\mathbf{3_B}$. All efforts to separate these two diastereomers by chromatographic methods failed due to their equal R_f values. However, one of these two diastereomers, $\mathbf{3_B}$, was isolated in pure form by means of fractional crystallization from benzene. When this isomer was examined by ^{1}H NMR spectroscopy after different times in $CDCl_3$ at room temperature, we found that isomer $\mathbf{3_B}$ transformed into $\mathbf{3_A}$ in a ratio of 4:5 after two days and 1:2 after one week.

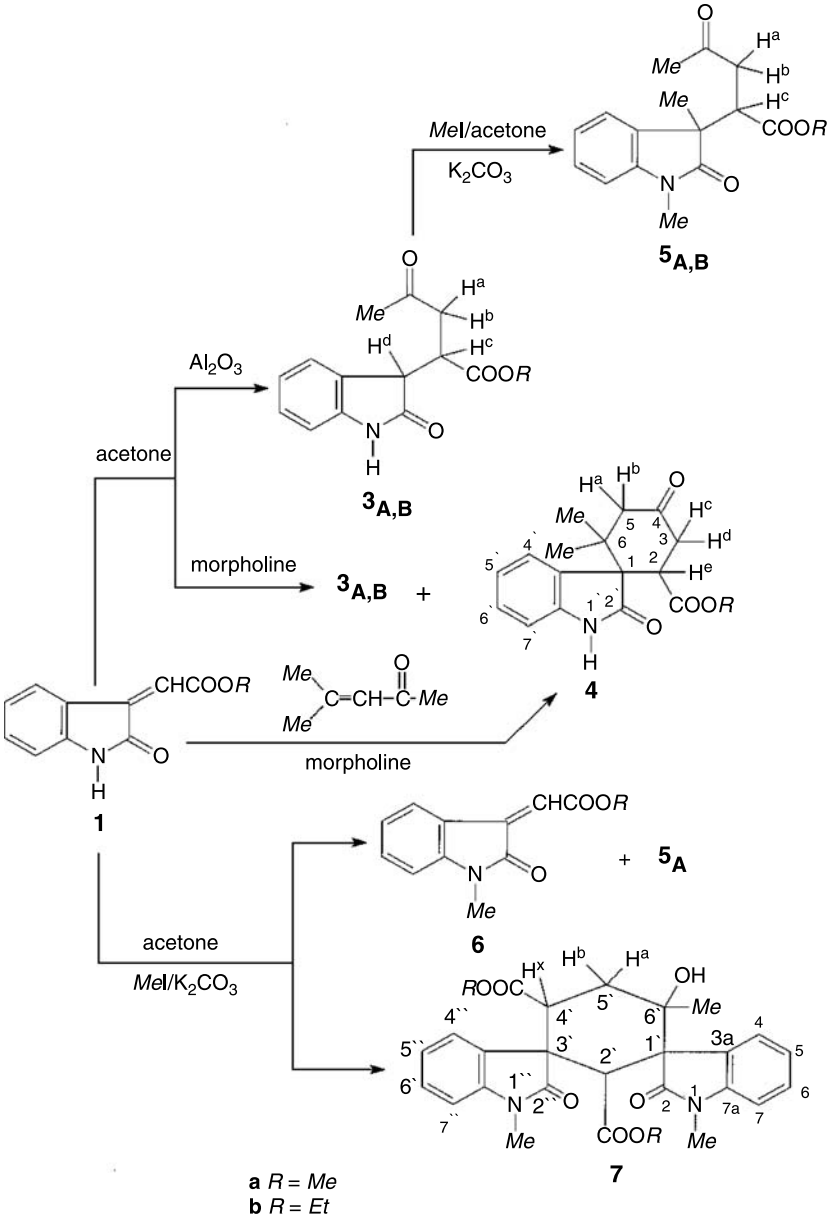
The constitution of $\mathbf{3_A}$ and $\mathbf{3_B}$ was established from their spectroscopic properties. These compounds contain a methylene group with a proton on the adjacent asymmetric carbon atom. The nature of these compounds makes the proton NMR study particularly interesting due to the non-equivalence of the methylene protons. H^a and H^b appear as two doublets of doublets with different chemical shifts. The shift at higher field can be assigned to the proton H^a. The proton H^c appeared as doublet of triplets, due to its coupling with the protons H^a, H^b, and H^d and was located downfield. The proton H^d is coupled with H^c to form a doublet at lower field to H^c [15]. Reaction of **1** with acetone using morpholine as the base produced the unexpected product **4**. It was obtained as colourless crystals in 9% yield besides the major products $\mathbf{3_A}$ and $\mathbf{3_B}$ (79%). The constitution of the spiro compounds **4** was elucidated by elemental analyses, molecular weight determinations (MS), and spectroscopic results. The IR spectrum of **4a**, taken as an example, disclosed the presence of absorption bands at $\bar{\nu} = 3136$ (NH) and 1740, 1710 cm^{-1} (C=O). Its ^{1}H NMR spectrum shows the protons of the two methyl groups at C-6 as two singlets at $\delta = 0.69$ and 1.27 ppm. The two methylene protons H^a and H^b at C-5 are mutually coupled to give rise to an AB system as two doublets with different chemical shifts, located at $\delta = 2.14$ and 2.95 ppm ($J_{H}a_{H}b = 14.4$ Hz). The other three protons H^c, H^d, and H^e showed an ABX system and appeared as three doublets of doublets at $\delta = 2.89$, 3.08, 3.77 ppm ($J_{H}c_{H}d = 16.8$ Hz, $J_{H}c_{H}e = 7$ Hz, $J_{H}d_{H}e = 12.2$ Hz).

The formation of the spiro product **4** might start with the reaction of **1** with acetone *via* nucleophilic attack of the carbon of one methyl group of acetone at the exocylic β-carbon of **1**, affording the adduct **3** (as a major product). Some of **3** is then condensed with another molecule of acetone. Elimination of water and basic catalysis cyclization could yield the spiro compound **4** (as a minor product). Further evidence supporting this mechanism is the formation of **4** as the sole product from the reaction of **1** with mesityl oxide in presence of morpholine as the base.

Methylation of a mixture of the two isomers $\mathbf{3_A}$ and $\mathbf{3_B}$ with methyl iodide in presence of acetone and anhydrous potassium carbonate at 60°C for about 50 h led to the formation of the relatively stable 4-oxo-2-(2-oxo-2,3-dihydro-1,3-dimethyl-l*H*-indole-3-yl)pentanoic acid esters diastereomers $\mathbf{5_A}$ and $\mathbf{5_B}$. These diastereomers were

separated by column chromatography on silica gel and their constitutions were established by spectroscopic techniques as well as elemental analyses and molecular weight determination (MS). Their ^{1}H NMR spectra showed the presence of a singlet at $\delta = 1.40$ ppm, corresponding to the protons of the methyl group at C-3 and a singlet at $\delta = 3.22$ ppm, due to the protons of the *N*-methyl group. Moreover, the three protons H^a, H^b, and H^c appeared as three doublets of doublets (*cf.* Experimental).

Treatment of **1** with methyl iodide in dry acetone in presence of potassium carbonate with gentle heating gave a mixture of (2-oxo-1,2-dihydro-1-methylindol-3-ylidene)acetic acid esters (**6**) and $\mathbf{5_A}$ with the unexpected products **7** (Scheme 1). These



Scheme 1

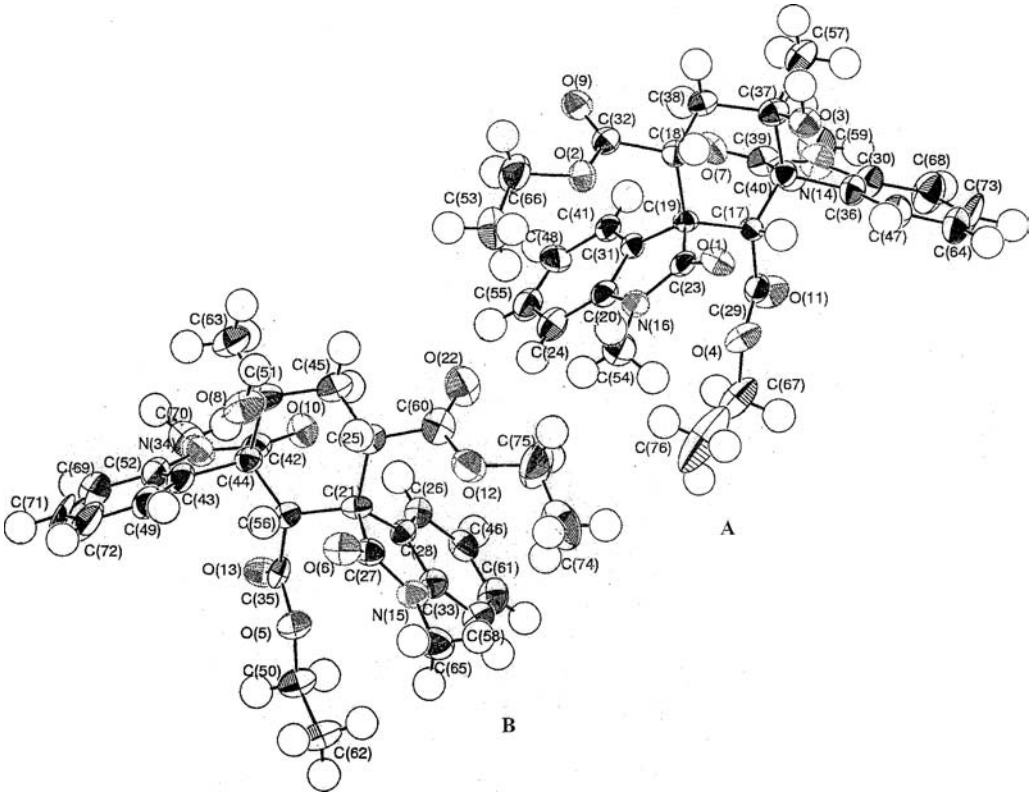


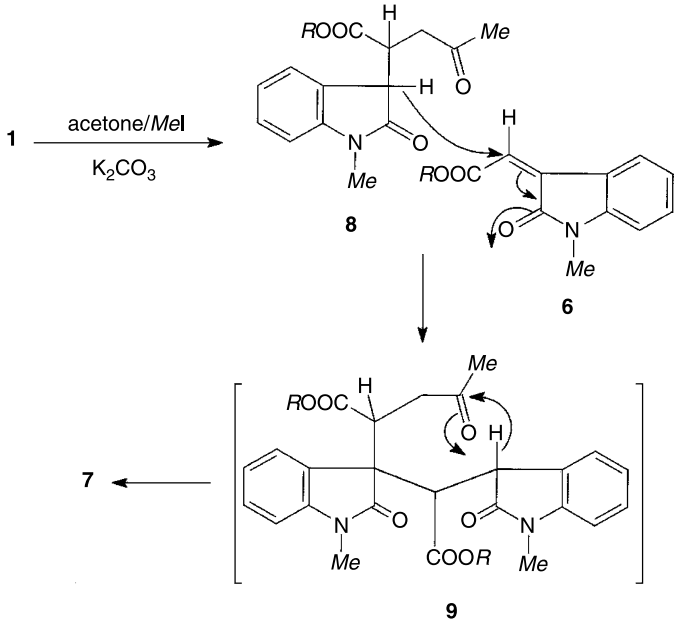
Fig. 1. ORTEP perspective view of **7b** with the enantiomers A and B in the unit cell

compounds were separated by column chromatography and their structures were elucidated by elemental analyses, molecular weight determination (MS), and spectroscopic results. The ^{1}H NMR spectra of **6** showed the characterstic signals at $\delta = 3.23$ ppm, due to the *N*-methyl group and at $\delta = 6.90$ ppm, for the exocyclic vinyl proton =CH–. The ^{1}H and ^{13}C NMR spectral data of the dispiro compounds **7** are consistent with expectation (*cf.* Experimental). Moreover, a single crystal X-ray diffraction analysis of **7b** confirmed the constitution. In the unit cell the two enantiomers (1′S,4′R,6′S), and (1′R,4′S,6′R) (Fig. 1) are present.

A mechanism for the formation of the dispiro compounds **7** from the reaction of **1** with acetone and methyl iodide in presence of potassium carbonate is proposed in Scheme 2. The reaction involves the initial formation of compounds **6** and **8**. Part of these intermediate products interact by nucleophilic attack of the methine carbon of **8** to the active exocyclic olefinic carbon of **6** to form the intermediate **9**, which is finally cyclized to give the dispiro compound **7**.

Experimental

Melting points were determined on an electrical digital-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 spectrometer for ^{1}H operating at 200 MHz and on a Jeol Ex-270 spectrometer for ^{13}C operating at 67.9 MHz. Chemical shifts are given



Scheme 2

for internal *TMS*. The mass spectra (MS) were determined at 70 eV on a Finnigan MAT SSQ 7000 spectrometer. Al_2O_3 S, basic, super active for column chromatography from Riedel-De Haen AG, Seelze, Hannover was used.

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 refined, using maXus (Nonius, Delft and MacScience, Japan). Mo-Kα radiation ($\lambda = 0.71073$ Å) and a graphite monochromator were used for data collection.

Compound **7b**: $C_{29}H_{32}N_2O_7$, $M_r = 520.582$, monoclinic, crystallizes in space group $P2_1$, $a = 12.8881(7)$, $b = 14.1348(7)$, $c = 14.5246(7)$ Å, $V = 2596.4(2)$ Å^3, $Z = 4$, $D_c = 1.332\,g\,cm^{-3}$, 2θ range 2.91–26.73°, μ(Mo-Kα) $= 0.10\,mm^{-1}$, $F(000) = 1104$. 9756 unique reflections were measured of which 6042 reflections with threshold expression $I > 3\sigma(I)$ were used in the structural analysis. Convergence for 684 variable parameters by least-squares refinement of F^2 with $w = 1/[\sigma^2 (F_o^2) + 0.03 + F_o^2]$ for 6042 reflections with $I > 3\sigma(I)$ was reached at $R = 0.056$ and $wR = 0.060$ with a goodness-of-fit of 1.610. 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 number 192387.

Reaction of Acetone with (E)-(2-Oxo-1,2-dihydroindol-3-ylidene)acetic Acid Methyl Ester (**1a**)

(A) In Presence of Aluminum Oxide

A mixture of **la** (2.3 mmol) and 4 g of Al_2O_3 in 20 cm^3 of dry acetone was gently heated under reflux for 5 h. The mixture was filtered, the solution was evaporated, and the residue was purified on silica

gel/*n*-hexane:acetone (3:1), to give the diastereomer mixture of **3a$_A$** and **3a$_B$** in 68%. Fractional recrystallization from benzene gave colorless crystals of **3a$_B$**.

4-Oxo-2-(2-oxo-2,3-dihydro-1H-indole-3-yl)pentanoic Acid Methyl Ester (**3a$_A$**, **3a$_B$**, $C_{14}H_{15}NO_4$)

3a$_A$: ^{1}H NMR: $\delta = 2.10$ (s, $COCH_3$), 2.47 (dd, $J_Ha_Hb = 18$ Hz, $J_Ha_Hc = 4.8$ Hz, H^a), 2.77 (dd, $J_Hb_Ha = 18$ Hz, $J_Hb_Hc = 8.8$ Hz, H^b), 3.72 (s, ester CH_3), 3.81 (dt, $J_Hc_Ha = 4.8$ Hz, $J_Hc_Hb = 8.8$ Hz, $J_Hc_Hd = 3.6$ Hz, H^c), 3.87 (d, $J_Hd_Hc = 3.6$ Hz, H^d), 6.91, 7.02 (2d, $J = 7.6$ Hz, ArH at C-4, C-7), 7.07, 7.23 (2t, $J = 7.2$ Hz, ArH at C-5, C-6), 9.18 (s, NH) ppm (spectrum taken from the mixture).

3a$_B$: mp 153–155°C; IR: $\bar{\nu} = 3186$ (NH), 1738, 1718 (C=O), 1620 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 2.14$ (s, $COCH_3$), 2.17 (dd, $J_Ha_Hb = 17.4$ Hz, $J_Ha_Hc = 3.8$ Hz, H^a), 3.05 (dd, $J_Hb_Ha = 17.4$ Hz, $J_Hb_Hc = 10$ Hz, H^b), 3.71 (s, ester CH_3), 3.74 (dt, $J_Hc_Ha = 3.8$ Hz, $J_Hc_Hb = 10$ Hz, $J_Hc_Hd = 3.8$ Hz, H^c), 3.99 (d, $J_Hd_Hc = 4$ Hz, H^d), 6.90, 7.04 (2d, $J = 7.6$ Hz, ArH at C-4, C-7), 7.18–7.29 (m, ArH at C-5, C-6), 8.67 (s, NH) ppm; MS: m/z (%) = 261 (M$^+$, 29).

4-Oxo-2-(2-oxo-2,3-dihydro-1H-indole-3-yl)pentanoic Acid Ethyl Ester (**3b$_A$**, **3b$_B$**, $C_{15}H_{17}NO_4$)

Similarly, **3b$_A$** and **3b$_B$** were obtained in 73% from the reaction of acetone with **1b**.

3b$_A$: ^{1}H NMR: $\delta = 1.20$ (t, $J = 7.2$ Hz, ester CH_3), 2.10 (s, $COCH_3$), 2.49 (dd, $J_Ha_Hb =$ 17.8 Hz, $J_Ha_Hc = 4.8$ Hz, H^a), 2.80 (dd, $J_Hb_Ha = 17.8$ Hz, $J_Hb_Hc = 9$ Hz, H^b), 3.75 (dt, $J_Hc_Ha = 3.6$ Hz, $J_Hc_Hb = 9$ Hz, H^c), 3.88 (d, $J_Hd_Hc = 3.6$ Hz, H^d), 4.13 (m, ester CH_2), 6.91, 7.21 (2d, $J = 7.6$ Hz, ArH at C-4, C-7), 7.11, 7.25 (2t, $J = 7.6$ Hz, ArH at C-5, C-6), 9.15 (s, NH) ppm (spectrum taken from the mixture).

3b$_B$: mp 145–146°C; IR: $\bar{\nu} = 3178$ (NH), 1703 (C=O), 1620 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.16$ (t, $J = 7.2$ Hz, ester CH_3), 2.15 (s, $COCH_3$), 2.20 (dd, $J_Ha_Hb = 17.4$ Hz, $J_Ha_Hc = 3.6$ Hz, H^a), 3.09 (dd, $J_Hb_Ha = 17.4$ Hz, $J_Hb_Hc = 10$ Hz, H^b), 3.75 (dt, $J_Hc_Ha = 3.6$ Hz, $J_Hc_Hb = 10$ Hz, $J_Hc_Hd = 4$ Hz, H^c), 3.95 (d, $J_Hd_Hc = 4$ Hz, H^d), 4.14 (m, ester CH_2), 6.90, 7.21 (2d, $J = 7.6$ Hz, ArH at C-4, C-7), 7.02, 7.24 (2t, $J = 7.6$ Hz, ArH at C-5, C-6), 9.19 (s, NH) ppm; MS: m/z (%) = 275 (M$^+$, 25).

(B) In Presence of Morpholine

To a solution of **1a** (3.5 mmol) in 40 cm^3 of dry acetone, 1 cm^3 of morpholine was added and the mixture was heated under reflux for about 2 h. The solution was evaporated and the residue was chromatographed on silica gel/*n*-hexane:acetone (3:1) to yield a mixture of **4a**, **3a$_A$**, and **3a$_B$**.

Methyl 1′,2′-dihydro-6,6-dimethyl-2′,4-dioxospiro[cyclohexane-1, 3′-(3′H)-indole]-2-carboxylate (**4a**, $C_{17}H_{19}NO_4$)

Yield: 9%; colorless crystals; mp 184–185°C (chloroform/*n*-hexane); IR: $\bar{\nu} =$ 3136 (NH), 1740, 1710 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 0.69$, 1.27 (2s, $2CH_3$ at C-6), 2.14, 2.95 (2d, $J_Ha_Hb = 14.4$ Hz, H^a and H^b at C-5), 2.89 (dd, $J_Hc_Hd = 16.8$ Hz, $J_Hc_He = 7$ Hz, H^c at C-3), 3.08 (dd, $J_Hd_Hc = 16.8$ Hz, $J_Hd_He = 12.2$ Hz, H^d at C-3), 3.40 (s, ester CH_3), 3.77 (dd, $J_He_Hd = 12.2$ Hz, $J_He_Hc = 7$ Hz, H^e at C-2), 6.92, 7.30 (2d, $J = 7.8$ Hz, ArH at C-4′, C-7′), 7.03, 7.28 (2t, $J = 7.6$ Hz, ArH at C-5′, C-6′), 7.77 (s, NH) ppm; MS: m/z (%) = 301 (M$^+$, 21).

3a$_A$ and **3a$_B$**: Yield 79%; identified by ^{1}H NMR spectrum.

Ethyl 1′,2′-dihydro-6,6-dimethyl-2′,4-dioxospiro[cyclohexane-1, 3′-(3′H)-indole]-2-carboxylate (**4b**, $C_{18}H_{21}NO_4$)

By the same manner, **4b**, $\mathbf{3b_A}$, and $\mathbf{3b_B}$ were obtained from the reaction of **1b** with acetone.

4b: Yield 8%; colorless crystals; mp 202–203°C (chloroform/*n*-hexane); IR: $\bar{\nu} = 3140$ (NH), 1734, 1711 (C=O) cm^{-1}; ^1H NMR: $\delta = 0.69$, 1.27 (2s, $2CH_3$ at C-6), 0.90 (t, $J = 7.2$ Hz, ester CH_3), 2.12, 2.90 (2d, $J_Ha_Hb = 15.2$ Hz, H^a and H^b at C-5), 2.88 (dd, $J_Hc_Hd = 17$ Hz, $J_Hc_He = 7$ Hz, H^c at C-3), 3.10 (dd, $J_Hd_Hc = 17$ Hz, $J_Hd_He = 12.4$ Hz, H^d at C-3), 3.69–3.93 (m, ester CH_2 and H^e at C-2), 6.95, 7.30 (2d, $J = 7.6$ Hz, ArH at C-4′, C-7′), 7.01, 7.27 (2t, $J = 7.6$ Hz, ArH at C-5′, C-6′), 8.98 (s, NH) ppm; MS: m/z (%) = 315 (M^+, 82).

$\mathbf{3b_A}$ and $\mathbf{3b_B}$: Yield 75%; identified by the ^1H NMR spectrum.

Reaction of Mesityl Oxide with **1**

A mixture of 2 mmol of **1**, 5 cm^3 of mesityl oxide, and 1 cm^3 of morpholine in 15 cm^3 of dry benzene was heated under reflux for 5 h. The solution was evaporated under reduced pressure and the residue was chromatographed on silica gel with *n*-hexane:acetone (4:1) as eluent to yield **4** (63%), which was identified by mp, mixed mp, and ^1H NMR spectra of authentic samples previously obtained.

Reaction of Methyl Iodide with **3a** (*as a Mixture of Two Diastereomers* $\mathbf{3a_A}$, $\mathbf{3a_B}$)

A mixture of **3a** (2 mmol), 10 cm^3 of freshly distilled CH_3I, 3 g of anhydrous K_2CO_3 in 20 cm^3 of dry acetone was gently heated under reflux for 50 h. The inorganic materials were filtered off, and the solution was evaporated under reduced pressure. The residue was chromatographed on silica gel/ *n*-hexane:acetone (9:1) to give colorless crystals of $\mathbf{5a_A}$ and $\mathbf{5a_B}$.

4-Oxo-2-(2-oxo-2,3-dihydro-1,3-dimethyl-1H-indole-3-yl)pentanoic Acid Methyl Ester ($\mathbf{5a_A}$, $\mathbf{5a_B}$, $C_{16}H_{19}NO_4$)

$\mathbf{5a_A}$: Yield 36%; mp 111–112°C (benzene/*n*-hexane); IR: $\bar{\nu} = 1738$, 1717, 1701 (C=O), 1610 (C=C) cm^{-1}; ^1H NMR: $\delta = 1.38$ (s, CH_3 at C-3), 2.03 (s, $COCH_3$), 2.33 (dd, $J_Ha_Hb = 18.2$ Hz, $J_Ha_Hc = 3.4$ Hz, H^a); 2.67 (dd, $J_Hb_Hc = 18.2$ Hz, $J_Hb_Hc = 11$ Hz, H^b), 3.23 (s, *N*-Me), 3.41 (dd, $J_Hc_Ha = 3.4$ Hz, $J_Hc_Hb = 11$ Hz, H^c), 3.66 (s, ester CH_3), 6.87, 7.25 (2d, $J = 7.6$ Hz, ArH at C-4, C-7), 7.08, 7.31 (2t, $J = 7.6$ Hz, ArH at C-5, C-6) ppm; MS: m/z (%) = 289 (M^+, 48).

$\mathbf{5a_B}$: Yield 7%; mp 87–88°C (*n*-hexane); IR: $\bar{\nu} = 1718$ (C=O), 1612 (C=C) cm^{-1}; ^1H NMR: $\delta = 1.44$ (s, CH_3 at C-3), 2.12 (s, $COCH_3$), 2.56 (dd, $J_Ha_Hb = 17.4$ Hz, $J_Ha_Hc = 3$ Hz, H^a), 3.02 (dd, $J_Hb_Ha = 17.4$ Hz, $J_Hb_Hc = 11.4$ Hz, H^b), 3.22 (s, *N*-CH_3), 3.36 (dd, $J_Hc_Ha = 3$ Hz, $J_Hc_Hb = 11.4$ Hz, H^c), 3.56 (s, ester CH_3), 6.85, 7.06 (2d, $J = 7.6$ Hz, ArH at C-4, C-7), 7.11, 7.29 (2t, $J = 7.8$ Hz, ArH at C-5, C-6) ppm; MS: m/z (%) = 289 (M^+, 33).

4-Oxo-2-(2-oxo-2,3-dihydro-1,3-dimethyl-1H-indole-3-yl)pentanoic Acid Ethyl Ester ($\mathbf{5b_A}$, $\mathbf{5b_B}$, $C_{17}H_{21}NO_4$)

Similarly, $\mathbf{5b_A}$ and $\mathbf{5b_B}$ were isolated from the reaction of **3b** as diastereomer mixture of $\mathbf{3b_A}$ and $\mathbf{3b_B}$ with methyl iodide.

$\mathbf{5b_A}$: Yield 38%; mp 112–113°C (benzene/petroleum ether); IR: $\bar{\nu} = 1711$ (C=O), 1610 (C=C) cm^{-1}; ^1H NMR: $\delta = 1.16$ (t, $J = 7$ Hz, ester CH_3), 1.39 (s, CH_3 at C-3), 2.04 (s, $COCH_3$), 2.38 (dd, $J_Ha_Hb = 18.2$ Hz, $J_Ha_Hc = 3.4$ Hz, H^a), 2.73 (dd, $J_Hb_Ha = 18.2$ Hz, $J_Hb_Hc = 11$ Hz, H^b), 3.22 (s, *N*-CH_3), 3.39 (dd, $J_Hc_Ha = 3.4$ Hz, $J_Hc_Hb = 11$ Hz, H^c), 4.08 (q, $J = 7$ Hz, ester CH_2), 6.85, 7.26 (2d, $J = 7.6$ Hz, ArH at C-4, C-7), 7.06, 7.29 (2dt, $J_{HH} = 7.6$, 1.4 Hz, ArH at C-5, C-6) ppm; MS: m/z (%) = 303 (M^+, 94).

5b$_B$: Yield 3%; mp 98–99°C (petroleum ether); IR: $\bar{\nu} = 1718$ (C=O), 1612 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.06$ (t, $J = 7$ Hz, ester CH_3), 1.42 (s, CH_3 at C-3), 2.13 (s, $COCH_3$), 2.56 (dd, $J_Ha_Hb = 17.4$ Hz, $J_Ha_Hc = 3$ Hz, H^a), 3.05 (dd, $J_Hb_Ha = 17.4$ Hz, $J_Hb_Hc = 11.4$ Hz, H^b), 3.21 (s, *N*-CH_3), 3.40 (dd, $J_Hc_Ha = 3$ Hz, $J_Hc_Hb = 11.4$ Hz, H^c), 3.98 (q, $J = 7$ Hz, ester CH_2), 6.83, 7.14 (2d, $J = 7.6$ Hz, ArH at C-4, C-7), 7.03, 7.28 (2dt, $J = 7.6$, 1.6 Hz, ArH at C-5, C-6) ppm; MS: m/z (%) = 303 (M$^+$, 32).

Reaction of ***la*** *with Methyl Iodide*

A mixture of 7.4 mmol of **1a** and 5 g of anhydrous K_2CO_3 in 50 cm^3 of dry acetone was gently heated under reflux. Then, 8 cm^3 of freshly distilled CH_3I were added portion wise with continuous heating. After about 10 h, the inorganic material was filtered off and the solution was evaporated under reduced pressure. The residue was chromatographed, using silica gel/*n*-hexane:acetone (3:2) to yield **6a**, **5a$_A$**, and **7a**.

(2-Oxo-1,2-dihydro-1-methylindol-3-ylidene)acetic Acid Methyl Ester (**6a**, $C_{12}H_{11}NO_3$)

Yield: 35%; orange red crystals; mp 137–138°C (benzene/*n*-hexane); IR: $\bar{\nu} = 1709$ (C=O), 1647, 1606 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 3.22$ (s, *N*-CH_3), 3.87 (s, ester CH_3), 6.79 (d, $J = 7.6$ Hz, ArH at C-7), 6.90 (s, =CH–), 7.06, 7.37 (2t, $J = 7.6$ Hz, ArH at C-5, C-6), 8.54 (d, $J = 7.6$ Hz, ArH at C-4) ppm; MS: m/z (%) = 217 (M$^+$, 100).

5a$_A$: Yield 5%; identified by its mp, mixed mp, and comparative ^{1}H NMR spectrum with an authentic sample.

Dimethyl 1,1″,2,2″-tetrahydro-6′-hydroxy-1,1″,6′-trimethyl-2,2″-dioxodispiro[3H-indole-3, 1′-cyclohexan-3′,3″-(3H)-indole]-2′,4′-dicarboxylate (**7a**, $C_{27}H_{28}N_2O_7$)

Yield: 8%; colorless crystals; mp 250–252°C (benzene/*n*-hexane); IR: $\bar{\nu} = 3460$ (OH), 1713 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 0.998$ (s, CH_3 at C-6′), 1.97 (dd, $J_Ha_Hb = 14.5$ Hz, $J_Ha_Hx = 3.6$ Hz, H^a), 2.16 (s, OH at C-6′, exchangeable with D_2O), 2.93, 3.14 (2s, 2 ester CH_3), 3.24, 3.26 (2s, 2 *N*-CH_3); 3.25 (dd overlapped with the two singlets of 2 *N*-CH_3, $J_Hb_Ha = 14.5$ Hz, $J_Hb_Hx = 13.6$ Hz, H^b), 3.88 (dd, $J_Hx_Ha = 3.6$ Hz, $J_Hx_Hb = 13.6$ Hz, H^x), 4.25 (s, H at C-2′), 6.75, 6.80 (2d, $J = 7.6$ Hz, ArH at C-7, C-7″), 7.02, 7.08 (2dt, $J = 7.6$, 1.1 Hz, ArH at C-5, C-5″), 7.23, 7.29 (2dt, $J = 7.6$, 1.1 Hz, ArH at C-6, C-6″), 7.48, 8.69 (2d, $J = 6.7$ Hz, ArH at C-4, C-4″) ppm; ^{13}C NMR: $\delta = 25.3$ (CH_3 at C-6′), 26.4, 26.7 (2 *N*-CH_3), 31.6 (C-5′); 43.9 (C-4′); 51.4, 51.6 (2 CH_3 esters), 52.6 (spiro C-3′), 53.0 (C-2′), 56.2 (spiro C-1′), 71.0 (C-6′), 106.9, 107.7, 122.1, 122.7, 124.9, 128.3, 128.7, 129.0 (8 aromatic CH), 127.3, 129.6 (aromatic quaternary C-3a, C-3″a), 144.3, 144.8 (aromatic quaternary C-7a, C-7″a), 169.4, 171.6 (2 CO esters), 176.7, 180.1 (C-2, C-2″) ppm; MS: m/z (%) = 492 (M$^+$, 51).

(2-Oxo-1,2-dihydro-1-methylindol-3-ylidene)acetic Acid Ethyl Ester (**6b**, $C_{13}H_{13}NO_3$) *and Diethyl 1,1″,2,2″-tetrahydro-6′-hydroxy-1,1″,6′-trimethyl-2,2″-dioxodispiro[3H-indole-3, 1′-cyclohexane-3′,3″-(3H)-indole]-2′,4′-dicarboxylate* (**7b**, $C_{29}H_{32}N_2O_7$)

Carrying out the same experiment described above, **6b**, **5b$_A$**, and **7b** were isolated from the reaction of **1b** with CH_3I.

6b: Yield 32%; orange red crystals; mp 83–85°C (benzene/petroleum ether); IR: $\bar{\nu} = 1710$ (C=O), 1654, 1604 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.35$ (t, $J = 7.2$ Hz, ester CH_3), 3.23 (s, *N*-CH_3), 4.30 (q, $J = 7.2$ Hz, ester CH_2), 6.78 (d, $J = 7.6$ Hz, ArH at C-7), 6.90 (s, =CH–), 7.05, 7.35 (2dt, $J = 7.6$, 1.6 Hz, ArH at C-5, C-6), 8.55 (d, $J = 7.6$ Hz, ArH at C-4) ppm; MS: m/z (%) = 231 (M$^+$, 100).

$5b_A$: Yield 7%; identified by its mp, mixed mp, and comparative ^{1}H NMR spectrum with an authentic sample.

7b: Yield 10%; colorless crystals; mp 204–205°C (benzene/*n*-hexane); IR: $\bar{\nu} = 3453$ (OH), 1710 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 0.59$, 0.78 (2t, $J = 7$ Hz, 2 ester CH_3), 0.98 (s, CH_3 at C-6′), 1.93 (dd, $J_Ha_Hb = 14.5$ Hz, $J_Ha_Hx = 3.8$ Hz, H^a), 2.14 (s, OH at C-6′, exchangeable with D_2O), 3.22, 3.23 (2s, 2 *N*-CH_3); 3.23 (dd overlapped with the two singlets of 2 *N*-CH_3, $J_Hb_Ha = 14.5$ Hz, $J_Hb_Hx = 13.6$ Hz, H^b), 3.39 (q, $J = 7$ Hz, ester CH_2), 3.61 (m, ester CH_2), 3.82 (dd, $J_Hx_Hb = 13.6$ Hz, $J_Hx_Ha = 3.6$ Hz, H^x), 4.22 (s, H at C-2′), 6.72, 6.78 (2d, $J = 7.6$ Hz, ArH at C-7, C-7″), 7.02, 7.07 (2dt, $J = 7.6$, 1.1 Hz, ArH at C-5, C-5″), 7.21, 7.27 (2dt, $J = 7.5$, 1.1 Hz, ArH at C-6, C-6″), 7.49, 8.68 (2d, $J = 7.6$ Hz, ArH at C-4, C-4″) ppm; ^{13}C NMR: $\delta = 13.4$, 13.7 (2 CH_3 esters), 25.3 (CH_3 at C-6′), 26.3, 26.6 (2 *N*-CH_3), 31.6 (C-5′), 43.9 (C-4′), 52.5 (spiro C-3′), 52.9 (C-2′), 56.3 (spiro C-1′), 60.3, 60.6 (2 CH_2 esters), 71.0 (C-6′), 107.0, 107.6, 122.1, 122.6, 125.0, 128.6, 128.9, 129.0 (8 aromatic CH), 127.4, 129.8 (aromatic quaternary C-3a, C-3″a), 144.6, 144.8 (aromatic quaternary C-7a, C-7″a), 168.8, 171.2 (2 CO esters), 176.6, 180.0 (C-2, C-2″) ppm; MS: m/z (%) = 520 (M^+, 72).

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