Chemistry of Heterocyclic Compounds, Vol. 40, No. 2, 2004

CONDENSATION OF ETHYL 2-OXOINDOLINE-3-GLYOXYLATE WITH *o*-AMINOPHENOL AND *o*-PHENYLENEDIAMINE

V. V. Bolotov, S. N. Kovalenko, S. V. Kovaleva, and V. I. Stepanenko

A method is presented for the synthesis of 3-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1,4-dihydroquinoxalin-2-one and 2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-2H-1,4-benzoxazin-3(4H)-one by the reaction of ethyl 2-oxoindoline-2-glyoxylate with o-aminophenol and o-phenylenediamine. Proposed reaction mechanisms are presented.

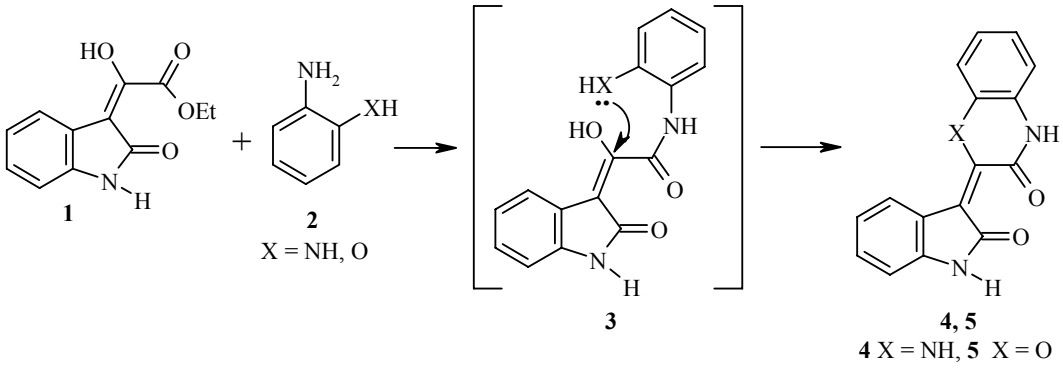
Keywords: 2H-1,4-benzoxazin-3(4H)-one, 1,4-dihydroquinoxalin-2-one, 2-oxo-1,2-dihydro-1H-indole, *cis-trans* izomerism.

In continuing our study of the reactivity of ethyl 2-oxoindoline-3-glyoxylate (**1**) [1] it was of interest to introduce *o*-substituted anilines **2** containing a second nucleophilic group (*o*-aminophenol, *o*-phenylenediamine) into the scope of the investigation.

The presence of the two electrophilic centers in the ethoxalyl residue in ester **1** gives the possibility of reaction with the amines indicated to give the 1,4-dihydroquinoxalin-2-one and 2H-1,4-benzoxazin-3(4H)-one rings respectively.

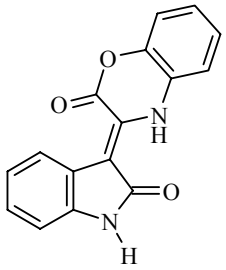
The ester **1** needed for this target was prepared by a Claisen reaction of 2-oxoindoline with diethyloxalate in absolute ethanol in the presence of sodium ethylate [2].

We have previously shown [1] that the ester **1** reacts with arylamine ester groups to give the corresponding 2-oxoindoline-3-glyoxylic acid arylamides. In this respect the reaction of *o*-phenylenediamine and *o*-aminophenol with the ester **1** can be represented by the following scheme:



Ukraine National Pharmaceutical Academy, Kharkov 61002; e-mail: igor@uiv.kharkov.ua. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 249-251, February, 2004. Original article submitted May 17, 2001.

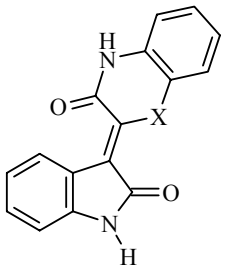
According to this scheme the first stage of the reaction is the formation of the intermediate arylamides **3** which then undergo an intramolecular cyclization to give the heterocycles **4** and **5**. In the reaction with *o*-aminophenol it is theoretically possible to suggest the formation of compound **6** which is an isomer of compound **5**.



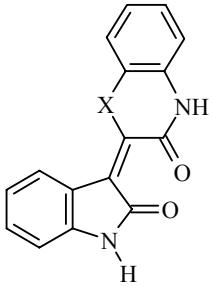
6

However, bearing in mind that in the *o*-aminophenol the amino group is a better nucleophile than the hydroxy group, it might be expected that the arylamide **3** is formed in the first stage of the reaction and that this is then converted to compound **5**. The correctness of this proposal is confirmed also by the reaction of ester **1** with *p*-aminophenol in which the product is the 2-oxo-1,2-dihydro-3H-indoline-3-glyoxylic acid 4-hydroxyphenylamide [1].

The presence of the double bond between the heterocyclic rings in compounds **4** and **5** leads to the possibility of forming their *cis* and *trans* isomers.



trans isomer



cis isomer

Calculations of the overall energy of two of the possible isomers of compound **4** (X = NH) were carried out using the SCF LCAO MO quantum-chemical method in the MNDO semiempirical approximation with PM3 parameterization [4, 5] and this has shown that the *trans* isomer of compound **4** is energetically more favored than the *cis* isomer with an overall energy difference of 4.391 kcal/mole. If in the *trans* isomer the deviation from ring coplanarity is 5.3° then it is increased to 14.6° in the *cis* isomer due to the steric interaction between the carbonyl groups. These results give a basis for assuming that compounds **4**, **5** are formed in the *trans* configuration in the course of the reaction.

EXPERIMENTAL

^{1}H NMR spectra were measured on a Bruker WP-300 SY instrument (300 MHz) using DMSO-d_6 solvent and TMS internal standard. Mass spectra were taken on a Finnigan MAT-4615B instrument with ballistic heating of the sample and ionization energy of 70 eV.

3-(2-Oxo-1,2-dihydro-3H-indol-3-ylidene)-1,4-dihydroquinoxalin-2-one (4). *o*-Phenylenediamine (5.0 mmol) was added to the ethyl ester **1** (5.0 mmol) in DMF (3 ml). Within 5 min of the start of refluxing a red colored precipitate was formed and this was filtered off and crystallized from DMF. Yield 1.1 g (76%); mp 298-299°C. ^{1}H NMR spectrum, δ, ppm: 14.11 (1H, s, NH); 11.91 (1H, s, NH); 10.77 (1H, s, NH); 8.65 (1H, d, Ar); 6.78-7.22 (7H, m, Ar). Mass spectrum, *m/z* (I_{rel}, %): 277 (100) $[M]^+$, 279 (21) $[M\text{-}CO]^+$, 220 (41), 144 (24), 90 (29), 76 (32), 65 (41), 44 (89). Found %: C 69.28; H 3.98; N 15.18. $C_{16}H_{11}N_3O_2$. Calculated, %: C 69.31; H 4.02; N 15.15.

2-(2-Oxo-1,2-dihydro-3H-indol-3-ylidene)-2H-1,4-benzoxazin-3(4H)-one (5). *o*-Aminophenol (5.0 mmol) was added to the ethyl ester **1** (5.0 mmol) in DMF (3 ml) and the product was refluxed for 1 h. The reaction mixture was diluted with water and acidified using hydrochloric acid to pH 3-4. The bright orange colored precipitate formed was filtered off, washed with water to pH 7, and crystallized from aqueous DMF to give 0.82 g (61%) of product with mp 310-311°C. ^{1}H NMR spectrum, δ, ppm: 13.61 (1H, s, NH); 11.07 (1H, s, NH); 8.48 (1H, d, Ar); 6.75-7.26 (7H, m, Ar). Mass spectrum, *m/z* (I_{rel}, %): 278 (64) $[M]^+$, 250 (100) $[M\text{-}CO]^+$, 221 (35), 193 (47), 167 (15), 157 (22), 125 (18), 103 (36), 76 (46), 63 (74), 51 (53). Found, %: C 69.12; H 3.59; N 10.12. $C_{16}H_{10}N_2O_3$. Calculated, %: C 69.06; H 3.62; N 10.07.

REFERENCES

1. V. V. Bolotov, S. V. Kovaleva, V. I. Stepanenko, and D. Yu. Matvienko, *Fiziologicheski Akt. Veshchestva*, No. 1, 51 (1999).
2. L. Horner, *Liebigs Ann. Chem.*, **548**, 117 (1941).
3. J. J. P. Stewart, *J. Comput. Chem.,* **10**, 209 (1989).
4. J. J. P. Stewart, *J. Comput. Aided Mol. Design,* **4**, 1 (1990).