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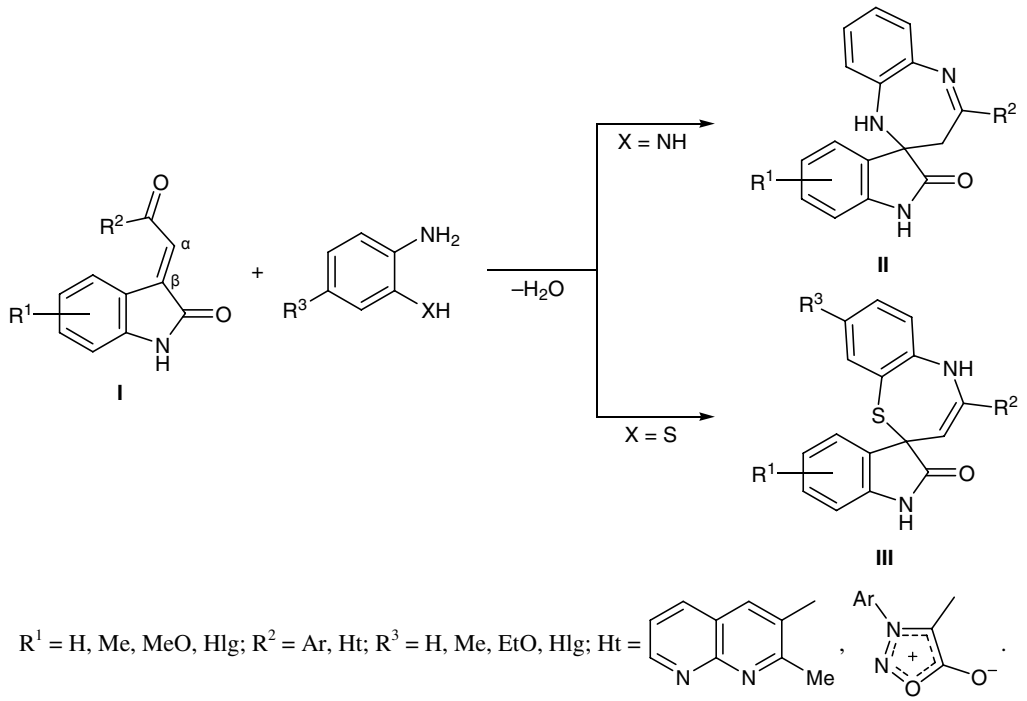
3-[2-Oxo-2-aryl(hetaryl)ethylidene]-1*H*-indol-2-ones (**I**) were reported to react with benzene-1,2-diamine (*o*-phenylenediamine) or 2-aminobenzenethiols to give 1,3-dihydrospiro[1,5-benzodiazepine-2,3'-indole]-2'(1'*H*)-one (**II**) [1–3] or 5*H*-spiro[1,5-benzothiazepine-2,3'-indole]-2'(1'*H*)-one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

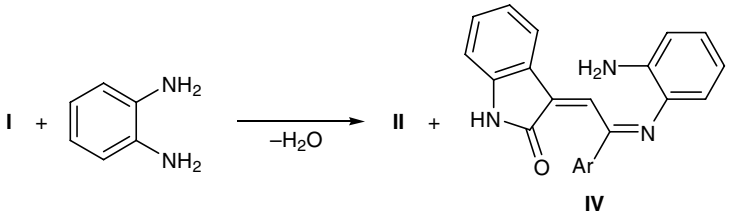
In the reactions of 3-aroylmethylidene-1*H*-indol-2-ones **I** with *o*-phenylenediamine, Bajpai et al. [1] isolated minor products, 3-[2-(2-aminophenylimino)-2-arylethylidene]-2,3-dihydro-1*H*-indol-2-ones **IV**, together with compounds **II** (Scheme 2). In this case,

Scheme 1.



R^1 = H, Me, MeO, Hlg; R^2 = Ar, Ht; R^3 = H, Me, EtO, Hlg; Ht =

Scheme 2.



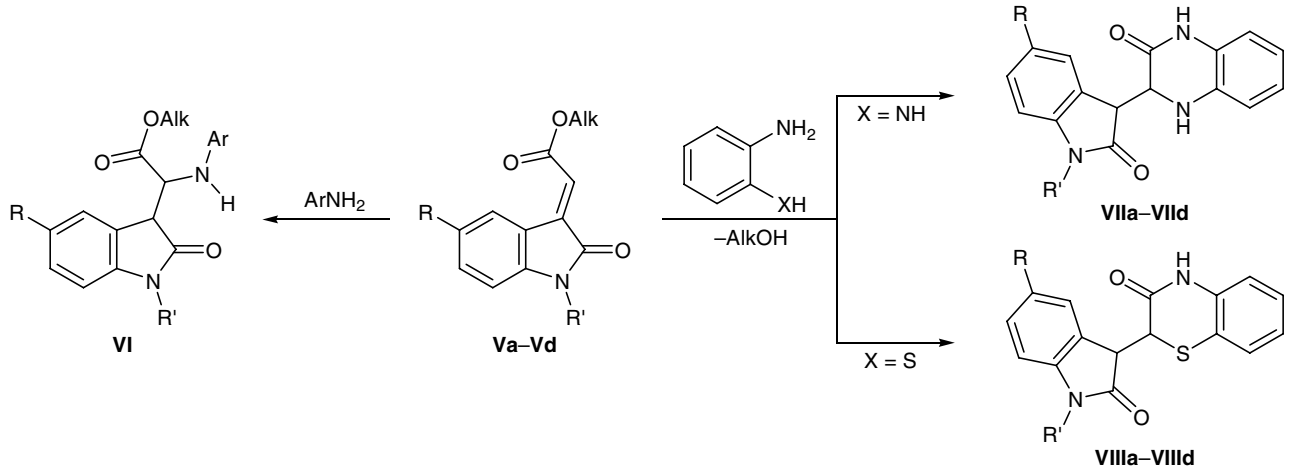
the initial attack by amino group of the reagent was directed at both electrophilic C^3 atom in the indole ring of **I** and the aroyl carbonyl carbon atom. Probably, dihydroindoles **II** were also formed by heterocyclization of intermediates **IV**. Taking into account that compounds **II** and **III** 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-1*H*-indol-2-ones **I**, structurally related 2-(2-oxo-2,3-dihydro-1*H*-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-1*H*-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-1*H*-indol-3-ylidene)acetic acid esters **Va**–**Vd** with *o*-phenylenediamine or *o*-aminobenzenethiol in boiling ethanol or acetic acid we obtained the corrsponding 3-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-3,4-dihydroquinoxaline-2(1*H*)-ones **VIIa**–**VIId** or 2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-2*H*-1,4-benzothiazin-3(4*H*)-ones **VIIIa**–**VIIId**, 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-C^3 atom, as might be expected), followed by heterocyclization with participation of the *ortho*-amino group.

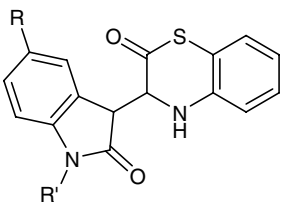
Compounds **VIIa**–**VIId** and **VIIIa**–**VIIId** are yellow crystalline substances, which are insoluble in water, poorly soluble in common organic solvents, and readily soluble in DMF and DMSO. In the IR spectra of indolyl-substituted quinoxalines **VIIa**–**VIId** and benzothiazines **VIIIa**–**VIIId**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

Scheme 3.

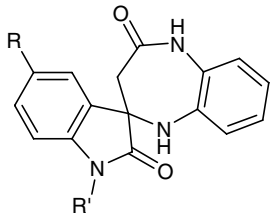


V, Alk = Me: R = H, R' = H (**a**), MeCO (**b**), R = Br, R' = H (**c**); Alk = Et: R = Br, R' = MeCO (**d**); **VII**, **VIII**, R = R' = H (**a**); R = H, R = MeCO (**b**); R = Br, R' = H (**c**); R = Br, R' = MeCO (**d**).

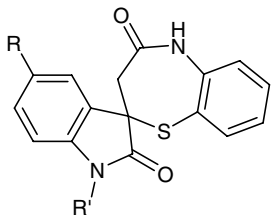
IX. The lack of signals assignable to amino group protons in the ^{1}H NMR spectra of compounds **VIIIa**–**VIIId** (only those belonging to amide proton) also argues against alternative structure **IX**. The corresponding signals in the spectra of compounds **VIIa**–**VIId** are located in a relatively strong field, at δ 6.15–6.34 ppm. The ^{1}H NMR spectra of **VII** and **VIII** contained signals from coupled protons of the C^3H–$C^{3'}H$ fragment at δ 3.65–4.17 and 4.3–4.71 ppm. The difference in the chemical shifts of 3'-H and 3-H is smaller for benzothiazine derivatives **VIII** as compared to quinoxalines **VII**: Δδ(**VII**) = δ(3'-H) – δ(3-H) = 0.92 ppm; Δδ(**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]).



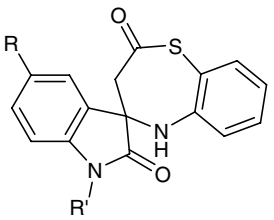
IX



X



XI



XII

We can conclude that the reactions of oxoindolylideneacetates **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* M_{17}.

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 instrument (500 MHz) from solutions in 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–VIId 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**–**VIId**) or 25–30 ml of acetic acid (in the synthesis of **VIIIa**–**VIIId**), 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 (N^4–H), 3188 (N^1–H), 1686, 1620 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.71 s (1H, 3-H), 4.58 s (1H, 3'-H), 6.21 s (1H, 4-H), 6.57–7.22 (8H, C_6H_4), 10.02 s (1H, 1-H), 10.21 s (1H, 1'-H). Found, %: C 68.56; H 4.90; N 14.88. $C_{16}H_{13}N_3O_2$. 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 (N^4–H), 3185 (N^1–H), 1678, 1640 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.61 s (3H, CH_3CO), 3.68 s (1H, 3-H), 4.71 s (1H, 3'-H), 6.15 s (1H, 4-H), 6.63–7.97 m (8H, C_6H_4), 10.14 s (1H, 1-H). Found, %: C 67.52; H 4.62; N 12.89. $C_{18}H_{15}N_3O_3$. 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 (N^4–H_{amine}), 3180 (N^1–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. $C_{16}H_{12}BrN_3O_2$. Calculated, %: C 53.65; H 3.38; Br 22.31; N 11.73.

3-(1-Acetyl-5-bromo-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-3,4-dihydroquinoxalin-2(1*H*)-one (VIId). Yield 0.96 g (48%), mp 194–195°C (from EtOH). IR spectrum, ν, cm^{-1}: 3270 (N^4–H), 3174 (N^1–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. $C_{18}H_{14}BrN_3O_3$. Calculated, %: C 54.02; H 3.53; Br 19.96; N 10.50.

2-(2-Oxo-2,3-dihydro-1*H*-indol-3-yl)-2*H*-1,4-benzothiazin-3(4*H*)-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. $C_{16}H_{12}N_2O_2S$. Calculated, %: C 64.85; H 4.08; N 9.45.

2-(1-Acetyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-2*H*-1,4-benzothiazin-3(4*H*)-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. $C_{18}H_{14}N_2O_3S$. Calculated, %: C 63.89; H 4.17; N 8.28.

2-(5-Bromo-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-2*H*-1,4-benzothiazin-3(4*H*)-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. $C_{16}H_{11}BrN_2O_2S$. Calculated, %: C 51.21; H 2.95; Br 21.29; N 7.47.

2-(1-Acetyl-5-bromo-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-2*H*-1,4-benzothiazin-3(4*H*)-one (VIIId). 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. $C_{18}H_{13}BrN_2O_3S$. Calculated, %: C 51.81; H 3.14; Br 19.15; N 6.71.

REFERENCES

1. Bajpai, S.N., Jain, R., and Joshi, K.C., *Indian J. Chem., Sect. B*, 1997, vol. 36, p. 1005; *Chem. Abstr.*, 1998, vol. 128, no. 294763z.
2. Mogilaiah, K. and Rao, R.B., *Indian J. Chem., Sect. B*, 1998, vol. 37, p. 139; *Ref. Zh., Khim.*, 1999, no. 14Zh223.
3. Kavali, J.R. and Badami, B.V., *J. Chem. Res., Synop.*, 2000, p. 546; *Ref. Zh., Khim.*, 2001, no. 19Zh318.
4. Dandia, A., Upreti, M., Rani, B., and Pant, U.C., *J. Chem. Res., Synop.*, 1998, p. 752; *Chem. Abstr.*, 1999, vol. 130, no. 153647u.
5. Dandia, A., Upreti, M., Rani, B., Pant, U.C., and Gupta, I.J., *J. Fluorine Chem.*, 1998, vol. 91, p. 171; *Chem. Abstr.*, 1999, vol. 130, no. 66476u.
6. Berezin, A.N., Koz'minykh, E.N., and Koz'minykh, V.O., Abstracts of Papers, *V Molodezhnaya nauchnaya shkola-konferentsiya po organicheskoi khimii* (Vth Youth Scientific School–Conf. on Organic Chemistry), Yekaterinburg: Ural. Otd. Ross. Akad. Nauk, 2002, p. 89.
7. Koz'minykh, E.N., Berezin, A.N., Lomidze, K.Sh., and Koz'minykh, V.O., *Izbrannye metody sinteza i modifikatsii geterotsiklov* (Selected Methods of Synthesis and Modification of Heterocycles), Kartsev, V.G., Ed., Moscow: IBS, 2004, vol. 3, p. 535.
8. Lomidze, K.Sh., Koz'minykh, E.N., Berezin, A.N., and Koz'minykh, V.O., *Izbrannye metody sinteza i modifikatsii geterotsiklov* (Selected Methods of Synthesis and Modification of Heterocycles), Kartsev, V.G., Ed., Moscow: IBS, 2004, vol. 3, p. 547.
9. Koz'minykh, V.O., Lomidze, K.Sh., Goncharov, V.I., and Koz'minykh, E.N., *Materialy XXXIV nauchno-tekhnicheskoi konferentsii. Estestvennye i tochnye nauki. Tekhnicheskie i prikladnye nauki* (Proc. XXXIVth Scientific–Technical Conf. Natural and Exact Sciences. Technical and Applied Sciences), Stavropol: Sev.-Kavkaz. Gos. Tekh. Univ., 2005, vol. 1, p. 33.
10. Koz'minykh, E.N., Berezina, E.S., and Koz'minykh, V.O., *Russ. J. Gen. Chem.*, 1996, vol. 66, p. 1100.
11. Koz'minykh, E.N., Berezina, E.S., Kolla, V.E., Shelenkova, S.A., Voronina, E.V., and Koz'minykh, V.O., *Khim.-Farm. Zh.*, 1997, vol. 31, no. 2, p. 31.
12. Koz'minykh, V.O., Lomidze, K.Sh., Goncharov, V.I., Koz'minykh, E.N., and Berezin, A.N., *Vestn. Sev.-Kav. Gos. Tekh. Univ.*, 2005, no. 3, p. 18.