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Reaction of 2-(2-Oxo-1,2-dihydro-3*H*-indol-3-ylidene)acetic Acids Esters with Phenylhydrazine

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Abstract—2-(2-Oxo-1,2-dihydro-3*H*-indol-3-ylidene)acetic acids esters reacted with phenylhydrazine yielding products of the regioselective addition of the latter in the α-(C^2)-position of the exo ethylene bond, (2-oxo-2,3-dihydro-1*H*-indol-3-yl)(2-phenylhydrazino)acetic acids esters.

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A reaction of 3-(2-oxo-2-X-ethylidene)-1*H*-indol-2-ones (**I**, X = Alk, Ar, Ht) with hydrazines under mild conditions is known to provide 2',4'-dihydrospiro-[indol-3,3'-pyrazol]-2(1*H*)-ones **II** [1–7] (Scheme 1). Compounds **II** form apparently as a result of an intramolecular spiroheterocyclization of intermediate 3-(2-hydrazono-2-X-ethylidene)-1*H*-indol-2-ones **III** at the 3-exo ethylene bond into the β-position (C^3) of the indole ring. In some cases stable hydrazones (**III**, X = Ar) were isolated and identified [5, 8] (Scheme 1).

At treating 3-(2-aryl-2-oxoethylidene)-1*H*-indol-2-ones (**I**, X = Ar) with 2-hydrazino-1*H*-benzimidazole formed both the corresponding hydrazones (**III**, R^1 = Me, Ac) and products of cyclization at the carbonyl group of lactam, 3-aryl-1-(1*H*-benzimidazol-2-yl)-1*H*-pyridazino[3,4-*b*]indoles (**IV**, R^1 = H) [8] (Scheme 1). It was reported that the heating of phenacylideneoxindole (**I**, $R^1 = R^2$ = H, X = Ph) with hydrazine resulted in reduction to oxindole and elimination of phenylglyoxal hydrazone [1, 2]. The hydrazine attack occurred here evidently at the electron-deficient site α-($C^{1'}$) of indolinone **I**. Note that some spiroheterocycles **II** exhibited antimicrobial activity [7], and compounds **III** and **IV**, insecticidal action [8]; these facts demonstrated the practical importance of products of N-nucleophilic transformations of ylideneoxindoles **I**.

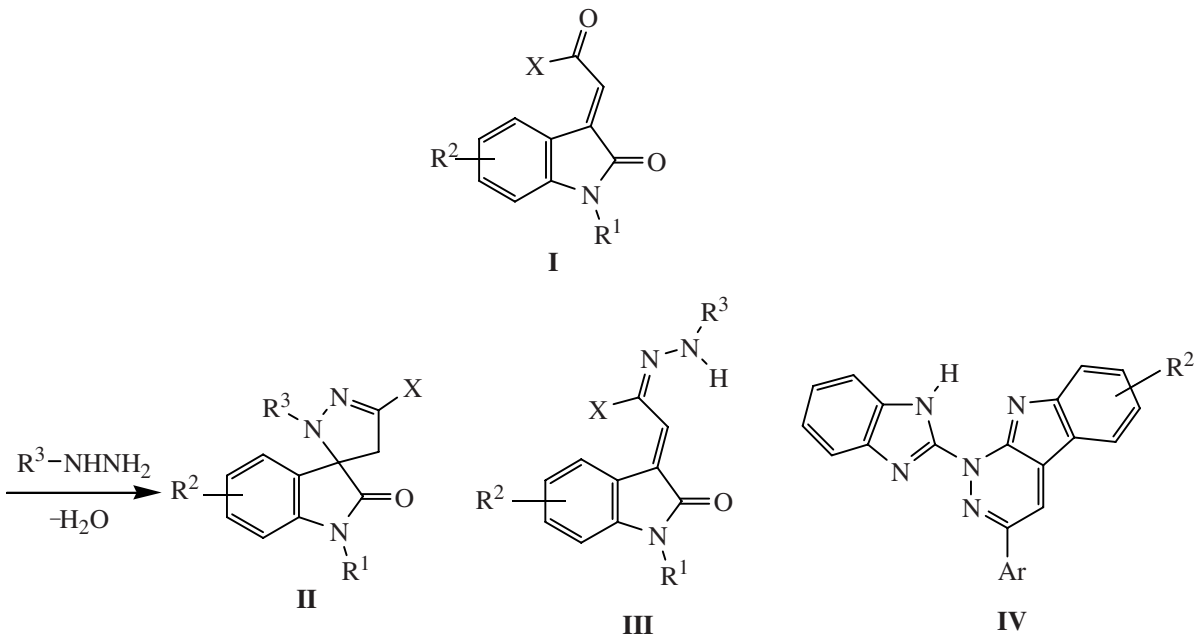
We recently showed that unlike X-acyl derivatives of ylideneoxindoles (**I**, X = Alk, Ar, Ht) similar in structure esters of 2-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)acetic acids (**I**, X = OAlk) differently reacted with hydrazine. Thus in acetic acid formed a mixture of products of α-addition to the exo ethylene bond with respect to the ester group (followed by recyclization), 3,3*a*,5,9*b*-tetrahydro-1*H*-pyrazolo[3,4-*c*]quinoline-1,4(2*H*)-dione (**V**) and of β-addition, 1-acetyl-5'*H*-spiro[indole-3,3'-pyrazolidine]-2,5'(1*H*)-dione (**VI**) [9, 10]. The addition of aromatic amines to the exocyclic multiple bond of substrates (**I**, X = OAlk) in contrast to hydrazine occurred regioselectively into the α-position leading to the formation of 2-arylamino-2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetic acid esters **VII** [11, 12] (Scheme 1). According to our findings the attack of mono- and binucleophiles is directed prevailingly on the electrophilic site α-(C^2) of oxindolylideneacetates (**I**, X = OAlk) [9, 12–14].

Thus the published data show that to the attack of hydrazines (and amines) are subjected four electrophilic sites of ylideneoxindoles (**I**, X = Alk, Ar, Ht, OAlk): at the atioms C^2 (NC^2=O), C^3 (β-position of 3-exo ethylene bond), $C^{1'}$ (α-position), and $C^{2'}$ ($XC^{2'}$=O); it is difficult a priori predict the direction of the nucleophilic attack.

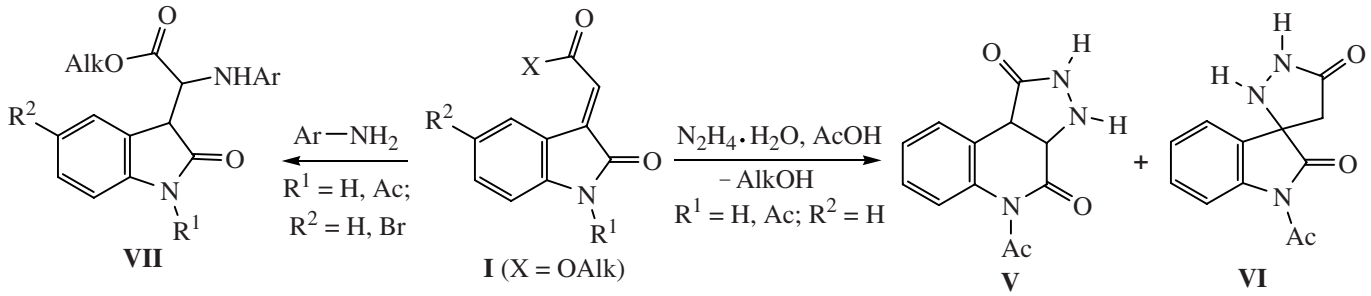
We established that by treating with phenylhydrazine 2-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-acetic acids esters **Ia–If** at boiling the mixture in ethanol esters of (2-oxo-2,3-dihydro-1*H*-indol-3-yl)-(2-phenylhydrazino)-acetic acids **VIIIa–VIIIf** were obtained in a preparative yield (Scheme 2). Compounds **VIII** result from

a regioselective addition of the primary amino group of phenylhydrazine to the *exo* ethylene bond of substrate **I** not in the β-($C^{3'}$)-position as might be expected by analogy with the similar reactions of acylmethyleneoxindoles (**I**, X = Alk, Ar, Ht) but in the α-(C^2)-position with respect to the ester moiety. Compounds obtained **VIIIa–VIIIf** are colorless or off-yellow crystalline substances insoluble in water, sparingly soluble in the common organic solvents, and readily soluble in DMF and DMSO.

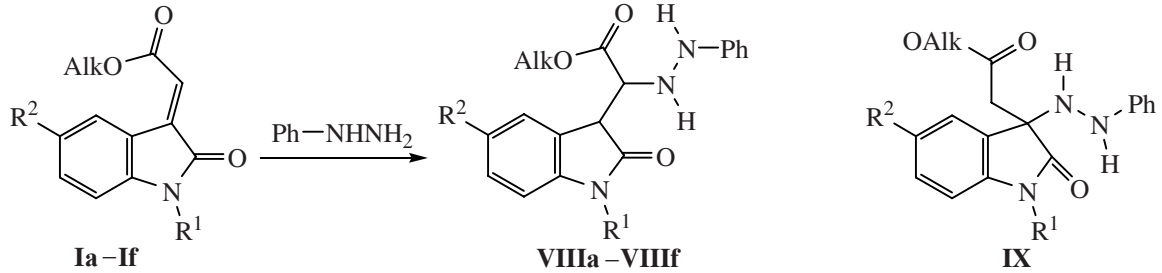
Scheme 1.



R^1 = H, Alk, All, Ac; R^2 = H, Alk, All, AlkO, Ac, Hlg; X = Alk, Ar, Ht; R^3 = H, Ph, Ht, Ac.



Scheme 2.



I, VIII, Alk = Me: R^1 = H, R^2 = H (**a**), Br (**b**); R^1 = Ac, R^2 = H (**c**); Alk = Et: R^1 = H, R^2 = H (**d**), Br (**e**); R^1 = Ac, R^2 = H (**f**).

In the IR spectra of compounds **VIII** are present well consistent with the structure wide bands of the stretching vibrations of amino groups from the phenylhydrazine fragment and of the amide group of lactam at 3130–3293 cm^{-1}, and also absorption bands of carbonyl groups of ester (1720–1732 cm^{-1}) and lactam (1673–1696 cm^{-1}).

The proton signals in the ^{1}H NMR spectra of indolinones **VIIIa–VIIIf** appear in a double set, in particular, pairs of signals are present from two vicinal methine protons of the fragment C^{2}H–C$^{3'}$H at δ 4.11–4.38 and 4.35–4.73 ppm. The character of these signals indicates the presence of at least two diastereomers, and the findings obtained are in agreement with the spectral characteristics of 2-arylamino-2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetic acids esters **VII** [12]. The presence of a pair of coupled methine protons permits a rejection of the regioisomeric structure of 2-oxo-3-(2-phenylhydrazino)-2,3-dihydro-1*H*-indol-3-ylacetic acids esters **IX** containing a methylene group CH_2 (Scheme 2). It was not possible to exclude preliminary the formation of the latter taking into account published data, in particular, on the β-addition of amines to the exo ethylene bond of ylideneoxindoles **I** [15].

Thus the reaction of compounds **Ia–If** with hydrazine proceeds as a regioselective addition of the latter to the exo ethylene bond into the α-position with respect to the ester group. The changed nucleophiles addition direction, in particular, that of phenylhydrazine, into the α-C^2-position of oxindolylideneacetates (**I**, X = OAlk) [11–14] unlike the usual β-C$^{3'}$-attack of 3-acylmethylene-1*H*-indol-2-ones (**I**, X = Alk, Ar, Ht), probably is caused by stronger electron-acceptor effect of the ester group in the former substrates compared to the het(aroyl) moiety of the latter.

EXPERIMENTAL

IR spectra of compounds **VIII** were recorded on a spectrophotometer Specord M-80 from mulls in mineral oil. ^{1}H NMR spectra of indolinones **VIII** were registered on a spectrometer Bruker DRX-500 (500.13 MHz) in DMSO-d_6, internal reference TMS. Mass spectrum of compound **VIIIa** was measured on a Finnigan MAT INCOS-50 instrumen at the direct admission mode (electron impact). The reactions progress was monitored and the homogeneity of compounds **VIIIa–VIIIf** was checke by TLC on Silufol UV-254 plates in a system benzene–ether–acetone, 10:9:1, development in iodine vapor. Initial esters **Ia–If** were obtained by procedures [16–18].

(2-Oxo-2,3-dihydro-1*H*-indol-3-yl)-(2-phenylhydrazino)acetic acids esters VIIIa–VIIIf. To a solution of 10 mmol of esters **Ia–If** in 70–100 ml of ethanol was added at stirring 1.08 g (10 mmol) of phenylhydrazine, and the mixture was boiled for 0.5–2 h (TLC monitoring). The separated precipitate was filtered off and recrystallized from ethanol.

Methyl (2-oxo-2,3-dihydro-1*H*-indol-3-yl)(2-phenylhydrazino)acetate (VIIIa). Yield 2.46 g (79%), mp 148–149°C. IR spectrum, ν, cm^{-1}: 3287 ($C_6H_5\underline{NH}NH$), 3130–3185 ($\underline{N^1H}CO$, $C_6H_5NH\underline{NH}$), 1728 ($C{=}O_{ester}$), 1696 ($N^1H\underline{CO}$), 1618, 1597, 1466. ^{1}H NMR spectrum, δ, ppm: 3.65 s (3H, $COOC\underline{H}_3$), 3.82 s (3H, $COOC\underline{H}_3$), 4.18 d, 4.32 d (2H, C$^{3'}$H, C^{2}H, *J* 4.3 Hz), 4.47 d, 4.65 d (2H, C$^{3'}$H, C^{2}H, *J* 5.6 Hz), 5.22 br.s (2H, $2C_6H_5\underline{NH}NH$), 6.62 s (1H, $C_6H_5NH\underline{NH}$), 6.77–7.36 group of signals (18H, 2 C_6H_4, $2C_6H_5$), 7.38 s (1H, $C_6H_5NH\underline{NH}$), 10.26 s (1H, N$^{1'}$H), 10.64 s (1H, N$^{1'}$H). Mass spectrum, *m/z* (I_{rel}, %): 311 (14) $[M]^+$, 252 (3) $[M - COOCH_3]^+$ or $[C_{15}H_{14}N_3O]^+$, 203 (37) $[M - C_6H_5NHNH_2]^+$ or $[C_{11}H_9NO_3]^+$, 172 (35) $[M - C_6H_5NHNH_2 - OCH_3]^+$ or $[C_9H_6NO_2]^+$, 147 (40) $[C_9H_9NO]^+$ or $[C_8H_5NO_2]^+$, 144 (34) $[M - C_6H_5NHNH_2 - COOCH_3]^+$ or $[C_9H_6NO]^+$, 133 (100) [oxindole = $C_8H_7NO]^+$, 108 (38) $[C_6H_5NHNH_2]^+$, 92 (72) $[C_6H_5NH]^+$, 77 (61) $[C_6H_5]^+$. Found, %: C 65.29; H 5.72; N 13.34. $C_{17}H_{17}N_3O_3$. Calculated, %: C 65.58; H 5.50; N 13.50. *M* 311.33.

Methyl (5-bromo-2-oxo-2,3-dihydro-1*H*-indol-3-yl)(2-phenylhydrazino)acetate (VIIIb). Yield 2.50 g (64%), mp 166–167°C. IR spectrum, ν, cm^{-1}: 3275 ($C_6H_5\underline{NH}NH$), 3140–3192 ($\underline{N^1H}CO$, $C_6H_5NH\underline{NH}$), 1722 ($C{=}O_{ester}$), 1688 ($N^1H\underline{CO}$), 1623, 1605, 1470. ^{1}H NMR spectrum, δ, ppm: 3.72 s (3H, $COOC\underline{H}_3$), 3.86 s (3H, $COOC\underline{H}_3$), 4.23 d, 4.38 d (2H, C$^{3'}$H, C^{2}H, *J* 4.6 Hz), 4.54 d, 4.73 d (2H, C$^{3'}$H, C^{2}H, *J* 5.8 Hz), 5.48 br.s (2H, $2C_6H_5\underline{NH}NH$), 6.55 s (1H, $C_6H_5NH\underline{NH}$), 6.75–7.48 group of signals (16H, $2C_6H_3$, $2C_6H_5$), 7.52 s (1H, $C_6H_5NH\underline{NH}$), 10.15 s (1H, N$^{1'}$H), 10.47 s (1H, N$^{1'}$H). Found, %: C 52.12; H 3.97; Br 20.23; N 10.59. $C_{17}H_{16}BrN_3O_3$. Calculated, %: C 52.32; H 4.13; Br 20.48; N 10.77.

Methyl (1-acetyl-2-oxo-2,3-dihydroO-1*H*-indol-3-yl)(2-phenylhydrazino)acetate (VIIIc). Yield 2.60 g (73%), mp 137–138°C. IR spectrum, ν, cm^{-1}: 3265 ($C_6H_5\underline{NH}NH$), 3135–3172 ($\underline{N^1}CO$, $C_6H_5NH\underline{NH}$), 1720 ($C{=}O_{ester}$), 1685, 1673 ($N^1\underline{CO}$), 1610, 1590, 1455. ^{1}H NMR spectrum, δ, ppm: 2.62 s (3H, $C\underline{H}_3CO$), 2.66 s (3H, $C\underline{H}_3CO$), 3.60 s (3H, $COOC\underline{H}_3$), 3.73 s (3H, $COOC\underline{H}_3$), 4.12 d, 4.24 d (2H, C$^{3'}$H, C^{2}H, *J* 4.0 Hz), 4.35 d, 4.56 d

(2H, C$^{3'}$H, C^{2}H, *J* 5.2 Hz), 5.40 br.s (2H, 2C_6H_5NHNH), 6.80 s (1H, C_6H_5NHNH), 6.84–7.48 group of signals (18H, 2C_6H_4, 2C_6H_5), 7.58 s (1H, C_6H_5NHNH). Found, %: C 64.70; H 5.58; N 11.77. $C_{19}H_{19}N_3O_4$. Calculated, %: C 64.58; H 5.42; N 11.89.

Ethyl (2-oxo-2,3-dihydro-1*H*-indol-3-yl)(2-phenylhydrazino)acetate (VIIId). Yield 2.63 g (81%), mp 150–151°C. IR spectrum, ν, cm^{-1}: 3293 (C_6H_5NHNH), 3135–3182 (N^{1}HCO, C_6H_5NHNH), 1732 (C=O$_{ester}$), 1692 (N^{1}HCO), 1615, 1604, 1470. ^{1}H NMR spectrum, δ, ppm: 1.20 t (3H, COOCH$_2$CH$_3$), 1.26 t (3H, COOCH$_2$CH$_3$), 3.82 q (2H, COOCH$_2$CH$_3$), 3.88 q (2H, COOCH$_2$CH$_3$), 4.16 d, 4.27 d (2H, C$^{3'}$H, C^{2}H, *J* 4.5 Hz), 4.50 d, 4.66 d (2H, C$^{3'}$H, C^{2}H, *J* 5.7 Hz), 5.44 br.s (2H, 2C_6H_5NHNH), 6.57 s (1H, C_6H_5NHNH), 6.75–7.32 group of signals (18H, 2C_6H_4, 2C_6H_5), 7.32 s (1H, C_6H_5NHNH), 10.47 s (1H, N$^{1'}$H), 10.65 s (1H, N$^{1'}$H). Found, %: C 66.52; H 5.67; N 13.11. $C_{18}H_{19}N_3O_3$. Calculated, %: C 66.45; H 5.89; N 12.91.

Ethyl (5-bromo-2-oxo-2,3-dihydro-1*H*-indol-3-yl)(2-phenylhydrazino)acetate (VIIIe). Yield 2.63 g (68%), mp 158–159°C. ^{1}H NMR spectrum, δ, ppm: 1.18 t (3H, COOCH$_2$CH$_3$), 1.23 t (3H, COOCH$_2$CH$_3$), 3.77 q (2H, COOCH$_2$CH$_3$), 3.84 q (2H, COOCH$_2$CH$_3$), 4.11 d, 4.23 d (2H, C$^{3'}$H, C^{2}H, *J* 4.9 Hz), 4.46 d, 4.61 d (2H, C$^{3'}$H, C^{2}H, *J* 6.2 Hz), 5.72 br.s (2H, 2C_6H_5NHNH), 6.43 s (1H, C_6H_5NHNH), 6.65–7.33 group of signals (16H, 2 C_6H_3, 2C_6H_5), 7.69 s (1H, C_6H_5NHNH), 10.73 s (1H, N$^{1'}$H), 10.90 s (1H, N$^{1'}$H). Found, %: C 53.61; H 4.58; Br 19.87; N 10.52. $C_{18}H_{18}BrN_3O_3$. Calculated, %: C 53.48; H 4.49; Br 19.77; N 10.39.

Ethyl (1-acetyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-(2-phenylhydrazino)acetate (VIIIf). Yield 2.60 g (70%), mp 144–145°C. ^{1}H NMR spectrum, δ, ppm: 2.55 s (3H, CH$_3$CO), 2.63 s (3H, CH$_3$CO), 1.22 t (3H, COOCH$_2$CH$_3$), 1.28 t (3H, COOCH$_2$CH$_3$), 3.78 q (2H, COOCH$_2$CH$_3$), 3.83 q (2H, COOCH$_2$CH$_3$), 4.15 d, 4.28 d (2H, C$^{3'}$H, C^{2}H, *J* 4.2 Hz), 4.38 d, 4.61 d (2H, C$^{3'}$H, C^{2}H, *J* 5.6 Hz), 5.53 br.s (2H, 2C_6H_5NHNH), 6.85 s (1H, C_6H_5NHNH), 6.90–7.57 group of signals (18H, 2C_6H_4, 2C_6H_5), 7.71 s (1H, C_6H_5NHNH). Found, %: C 65.09; H 5.71; N 11.27. $C_{20}H_{21}N_3O_4$. Calculated, %: C 65.38; H 5.76; N 11.44.

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