Cyclocondensation Reactions of Heterocyclic Carbonyl Compounds XII. [1] The Double Course of Cyclization of 3-(2-aminobenzyl)-1,2-dihydro-quinoxaline-2-one

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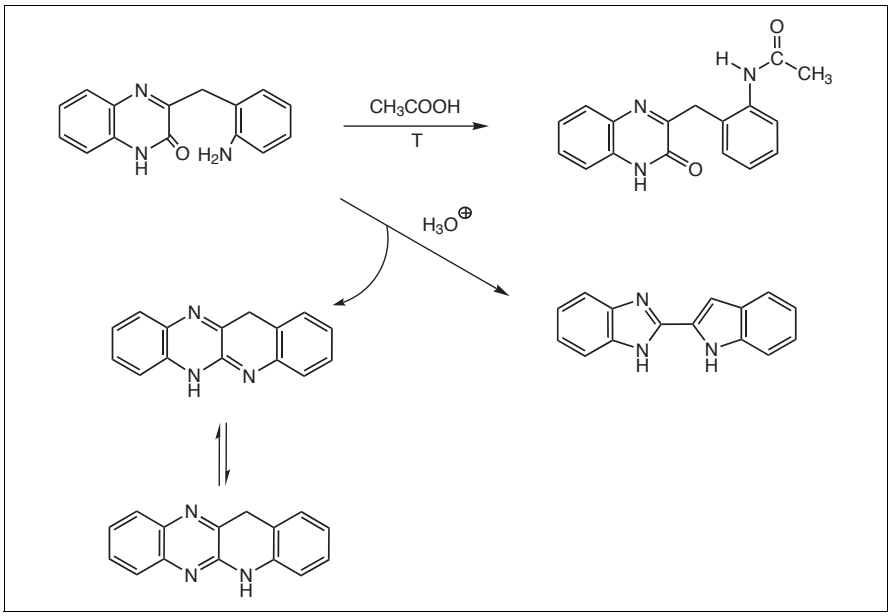

The cyclocondensation reaction of compound **1** in boiling hydrochloric acid had an unexpected course. Instead of supposed 5,11-dihydro-quinoxalino[2,3-*b*]quinoline **6a**, 2-(indol-2-yl)-benzimidazole **4** was isolated as the major product.

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A number of previous communications has concerned the use of cyclocondensation reactions for synthesis of condensed [1,2,4]triazine like derivatives [1,2,4]triazino-[2,3-*a*]quinazolines [2], [1,2,4]triazino[2,3-*a*]benzimidazoles [3-7], [1,2,4]triazino[5,6-*b*]quinolines [8], [1,2,4]-triazino[6,5-*b*]quinolines [9,23], [1,2,4]triazino[5,6-*c*]-isoquinolines [10,11], [1,2,4]triazino[6,5-*f*][1,7]naph-tyridines [12], [1,2,4]triazino[5,6-*c*]cinnolines [13-15], [1,2,4]triazino[5,6-*b*]indoles [14,15] and [1,2,4]triazino-[6,5-*a*]indoles [16]. In all the mentioned cases cyclocon-densation was performed on carbonyl groups in the positions 3, 5 and 6 of appropriate aminoderivatives of [1,2,4]triazines.

Analogous cyclocondensations, performed on carbonyl group of aminoderivatives of 1,2-dihydro-quinoxalin-2-one, have not been so much investigated. Only well known cyclocondensation of 3-(2-aminophenyl)-1,2-dihydro-quinoxalin-2-one affording 5*H*-indole[2,3-*b*]-quinoxalin-2-one [17] and some analogical reactions [18,19] are essentially.

We were interested in possible use of analogous cyclocondensation of 3-(2-aminobenzyl)-1,2-dihydro-quinoxalin-2-one **1** [21] for the preparation of hetero-cyclic system of quinolino[2,3-*b*]quinoxalines **6**, which has not been investigated so much up to now.

We assumed the cyclocondenzation should be carried out without any problems, similarly as in the case of cyclocondenzation of 5-(2-aminobenzyl)-6-azauracils [8]. Contemporaneously we expected its slower course in accordance with previously stated facts [20], that reactivity of carbonyl group of 1,2-dihydro-quinoxalin-2-one was much lower in comparison to reactivity of carbonyl group in the position 4 of 6-azauracile cycle.

These expectations were confirmed only partially. We found out, that during boiling of compound **1** in acetic acid the cyclocondensation did not proceed, because the acetylation of amino group, affording acetylderivative **7**, is faster.

An unexpected course was observed also in cyclization made by boiling of compound **1** in hydrochloric acid.

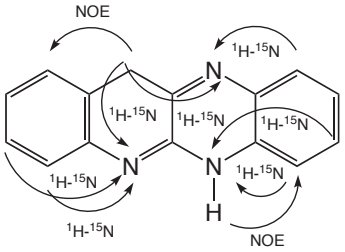
Under these conditions the formation of two isomeric compounds of summary formula $C_{15}H_{11}N_3$ look place. Chromatographie separation afforded two compounds – yellow (25.1 %) and collorless (74.9 %) ones.

According to IR and NMR spectral results it was found out, that structure of expected cyclocondensation product can be attributed to yellow isomer **6**, while colorless isomer **4** is a product of the reaction proceeding in parallel with the expected cyclocondensation reaction.

In accordance with spectroscopic data as well as to independent synthesis [22], this isomer was identified as 2-(indol-2-yl)-benzimidazole **4** (Scheme 1). The most probable explanation of this double directed dicyclization of *o*-aminobenzyl derivatives **1** is described in Scheme 2.

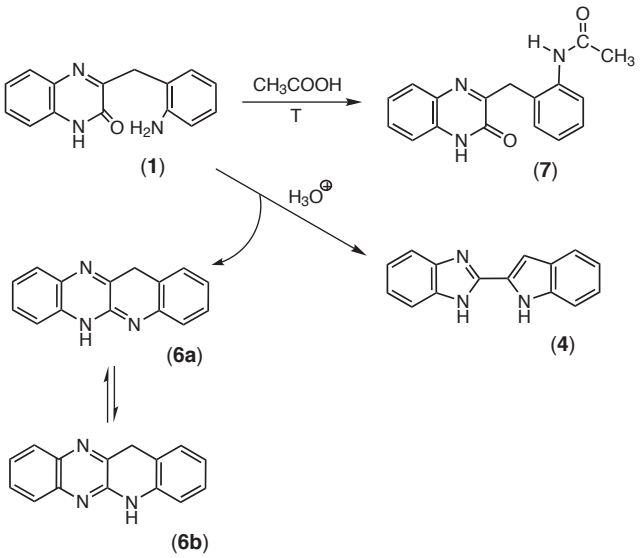
In strongly acidic medium, the nucleophillic addition of aminogroup to protonized C=N bond leading to spirocyclic intermediate **2** proceeds probably at first. The compound **1** is in an equilibrium with protonized form **2a**, which is probably the key intermediate of transformation to **4** resp **6**. Nucleophilic rearrangement of quinoxaline NH group to carbonyl group leads to formation of benzimidazole cycle **3**. Competitive nucleophilic transport of indoline N-H group to mentioned carbonyl group affords quinoline cycle **5**. After dehydratation and tautomerization both these products afford final products **4** and **6a** or **6b** respectively.

NMR spectroscopy was capable of determining the correct structure of compound **6** in DMSO. Signals of one methylene group were observed both in ^{1}H and ^{13}C NMR spectra ((δ = 4.59 and 36.78, respectively). The coupling constant $^1J(^{15}N, ^1H)$ = 90.2 Hz was extracted from 1D gradient-selected ^{1}H-^{15}N HMBC spectrum indicating the localisation of acidic proton with $\delta(^1H)$ = 12.53 *on one nitrogen atom only*. From NOESY spectrum, it follows that aromatic proton, which is through-space close to proton of NH group, has chemical shift $\delta(^1H)$ = 7.33. Further proton chemical shifts of three protons belonging to one 1,2-disubstituted benzene ring were assigned from H,H-COSY. No correlation of protons of this 1,2-disubstituted benzene ring with proton of methylene group was observed in NOESY spectrum. Proton with chemical shift $\delta(^1H)$ = 7.64 gave appropriate correlation with methylene group in NOESY spectrum and, thus, further three proton chemical shifts of the second 1,2-disubstituted benzene ring could be determined undoubtedly from H,H-COSY spectrum. Protonated carbons were assigned using gs-^{1}H-^{13}C HMQC and quaternary ones by gs-^{1}H-^{13}C HMBC. 2D gradient-selected ^{1}H-^{15}N HMBC was measured and three nitrogen resonances found ($\delta(^{15}N)$ = - 232.3 (NH). – 5.3 (-N=) and –56.7 (-N=). Correlation of nitrogen atoms with appropriate protons, enabling assignment of ^{15}N resonances, is shown in the following Figure 1.



We can conclude that the reaction product **6** exists completely in tautomeric form **6a** in DMSO.

Scheme 1



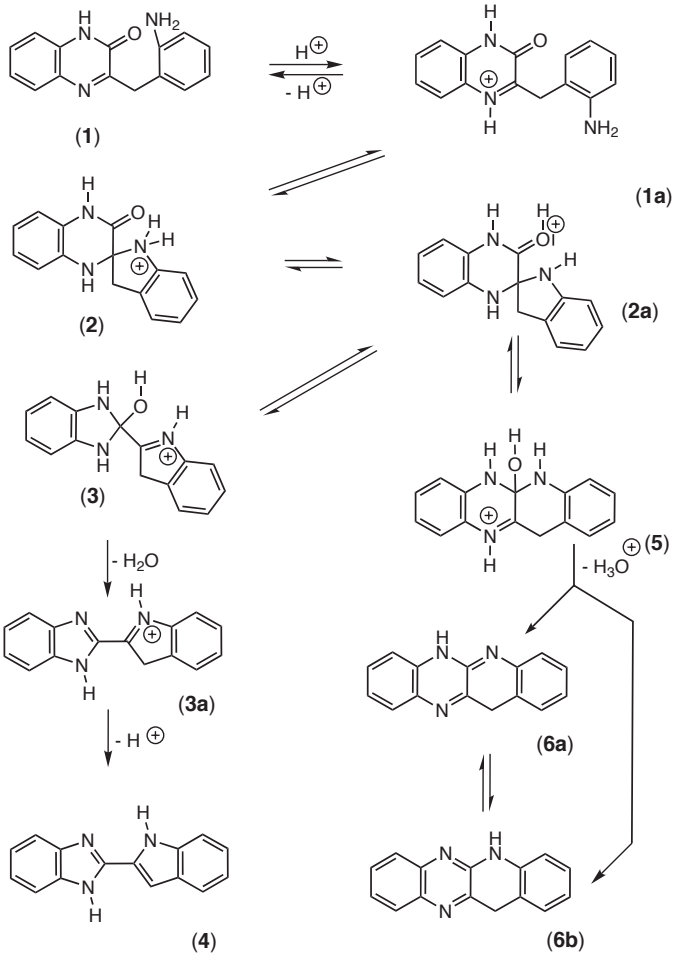
EXPERIMENTAL

Melting points were determined on a Boetius stage and are not corrected. Infrared spectra were measured in KBr disks and scanned on an ATI Unicam Genesis FTIR instrument and values are described in cm $^{-1}$. Elemental analyses were performed by using an EA 1108 Elemental Analyzer (Fison Instrument). Mass spectrometric experiments were performed using an LCQ ion trap mass spectrometer (Finnigan MAT, San Jose, CA, USA), HPLC experiments were performed using Dionex liquid chromatograph (P 680 HPLC Pump, PDA-100 Photodiode Array Detector). NMR spectra were recorded on a Bruker Avance spectrometer (500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C, 50.68 MHz for ^{15}N) in DMSO-d_6. ^{1}H and ^{13}C chemical shifts are given on the δ scale (ppm) and are referenced to internal TMS. ^{15}N chemical shifts were referred to external neat nitromethane in co-axial capillary (δ = 0.0). All 2D experiments (gradient-selected (gs)-COSY, (gs)-NOESY gs-HMQC, gs-HMBC) were performed using manufacturer's software.

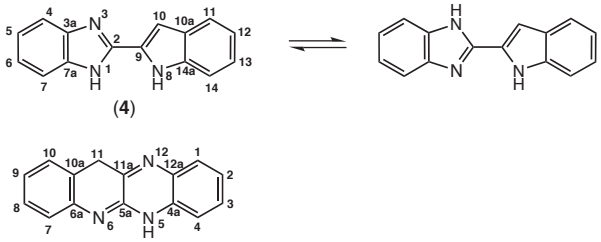
2-(Indol-2-yl)-benzimidazole (**4**).

The mixture of 3-(2-aminobenzyl)-1,2-dihydro-quinoxaline-2-one **1** (600.0 mg, 2.39 mmol) and 1.5 *M* hydrochloric acid (30

Scheme 2



Scheme 3



NMR numbering of compounds **4** and **6a**.

ml) was refluxed for 30 min and evaporated *in vacuo*. The residue was then intensively stirred and ultrasonified for 2 hours in absolute ethanol at room temperature. The colourless crystalline compounds was collected by filtration washed with a little of ethanol and dried. After crystallization from ethanol and 20% hydrochloric acid colourless crystals were obtained, mp =328-329 °C (lit. [22]: 328-329 °C), yield is 74,9 %, ir (cm $^{-1}$): 3172, 3104, 2967, 1605, 1569, 1517, 1470, 1412, 1320, 1139, 1100, 879, 753, 577.

Anal. Calcd. For $C_{15}H_{11}N_3$.HCl (269.78): C, 66.78; H, 4.48; N, 15.58. Found: C, 66.81; H, 4.43; N, 15.62.

^{1}H, ^{13}C and ^{15}N chemical shifts of compound **4** in DMSO-d_6 are given in Table 1 (for numbering see Scheme 3).

Table 1

^{1}H, ^{13}C and ^{15}N Chemical Shifts of Compound **4** in DMSO-d_6

H, C, N No.	δ(^{1}H)	δ(^{13}C)	H, C, N No.	δ(^{1}H)	δ(^{13}C)
1 = 3[a]	13.10	b,c	10	7.27	101.88
2	-	146.13	10a	-	127.91
3a = 7a[a]	-	137.28	11	7.69	120.87
4 = 7[a]	7.66	114.54	12	7.09	119.78
5 = 6[a]	7.28	122.25	13	7.22	122.80
8	12.04	-249.5[b,d]	14	7.51	112.03
9	-	128.60	14a	-	127.91

[a] Equivalence due to fast proton exchange between positions 1 and 3; [b] δ(^{15}N); [c] ^{15}N NMR signal not found; [d] ^{1}J(^{15}N, ^{1}H) = 99.2 Hz.

5,11-Dihydro-quinolino[2,3-*b*]quinoxaline **6a** resp. **6b**.

The residue after evaporation of combined filtrates after extraction of mixture of **4** and **6** (see previous procedure) was separated by column chromatography using toluene and acetonitrile (5:2) mixture as eluent. Mp = 218-219 °C, yield is 25,1 %, ir (cm $^{-1}$): 3172, 3104, 2967, 1612, 1569, 1517, 1481, 1432, 1348, 1143, 1108, 862, 755, 595.

Anal. Calcd. For $C_{15}H_{11}N_3$ (233.27): C, 77.23; H, 4.75; N, 18.02. Found: C, 77.20; H, 4.68; N, 18.12.

The ^{1}H, ^{13}C and ^{15}N chemical shifts of compound **6a** in DMSO-d_6 are given in Table 2 (for numbering see Scheme 3).

Table 2

^{1}H, ^{13}C and ^{15}N Chemical Shifts of Compound **6a** resp. **6b** in DMSO-d_6

H, C, N No.	δ(^{1}H)	δ(^{13}C)	H, C, N No.	δ(^{1}H)	δ(^{13}C)
1	7.49	128.17	7	8.41	124.72
2	7.26	123.24	8	7.60	128.17
3	7.50	128.32	9	7.74	133.61
4	7.33	115.41	10	7.64	133.51
4a	-	131.29	10a	-	131.29
5	12.23	-232.3[a, b]	11	4.59	36.78
5a	-	158.84	11a	-	154.35
6	-	-5.3[a]	12	-	-56.7[a]
6a	-	149.50	12a	-	131.29

[a] δ(^{15}N); [b] ^{1}J(^{15}N, ^{1}H) = 90.2 Hz.

3-(2-Acetylaminobenzyl)-1,2-dihydro-quinoxaline-2-one (**7**).

3-(2-Aminobenzyl)-1,2-dihydro-quinoxaline-2-one 1 (251.29 mg, 1.00 mmol) was refluxed in acetic acid (5 ml) for 4 h. After cooling to room temperature the crystalline compound was collected by filtration, washed with a little water and dried. Mp = 209-210 °C, yield is 79,1 %, m/s (m/z): 294.3 (100), ir (cm^{-1}): 3290, 3066, 3017, 2965, 1767, 1676, 1615, 1552, 1498, 1454, 1326, 1202, 1152, 945, 747, 601, 497, 470.

Anal. Calcd. For $C_{17}H_{15}N_3O_2$ (293.32): C, 69.61; H, 5.15; N, 14.33. Found: C, 69.50; H, 5.20; N, 14.21.

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