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Regioselective Addition of Aromatic Amines at the Exocyclic C=C Bond of 2-(2-Oxo-2,3-dihydro-1*H*-indol-3-ylidene)acetic Acid Esters

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Abstract—Methyl and ethyl 2-(2-oxo-2,3-dihydro-3*H*-indol-3-ylidene)acetates react with aromatic amines to give products of regioselective addition at the α-position of the activated exocyclic C=C bond, methyl and ethyl 2-arylamino-2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetates.

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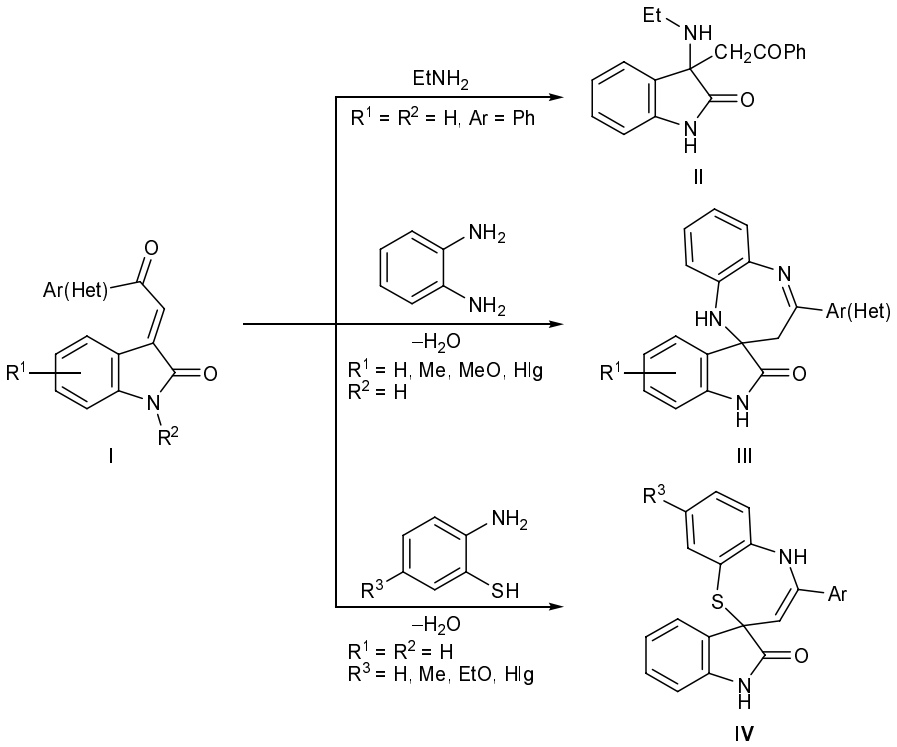
3-[2-Aryl(hetaryl)-2-oxoethylidene]-2,3-dihydro-1*H*-indol-2-ones **I** are known to readily react with ethylamine [1], *o*-phenylenediamine [2–4], and 2-aminobenzenethiol [5, 6], to give compounds **II**–**IV** via addition of the amino (or thiol) group at the activated exocyclic C=C bond in position *3* of the indole ring, followed by spiroheterocyclization (in reactions with difunctional nucleophiles; Scheme 1). Likewise, hydrazines add at the double C=C bond of 3-[2-(alkyl, aryl, or hetaryl)ethylidene]-2,3-dihydro-1*H*-indol-2-ones **I**, yielding 2',4'-dihydrospiro(indole-3,3'-pyrazol)-2(1*H*)-ones **V** [3, 7–12]. Here, as in the reactions with amines and thiols, the amino group of the hydrazine molecule adds to the C^3 atom of the indole ring (β-position with respect to the exocyclic carbonyl group; Scheme 1). Thus the attack by both N-mono- and S,N- and N,N-binucleophiles is directed at the electrophilic C^3 atom of 3-ylideneindol-2-ones.

We have found that methyl and ethyl (2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)acetates **VIa**–**VIe** (which are structurally related to compounds **I**) react with aromatic amines in boiling ethanol in a regioselective fashion to give products of nucleophilic addition at the α- rather than β-position (with respect to the ester group) of the exocyclic C=C bond, methyl and ethyl 2-arylamino-2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-acetates **VIIa**–**VIIh** (Scheme 2). It was proposed to call the process with participation of oxoindolylideneacetates "regioselective amino–methylenoxindole reaction" (for preliminary communications, see [13–15]).

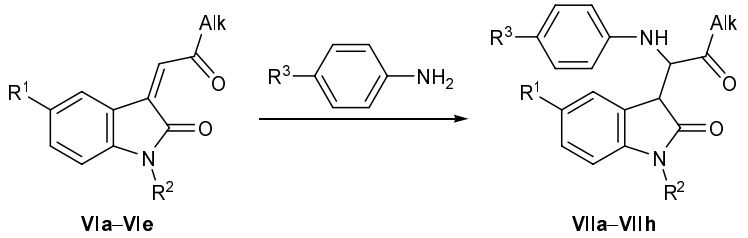
Compounds **VIIa**–**VIIh** were isolated as yellow crystalline substances which are insoluble in water, poorly soluble in common organic solvents, and readily soluble in DMF and DMSO. In keeping with the assumed structure, the IR spectra of **VIIa**–**VIIh** contained broadened absorption bands due to stretching vibrations of the N–H bond in the amino (3265–3290 cm^{-1}) and lactam groups (3160–3210 cm^{-1}), as well as ester (1715–1748 cm^{-1}) and lactam carbonyl bands (1702–1726 cm^{-1}).

Compounds **VIIa**–**VIIh** showed in the ^1H NMR spectra a set of signals in the δ range from 3.86 to 4.97 ppm from protons in the $C^{3'}H$–C^2H fragment. Among these, two pairs of doublets of doublets with a small coupling constant can be distinguished; these signals are typical of a common *AB* spin system (vicinal $H_α$ and $H_β$ protons), and they indicate the presence of at least two diastereoisomers. The spectral pattern somewhat resembles that reported previously for 2-hetarylmethyl derivatives of 2,3-dihydrofuran-3-ones [16, 17].

Scheme 1.



Scheme 2.



VI, $R^1 = R^2 = H$, Alk = Me (**a**), Et (**b**); $R^1 = H$, R^2 = MeCO, Alk = Me (**c**); R^1 = Br, R^2 = MeCO, Alk = Et (**d**); $R^1 = O_2N$, $R^2 = H$, Alk = Et (**e**); **VII**, $R^1 = R^2 = H$, Alk = Me, R^3 = Me (**a**), MeO (**b**); $R^1 = R^2 = H$, Alk = Et, R^3 = Me (**c**), MeO (**d**); $R^1 = H$, R^2 = MeCO, Alk = Me, R^3 = Me (**e**), MeO (**f**); R^1 = Br, R^2 = MeCO, Alk = Et, R^3 = Me (**g**); $R^1 = O_2N$, $R^2 = H$, Alk = Et, R^3 = Me (**h**).

Presumably, change in the regioselectivity of aromatic amine addition at the exocyclic C^3=C bond from the β-position in 3-acylmethylidene-2,3-dihydro-1*H*-indol-2-ones to the α-position in 2-(2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)acetates **VI** is determined by weaker electron-withdrawing effect of the ester group in **VI** as compared to the acyl moiety in **I**.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Bruker DRX-500 spectrometer (500 MHz) in DMSO-d_6 relative to TMS as internal reference. The purity of

compounds **VIIa**–**VIIh** was checked by thin-layer chromatography on Silufol UV-254 plates using benzene–diethyl ether–acetone (10:9:1) as eluent; spots were visualized by treatment with iodine vapor.

Initial 2-(2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)-acetates **VIa**–**VIe** were synthesized by the procedure described in [18–20].

Methyl and ethyl 2-arylamino-2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetates VIIa–VIIh (*general procedure***).** Ester **VIa**–**VIe**, 10 mmol, was dissolved in 50–80 ml of ethanol, 10 mmol of the corresponding amine (*p*-toluidine or *p*-anisidine) was added, and the mixture was heated for 1–2 h under reflux. The precipitate was filtered off and recrystallized from ethanol or propan-2-ol.

Methyl 2-(4-methylphenylamino)-2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (VIIa). Yield 1.68 g (54%), mp 143–144°C (from EtOH). IR spectrum, ν, cm^{-1}: 3285 (N–H, amine), 3205 (N–H, amide), 1737 (C=O, ester), 1722 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 2.23 s (3H, Me), 2.27 s (3H, Me), 3.60 s (3H, OMe), 3.64 s (3H, OMe), 4.05 d and 4.37 d (2H, 3'-H, 2-H, *J* = 3.8 Hz), 4.43 d and 4.88 d (2H, 3-H, 2-H, *J* = 5.3 Hz), 5.12 br.s (1H, NH), 6.85–7.40 m (16H, H_{arom}), 11.15 s (1H, 1'-H), 11.38 s (1H, 1'-H). Found, %: C 69.38; H 5.64; N 9.21. $C_{18}H_{18}N_2O_3$. *M* 310.35. Calculated, %: C 69.66; H 5.85; N 9.03.

Methyl 2-(4-methoxyphenylamino)-2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (VIIb). Yield 1.60 g (49%), mp 129–130°C (from EtOH). IR spectrum, ν, cm^{-1}: 3290 (N–H, amine), 3210 (N–H, amide), 1748 (C=O, ester), 1726 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 3.54 s (3H, OMe), 3.62 s (3H, OMe), 3.70 s (3H, COOMe), 3.76 s (3H, COOMe), 4.10 d and 4.24 d (2H, 3'-H, 2-H, *J* = 3.4 Hz), 4.35 d and 4.69 d (2H, 3'-H, 2-H, *J* = 4.8 Hz), 5.20 br.s (1H, NH), 6.62–7.35 m (16H, H_{arom}), 11.34 s (1H, 1'-H), 11.50 s (1H, 1'-H). Found, %: C 66.03; H 5.69; N 8.77. $C_{18}H_{18}N_2O_4$. *M* 326.35. Calculated, %: C 66.25; H 5.56; N 8.58.

Ethyl 2-(4-methylphenylamino)-2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (VIIc). Yield 1.52 g (47%), mp 137–138°C (from *i*-PrOH). IR spectrum, ν, cm^{-1}: 3280 (N–H, amine), 3175 (N–H, amide), 1725 (C=O, ester), 1702 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 1.15 t (3H, $CH_2C\mathbf{H}_3$), 1.30 t (3H, $CH_2C\mathbf{H}_3$), 2.25 s (3H, Me), 2.29 s (3H, Me), 3.95 d and 4.43 d (2H, 3'-H, 2-H, *J* = 3.5 Hz), 4.12 q (2H, $C\mathbf{H}_2CH_3$), 4.33 q (2H, $C\mathbf{H}_2CH_3$), 4.63 br.s (1H, NH), 4.65 d and 4.97 d (2H, 3'-H, 2-H, *J* = 5.0 Hz), 6.72–7.24 m (16H, H_{arom}), 10.53 s (1H, 1'-H), 10.70 s (1H, 1'-H). Found, %: C 69.98; H 6.45; N 8.86. $C_{19}H_{20}N_2O_3$. *M* 324.37. Calculated, %: C 70.35; H 6.21; N 8.64.

Ethyl 2-(4-methoxyphenylamino)-2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (VIId). Yield 1.74 g (51%), mp 131–132°C (from EtOH). IR spectrum, ν, cm^{-1}: 3275 (N–H, amine), 3190 (N–H, amide), 1732 (C=O, ester), 1710 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, $CH_2C\mathbf{H}_3$); 1.32 t (3H, $CH_2C\mathbf{H}_3$); 3.63 s (3H, OMe); 3.65 s (3H, OMe); 3.86 d and 4.53 d (2H, 3'-H, 2-H, *J* = 3.7 Hz); 4.08 q (2H, $C\mathbf{H}_2CH_3$); 4.29 q (2H, $C\mathbf{H}_2CH_3$); 4.45 br.s (1H, NH); 4.57 d and 4.89 d (2H, 3'-H, 2-H, *J* = 5.2 Hz); 6.50, 6.62–6.68, 6.81–6.87, 6.93–6.98, 7.20, and 7.33 (16H, H_{arom}); 10.42 s (1H, 1'-H); 10.68 s (1H, 1'-H). Found, %: C 66.79; H 6.14; N 8.47. $C_{19}H_{20}N_2O_4$. *M* 340.37. Calculated, %: C 67.05; H 5.92; N 8.23.

Methyl 2-(1-acetyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-2-(4-methylphenylamino)acetate (VIIe). Yield 1.55 g (44%), mp 162–163°C (from EtOH). IR spectrum, ν, cm^{-1}: 3262 (N–H, amine), 3205 (N–H, amide), 1732 (C=O, ester), 1718 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 2.17 s (3H, Me), 2.23 s (3H, Me), 2.64 s (3H, MeCO), 2.68 s (3H, MeCO), 3.57 s (3H, OMe), 3.62 s (3H, OMe), 4.20 d and 4.46 d (2H, 3'-H, 2-H, *J* = 4.0 Hz), 4.49 d and 4.67 d (2H, 3'-H, 2-H, *J* = 4.8 Hz), 5.35 br.s (1H, NH), 6.90–8.32 m (16H, H_{arom}). Found, %: C 68.31; H 5.59; N 8.14. $C_{20}H_{20}N_2O_4$. *M* 352.38. Calculated, %: C 68.17; H 5.72; N 7.95.

Methyl 2-(1-acetyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-2-(4-methoxyphenylamino)acetate (VIIf). Yield 1.47 g (40%), mp 147–148°C (from *i*-PrOH). IR spectrum, ν, cm^{-1}: 3270 (N–H, amine), 3210 (N–H, amide), 1735 (C=O, ester), 1720 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 2.66 s (3H, MeCO), 2.71 s (3H, MeCO), 3.56 s (3H, COOMe), 3.63 s (3H, COOMe), 4.17 d and 4.30 d (2H, 3'-H, 2-H, *J* = 3.8 Hz), 4.45 d and 4.68 d (2H, 3'-H, 2-H, *J* = 4.9 Hz), 5.20 br.s (1H, NH), 6.65–8.30 m (16H, H_{arom}). Found, %: C 65.46; H 5.68; N 7.72. $C_{20}H_{20}N_2O_5$. *M* 368.38. Calculated, %: C 65.21; H 5.47; N 7.60.

Ethyl 2-(1-acetyl-5-bromo-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-2-(4-methylphenylamino)acetate (VIIg). Yield 1.65 g (37%), mp 158–159°C (from EtOH). IR spectrum, ν, cm^{-1}: 3265 (N–H, amine), 3160 (N–H, amide), 1715 (C=O, ester), 1708 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, $CH_2C\mathbf{H}_3$), 1.25 t (3H, $CH_2C\mathbf{H}_3$), 2.20 s (3H, Me), 2.26 s (3H, Me), 2.62 s (3H, MeCO), 2.67 s (3H, MeCO), 3.95 q (2H, $C\mathbf{H}_2CH_3$), 4.02 q (2H, $C\mathbf{H}_2CH_3$), 4.15 d and 4.32 d (2H, 3'-H, 2-H, *J* = 3.6 Hz), 4.52 d and 4.88 d (2H, 3'-H, 2-H, *J* = 5.2 Hz), 5.12 br.s (1H,

NH), 6.92–7.78 m (14H, H_{arom}). Found, %: C 56.80; H 4.38; Br 17.72; N 6.12. $C_{21}H_{21}BrN_2O_4$. *M* 445.31. Calculated, %: C 56.64; H 4.75; Br 17.94; N 6.29.

Ethyl 2-(4-methylphenylamino)-2-(5-nitro-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (VIIh). Yield 1.18 g (32%), mp 270–272°C (from *i*-PrOH). IR spectrum, ν, cm^{-1}: 3270 (N–H, amine), 3165 (N–H, amide), 1720 (C=O, ester), 1710 (C=O, amide). ^1H NMR spectrum, δ, ppm: 1.20 t (3H, CH_2CH_3), 1.32 t (3H, CH_2CH_3), 2.20 s (3H, Me), 2.27 s (3H, Me), 3.90 q (2H, CH_2CH_3), 4.03 q (2H, CH_2CH_3), 4.20 d and 4.45 d (2H, 3'-H, 2-H, *J* = 3.8 Hz), 4.57 d and 4.80 d (2H, 3'-H, 2-H, *J* = 5.2 Hz), 5.17 br.s (1H, NH), 6.85–8.32 m (14H, H_{arom}), 11.82 s (1H, 1'-H), 12.03 s (1H, 1'-H). Found, %: C 61.56; H 5.30; N 11.17. $C_{19}H_{19}N_3O_5$. *M* 369.37. Calculated, %: C 61.78; H 5.18; N 11.38.

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