

Reaction of 2-(2-Oxo-2,3-dihydro-1*H*-indol-3-ylidene)acetic Acid Esters with Benzene-1,2-diamine and 2-Aminobenzenethiol

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Abstract—2-(2-Oxo-2,3-dihydro-1*H*-indol-3-ylidene)acetic acid esters reacted with benzene-1,2-diamine or 2-aminobenzenethiol to give (2-oxo-2,3-dihydro-1*H*-indol-3-yl)-substituted 3,4-dihydroquinoxalin-2(1*H*)-ones or 2*H*-1,4-benzothiazin-3(4*H*)-ones.

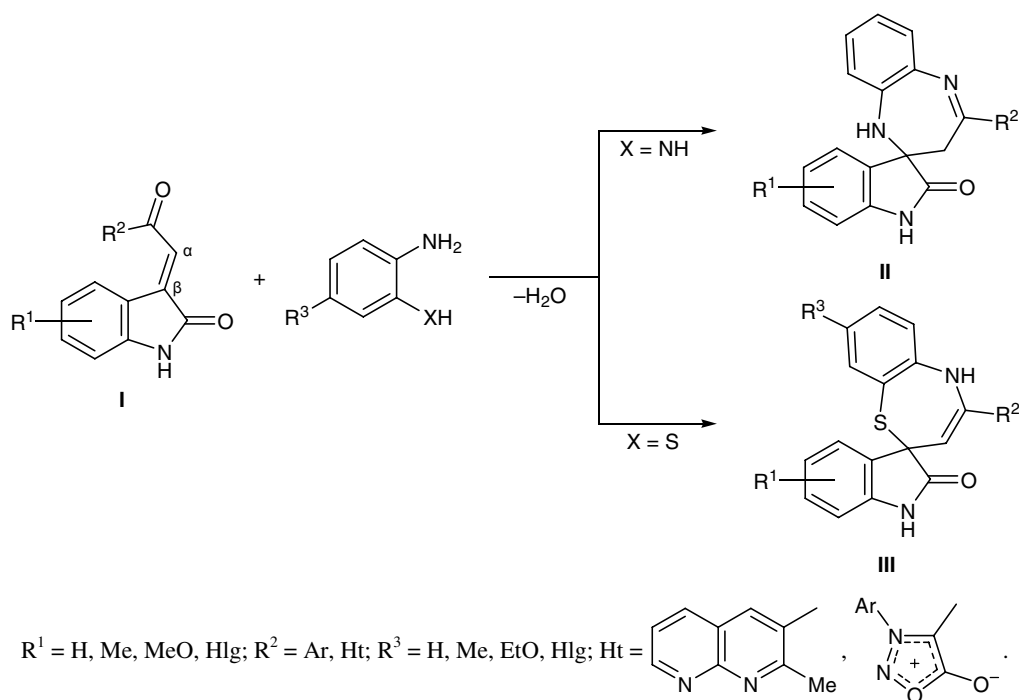
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3-[2-Oxo-2-aryl(hetaryl)ethylidene]-1*H*-indol-2-ones (**I**) were reported to react with benzene-1,2-diamine (*o*-phenylenediamine) or 2-aminobenzenethiols to give 1,3-dihydrospiro[1,5-benzodiazepine-2,3'-indole]-2'(1'*H*)-one (**II**) [1–3] or 5*H*-spiro[1,5-benzothiazepine-2,3'-indole]-2'(1'*H*)-one (**III**) [4, 5]. Compounds **II** and **III** are formed via addition of the amino or thiol group of the reagent at the β -position (C³ in the indole ring) of the activated (due to the presence of

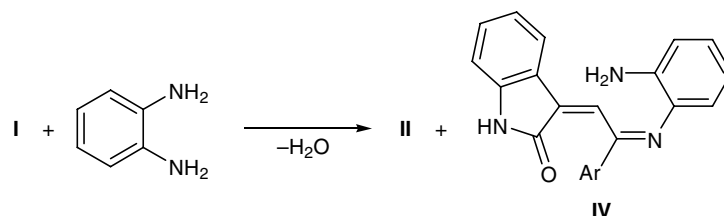
an aroyl or hetaroyl group) exocyclic double bond, followed by spiro-heterocyclization involving the second amino group in the *ortho* position of the reagent (Scheme 1).

In the reactions of 3-aroylethylidene-1*H*-indol-2-ones **I** with *o*-phenylenediamine, Bajpai et al. [1] isolated minor products, 3-[2-(2-aminophenylimino)-2-arylethylidene]-2,3-dihydro-1*H*-indol-2-ones **IV**, together with compounds **II** (Scheme 2). In this case,

Scheme 1.



Scheme 2.



the initial attack by amino group of the reagent was directed at both electrophilic C³ atom in the indole ring of **I** and the aroyl carbonyl carbon atom. Probably, dihydroindoles **II** were also formed by heterocyclization of intermediates **IV**. Taking into account that compounds **II** and **III** were found to exhibit antimicrobial and fungicide activity [3–5], the above oxoindole transformations attract interest from the viewpoint of practice.

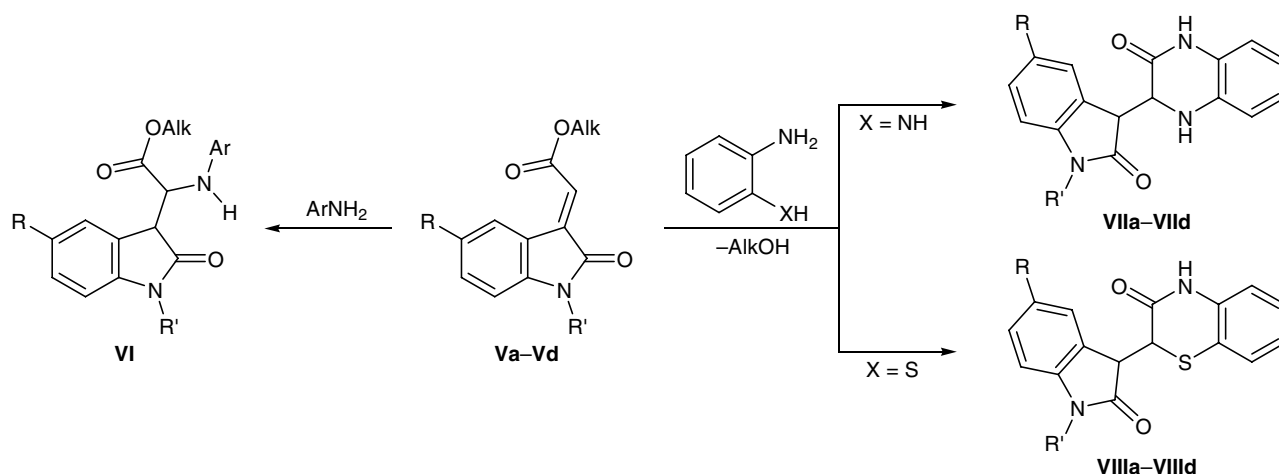
We recently showed that, unlike aroyl (or hetaroyl) derivatives of ylidene-substituted 2,3-dihydro-1H-indol-2-ones **I**, structurally related 2-(2-oxo-2,3-dihydro-1H-indol-3-ylidene)acetic acid esters **V** react with aromatic amines via regioselective addition of the latter at the exocyclic double C=C bond (at the α -position with respect to the ester group) to give 2-arylamino-2-(2-oxo-2,3-dihydro-1H-indol-3-yl)acetic acid esters **VI** (Scheme 3) [6, 7]. Presumably, the attack by both N-nucleophiles and S,N- and N,N-binucleophiles is directed just at the electrophilic α -carbon atom of acetates **V** [8, 9].

By treatment of 2-(2-oxo-2,3-dihydro-1H-indol-3-ylidene)acetic acid esters **Va–Vd** with *o*-phenylenediamine or *o*-aminobenzenethiol in boiling ethanol or

acetic acid we obtained the corresponding 3-(2-oxo-2,3-dihydro-1H-indol-3-yl)-3,4-dihydroquinoxaline-2(1H)-ones **VIIa–VIIId** or 2-(2-oxo-2,3-dihydro-1H-indol-3-yl)-2H-1,4-benzothiazin-3(4H)-ones **VIIIa–VIIIId**, respectively (Scheme 3). Compounds **VII** and **VIII** are products of regioselective addition of the amino- or thiol group of the reagent at the double-bonded carbon atom in the α -position with respect to the ester group (rather than at the β -C³ atom, as might be expected), followed by heterocyclization with participation of the *ortho*-amino group.

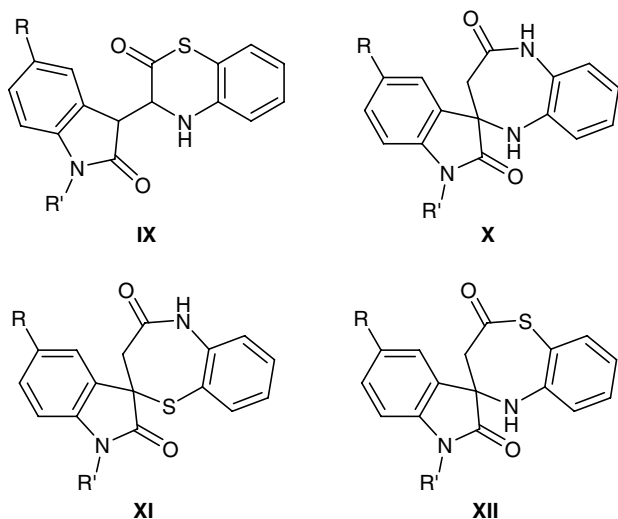
Compounds **VIIa–VIIId** and **VIIIa–VIIIId** are yellow crystalline substances, which are insoluble in water, poorly soluble in common organic solvents, and readily soluble in DMF and DMSO. In the IR spectra of indolyl-substituted quinoxalines **VIIa–VIIId** and benzothiazines **VIIIa–VIIIId** we observed absorption bands due to stretching vibrations of the lactam N–H bonds at 3174–3189 cm⁻¹; the spectra of **VIIa–VIIId** contained an additional strong N–H band at 3270–3287 cm⁻¹ (N⁴–H). The absence of such band in the spectra of thia analogs **VIIIa–VIIIId** rules out the structure of regioisomeric 3-(2-oxo-2,3-dihydro-1H-indol-3-yl)-3,4-dihydro-2H-1,4-benzothiazin-2-ones

Scheme 3.



V, Alk = Me: R = H, R' = H (**a**), MeCO (**b**), R = Br, R' = H (**c**); Alk = Et: R = Br, R' = MeCO (**d**); **VII**, **VIII**, R = R' = H (**a**); R = H, R = MeCO (**b**); R = Br, R' = H (**c**); R = Br, R' = MeCO (**d**).

IX. The lack of signals assignable to amino group protons in the ^1H NMR spectra of compounds **VIIIa–VIIId** (only those belonging to amide proton) also argues against alternative structure **IX**. The corresponding signals in the spectra of compounds **VIIa–VIIId** are located in a relatively strong field, at δ 6.15–6.34 ppm. The ^1H NMR spectra of **VII** and **VIII** contained signals from coupled protons of the $\text{C}^3\text{H}–\text{C}^3\text{H}$ fragment at δ 3.65–4.17 and 4.3–4.71 ppm. The difference in the chemical shifts of $3'\text{-H}$ and 3-H is smaller for benzothiazine derivatives **VIII** as compared to quinoxalines **VII**: $\Delta\delta(\text{VII}) = \delta(3'\text{-H}) - \delta(3\text{-H}) = 0.92$ ppm; $\Delta\delta(\text{VIII}) = 0.27$ ppm. The presence of a couple of interacting protons excludes spiro structures containing a methylene group, 1,5-dihydrospiro[1,5-benzodiazepine-2,3'-indole]-2',4(1'*H*,3*H*)-dione **X**, 3*H*-spiro[1,5-benzothiazepine-2,3'-indole]-2',4(1'*H*,5*H*)-dione **XI**, and 5*H*-spiro[1,5-benzothiazepine-4,3'-indole]-2,2'(1'*H*,3*H*)-dione **XII**; their formation could not be ruled out *a priori* (taking into account published data [1–5]).



We can conclude that the reactions of oxoindolyldeneacetates **Va–Vd** with *o*-phenylenediamine and *o*-aminobenzenethiol involve initial regioselective addition of the amino or sulfanyl group of the reagent at the double-bonded carbon atom in the α -position with respect to the ester group. The reason for the different regioselectivity as compared to 3-acylmethylidene-2,3-dihydro-1*H*-indol-2-ones **I** (which take up nucleophiles at the C^3 carbon atom) [1–5] is likely to be stronger electron-acceptor effect of the ester group in substrates **V**, as compared to the effect of aroyl (hetaroyl) moiety in compounds **I**.

Compounds **VII** and **VIII** showed a pronounced antimicrobial activity against *S. aureus* P-209 and *E. coli* M₁₇.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer from samples dispersed in mineral oil. The ^1H NMR spectra were measured on a Bruker DRX-500 instrument (500 MHz) from solutions in $\text{DMSO}-d_6$ using tetramethylsilane as internal reference. The purity of compounds **VII** and **VIII** was checked by TLC on Silufol UV-254 plates using benzene–diethyl ether–acetone (10:9:1) as eluent; development with iodine vapor.

Initial (2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)-acetic acid esters **Va–Vd** were synthesized by the procedure described in [10–12].

3-(2-Oxo-2,3-dihydro-1*H*-indol-3-yl)-3,4-dihydroquinoxalin-2(1*H*)-ones VIIa–VIIId and 2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-2*H*-1,4-benzothiazin-3(4*H*)-ones VIIIa–VIIId (general procedure). Ester **Va–Vd**, 5 mmol, was dissolved in 50–70 ml of ethanol (in the synthesis of compounds **VIIa–VIIId**) or 25–30 ml of acetic acid (in the synthesis of **VIIIa–VIIIId**), 0.54 g (5 mmol) of *o*-phenylenediamine or 0.63 g (5 mmol) of *o*-aminobenzenethiol was added, and the mixture was heated for 1.5–3 h under reflux. The precipitate was filtered off and recrystallized from ethanol, propan-2-ol, dioxane, chloroform, or acetic acid.

3-(2-Oxo-2,3-dihydro-1*H*-indol-3-yl)-3,4-dihydroquinoxalin-2(1*H*)-one (VIIa). Yield 1.10 g (79%), mp 234–235°C (from EtOH). IR spectrum, ν , cm^{-1} : 3287 ($\text{N}^4\text{-H}$), 3188 ($\text{N}^1\text{-H}$), 1686, 1620 ($\text{C}=\text{O}$). ^1H NMR spectrum, δ , ppm: 3.71 s (1*H*, 3-*H*), 4.58 s (1*H*, 3'-*H*), 6.21 s (1*H*, 4-*H*), 6.57–7.22 (8*H*, C_6H_4), 10.02 s (1*H*, 1-*H*), 10.21 s (1*H*, 1'-*H*). Found, %: C 68.56; H 4.90; N 14.88. $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_2$. Calculated, %: C 68.81; H 4.69; N 15.05.

3-(1-Acetyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-3,4-dihydroquinoxalin-2(1*H*)-one (VIIb). Yield 1.05 g (65%), mp 211–212°C (from *i*-PrOH). IR spectrum, ν , cm^{-1} : 3280 ($\text{N}^4\text{-H}$), 3185 ($\text{N}^1\text{-H}$), 1678, 1640 ($\text{C}=\text{O}$). ^1H NMR spectrum, δ , ppm: 2.61 s (3*H*, CH_3CO), 3.68 s (1*H*, 3-*H*), 4.71 s (1*H*, 3'-*H*), 6.15 s (1*H*, 4-*H*), 6.63–7.97 m (8*H*, C_6H_4), 10.14 s (1*H*, 1-*H*). Found, %: C 67.52; H 4.62; N 12.89. $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_3$. Calculated, %: C 67.28; H 4.71; N 13.08.

3-(5-Bromo-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-3,4-dihydroquinoxalin-2(1*H*)-one (VIIc). Yield 1.0 g

(57%), mp 215–216°C (from EtOH). IR spectrum, ν , cm^{-1} : 3275 ($\text{N}^4\text{-H}_{\text{amine}}$), 3180 ($\text{N}^1\text{-H}$), 1675, 1635 (C=O). ^1H NMR spectrum, δ , ppm: 3.65 s (1H, 3-H), 4.51 s (1H, 3'-H), 6.34 s (1H, 4-H), 6.68–7.47 m (7H, C_6H_4 , C_6H_3), 10.23 s (1H, 1-H), 10.51 s (1H, 1'-H). Found, %: C 53.81; H 3.54; Br 22.07; N 11.56. $\text{C}_{16}\text{H}_{12}\text{BrN}_3\text{O}_2$. Calculated, %: C 53.65; H 3.38; Br 22.31; N 11.73.

3-(1-Acetyl-5-bromo-2-oxo-2,3-dihydro-1H-indol-3-yl)-3,4-dihydroquinoxalin-2(1H)-one (VIId). Yield 0.96 g (48%), mp 194–195°C (from EtOH). IR spectrum, ν , cm^{-1} : 3270 ($\text{N}^4\text{-H}$), 3174 ($\text{N}^1\text{-H}$), 1667, 1632 (C=O). ^1H NMR spectrum, δ , ppm: 2.57 s (3H, CH_3CO), 3.65 s (1H, 3-H), 4.70 s (1H, 3'-H), 6.32 s (1H, 4-H), 6.75–8.07 m (7H, C_6H_4 , C_6H_3), 10.32 s (1H, 1-H). Found, %: C 53.86; H 3.70; Br 19.73; N 10.29. $\text{C}_{18}\text{H}_{14}\text{BrN}_3\text{O}_3$. Calculated, %: C 54.02; H 3.53; Br 19.96; N 10.50.

2-(2-Oxo-2,3-dihydro-1H-indol-3-yl)-2H-1,4-benzothiazin-3(4H)-one (VIIIa). Yield 0.98 g (66%), mp 259–260°C (from AcOH). IR spectrum, ν , cm^{-1} : 3189 (N-H), 1695, 1622 (C=O). ^1H NMR spectrum, δ , ppm: 4.12 s (1H, 3-H), 4.32 s (1H, 3'-H), 6.85–7.26 m (8H, C_6H_4), 10.52 s (1H, 1-H), 10.76 s (1H, 1'-H). Found, %: C 64.97; H 3.86; N 9.31. $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$. Calculated, %: C 64.85; H 4.08; N 9.45.

2-(1-Acetyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2H-1,4-benzothiazin-3(4H)-one (VIIIb). Yield 0.76 g (45%), mp 279–280°C (from CHCl_3). IR spectrum, ν , cm^{-1} : 3182 (N-H), 1686, 1628 (C=O). ^1H NMR spectrum, δ , ppm: 2.55 s (3H, CH_3CO), 4.08 s (1H, 3-H), 4.47 s (1H, 3'-H), 6.90–7.36 m (8H, C_6H_4), 10.62 s (1H, 1-H). Found, %: C 64.07; H 4.31; N 8.37. $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$. Calculated, %: C 63.89; H 4.17; N 8.28.

2-(5-Bromo-2-oxo-2,3-dihydro-1H-indol-3-yl)-2H-1,4-benzothiazin-3(4H)-one (VIIIc). Yield 0.92 g (49%), mp 279–280°C (from dioxane). IR spectrum, ν , cm^{-1} : 3185 (N-H), 1692, 1630 (C=O). ^1H NMR spectrum, δ , ppm: 4.17 s (1H, 3-H), 4.36 s (1H, 3'-H), 6.80–7.35 m (7H, C_6H_4 , C_6H_3), 10.69 s (1H, 1-H), 10.80 s (1H, 1'-H). Found, %: C 50.96; H 3.14; Br 20.87; N 7.63. $\text{C}_{16}\text{H}_{11}\text{BrN}_2\text{O}_2\text{S}$. Calculated, %: C 51.21; H 2.95; Br 21.29; N 7.47.

2-(1-Acetyl-5-bromo-2-oxo-2,3-dihydro-1H-indol-3-yl)-2H-1,4-benzothiazin-3(4H)-one (VIId). Yield 1.20 g (58%), mp 217–218°C (from CHCl_3). IR spectrum, ν , cm^{-1} : 3180 (N-H), 1684, 1632 (C=O). ^1H NMR spectrum, δ , ppm: 2.58 s (3H, CH_3CO),

4.10 s (1H, 3-H), 4.42 s (1H, 3'-H), 6.88–7.32 m (7H, C_6H_4 , C_6H_3), 10.50 s (1H, 1-H). Found, %: C 51.60; H 3.37; Br 18.92; N 6.88. $\text{C}_{18}\text{H}_{13}\text{BrN}_2\text{O}_3\text{S}$. Calculated, %: C 51.81; H 3.14; Br 19.15; N 6.71.

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