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Synthesis and structures of substituted 5,6-dihydrospiro(benz[4,5]imidazo[1,2-*c*]quinazoline-6,3´-indolin)-2´-ones*

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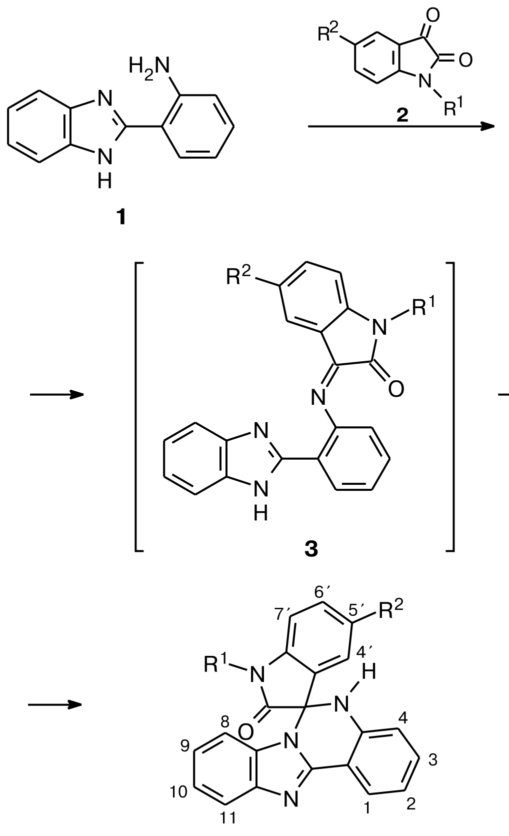
The reactions of 2-(2-aminophenyl)benzimidazole with substituted isatins afforded the corresponding 5,6-dihydrospiro(benz[4,5]imidazo[1,2-*c*]quinazoline-6,3´-indolin)-2´-ones. The spirocyclic structure of the reaction products was established by NMR spectroscopy and X-ray diffraction analysis.

Key words: 2-(2-aminophenyl)benzimidazole, isatin, spiranes.

Imidazole-annelated benzimidazoles exhibit a broad spectrum of biological activities.[1] In particular, 6-substituted 5,6-dihydrobenz[4,5]imidazo[1,2-*c*]quinazolines, which are condensation products of 2-(2-aminophenyl)benzimidazole with various aldehydes and ketones, are of considerable practical interest.[2,3] However, the reactions of 2-(2-aminophenyl)benzimidazole with isatins, which are characterized by a highly reactive carbonyl group and biological activity of derivatives,[4,5] have not been studied earlier. In the present study, we performed the synthesis and established the crystal structures of the products prepared by the reactions of 2-(2-aminophenyl)benzimidazole with 1- and 5-substituted isatins.

The reaction of 2-(2-aminophenyl)benzimidazole (**1**) with isatins **2** in ethanol and acetic acid afforded colorless crystalline products. The absence of the color characteristic of isatin imines indicates that the reaction does not stop at Schiff bases **3** and affords 5,6-dihydrospiro(benz[4,5]imidazo[1,2-*c*]quinazoline-6,3´-indolin)-2´-ones (**4**). The spirocyclic structure of products **4** is evidenced by the fact that the ^{1}H NMR spectra have an AB quartet for the protons of the diastereotopic benzyl group of spirane **4c** and a multiplet AA´BB´ for the H(8), H(11) and H(9), H(10) protons of the benzimidazole moiety, which is characteristic of all compounds **4a—d**. In the spectrum of the starting benzimidazole **1**, the sig-



Compound	R^1	R^2
a	H	H
b	Me	H
c	CH$_2$Ph	H
d	Me	Me

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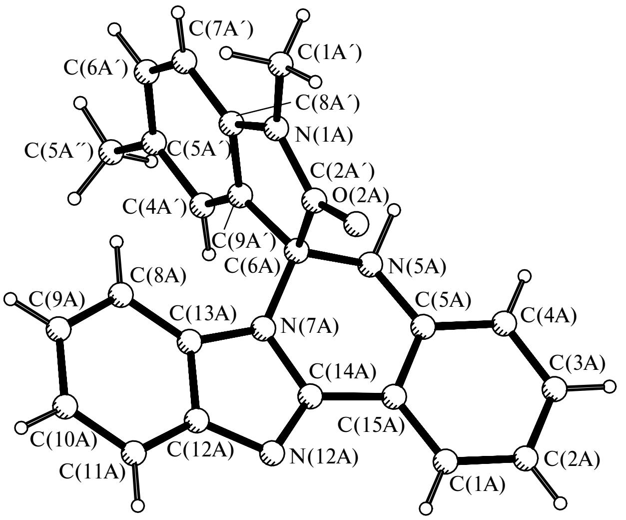

Fig. 1. Molecular structure of compound **4d**. One of two crystallographically independent molecules is shown.

nals for the same protons appear as a symmetrical multiplet A_2B_2 due to torsional rotation about the benzimidazolyl—aminophenyl bond and fast annular prototropy N(1) $\rightleftharpoons$ N(3). The signals for the protons of the oxindole fragment change only slightly and are observed in regions characteristic of isatin.

The spirocyclic structure of products **4** was unambiguously confirmed by X-ray diffraction analysis of the crystals of compound **4d** (Fig. 1). The benzo[4,5]imidazo[1,2-*c*]quinazoline fragment is virtually planar, except for the dihydropyrimidine ring in which the C(6) and N(5) atoms deviate from the N(7)—C(14)—C(15)—C(5) plane in opposite directions by 0.369 and 0.115 Å, respectively (hereinafter, the average values for two crystallographically independent molecules are given). The spiroannelated oxindole moiety is planar and is almost orthogonal to the tetracyclic benz[4,5]imidazo[1,2-*c*]quinazoline system (the dihedral angle between the N(5)—C(6)—N(7) and C(2′)—C(6)—C(9′) planes is 87.2°). Six bond angles in the spiro unit are in a range of 101.5—116.3°; the C(9′)—C(6)—C(2′) and N(7)—C(6)—C(9′) angles have the smallest and largest values, respectively.

Experimental

^{1}H NMR spectra were recorded on a Bruker DPX-250 spectrometer (250 MHz) at 25 °C in DMSO-d$_6$.

X-ray diffraction study. Single crystals of compound **4d** were grown by crystallization from MeOH. Platelet crystals of $C_{23}H_{18}N_4O \cdot 0.5CH_3OH$ (M = 382.44) belong to the triclinic system, space group $P\bar{1}$, at 110 K, $a = 12.177(3)$, $b = 12.351(3)$, $c = 15.631(4)$ Å, $\alpha = 99.423(6)$, $\beta = 110.636(5)$, $\gamma = 110.076(6)$°, $V = 1954.8(8)$ Å^3, $Z = 4$, $d_{\text{calc}} = 1.299$ g cm^{-3}. A total of 14658 reflections were collected on a Bruker SMART 1000 CCD diffractometer at 110 K (Mo-Kα radiation, λ = 0.71073 Å, ω scanning technique with a step of 0.3°, exposure time per frame was 10 s, $2\theta_{\max} = 56°$) from a single crystal of dimensions 0.5×0.4×0.1 mm^3. Merging of the equivalent reflections gave 9387 independent reflections ($R_{\text{int}} = 0.0285$), which were used in the structure solution and refinement. The structure was solved by direct methods and refined by the full-matrix least-squares method against F^2 with anisotropic thermal parameters for nonhydrogen atoms. The H(5A) and H(5B) atoms were revealed from difference electron density maps and refined isotropically. All other hydrogen atoms were placed in geometrically calculated positions and refined using the riding model. The final reliability factors were $R_1 = 0.0671$ (based on F_{hkl} for 5342 reflections with $I > 2\sigma(I)$), $wR_2 = 0.1637$ (based on F^2_{hkl} for all independent reflections), GOOF = 0.967, 549 parameters were refined. All calculations were carried out using the SHELXTL v.5 program package.^{6} The atomic coordinates, bond lengths, and bond angles were deposited with the Cambridge Structural Database. Selected bond lengths and bond angles are given in Tables 1 and 2, respectively.

Table 1. Bond lengths (Å) in two independent molecules (**A** and **B**) of compound **4d**

Bond	A	B
O(2)—C(2′)	1.223(3)	1.214(3)
N(1)—C(2′)	1.356(3)	1.364(3)
N(1)—C(8′)	1.412(3)	1.413(3)
N(1)—C(1′)	1.453(3)	1.460(3)
N(5)—C(5)	1.391(3)	1.391(3)
N(5)—C(6)	1.455(3)	1.444(3)
N(7)—C(14)	1.384(3)	1.379(3)
N(7)—C(13)	1.397(3)	1.395(3)
N(7)—C(6)	1.448(3)	1.461(3)
N(12)—C(14)	1.310(3)	1.315(3)
N(12)—C(12)	1.391(3)	1.384(3)
C(1)—C(2)	1.385(4)	1.370(3)
C(1)—C(15)	1.389(3)	1.400(3)
C(2)—C(3)	1.388(4)	1.393(4)
C(2′)—C(6)	1.576(4)	1.572(3)
C(3)—C(4)	1.386(4)	1.380(4)
C(4)—C(5)	1.395(3)	1.399(3)
C(4′)—C(9′)	1.376(3)	1.368(3)
C(4′)—C(5′)	1.404(4)	1.408(3)
C(5)—C(15)	1.403(3)	1.399(3)
C(5′)—C(6′)	1.390(4)	1.397(4)
C(5′)—C(5")	1.505(4)	1.507(4)
C(6)—C(9′)	1.505(3)	1.507(3)
C(6′)—C(7′)	1.382(4)	1.393(4)
C(7′)—C(8′)	1.381(3)	1.377(4)
C(8)—C(9)	1.387(4)	1.387(4)
C(8)—C(13)	1.389(3)	1.388(3)
C(8′)—C(9′)	1.392(3)	1.402(3)
C(9)—C(10)	1.389(4)	1.399(4)
C(10)—C(11)	1.384(4)	1.374(4)
C(11)—C(12)	1.394(3)	1.397(3)
C(12)—C(13)	1.409(3)	1.410(3)
C(14)—C(15)	1.450(3)	1.449(3)

Table 2. Bond angles (deg) in two independent molecules (**A** and **B**) of compound **4d**

Angle	A	B
C(2´)—N(1)—C(8´)	111.3(2)	111.3(2)
C(2´)—N(1)—C(1´)	123.7(2)	124.1(2)
C(8´)—N(1)—C(1´)	125.0(2)	124.6(2)
C(5)—N(5)—C(6)	121.3(2)	120.1(2)
C(14)—N(7)—C(13)	106.5(2)	107.0(2)
C(14)—N(7)—C(6)	123.0(2)	120.9(2)
C(13)—N(7)—C(6)	126.6(2)	129.9(2)
C(14)—N(12)—C(12)	105.0(2)	104.7(2)
C(2)—C(1)—C(15)	120.5(3)	119.9(2)
C(1)—C(2)—C(3)	119.7(2)	119.7(2)
O(2)—C(2´)—N(1)	127.6(2)	127.4(2)
O(2)—C(2´)—C(6)	124.6(2)	125.1(2)
N(1)—C(2´)—C(6)	107.8(2)	107.5(2)
C(4)—C(3)—C(2)	120.6(2)	121.2(2)
C(3)—C(4)—C(5)	120.0(2)	119.8(2)
C(9´)—C(4´)—C(5´)	119.3(2)	119.9(2)
N(5)—C(5)—C(4)	120.7(2)	121.8(2)
N(5)—C(5)—C(15)	119.7(2)	119.2(2)
C(4)—C(5)—C(15)	119.4(2)	118.8(2)
C(6´)—C(5´)—C(4´)	118.1(2)	117.8(2)
C(6´)—C(5´)—C(5")	121.4(2)	121.6(2)
C(4´)—C(5´)—C(5")	120.5(3)	120.7(3)
N(7)—C(6)—N(5)	108.9(2)	107.4(2)
N(7)—C(6)—C(9´)	115.5(2)	116.3(2)
N(5)—C(6)—C(9´)	110.8(2)	110.9(2)
N(7)—C(6)—C(2´)	108.5(2)	108.6(2)
N(5)—C(6)—C(2´)	111.5(2)	111.4(2)
C(9´)—C(6)—C(2´)	101.5(2)	102.1(2)
C(5´)—C(6´)—C(7´)	123.2(2)	122.7(2)
C(8´)—C(7´)—C(6´)	117.5(2)	117.9(3)
C(9)—C(8)—C(13)	116.8(2)	116.3(2)
C(7´)—C(8´)—C(9´)	120.9(2)	120.6(2)
C(7´)—C(8´)—N(1)	128.9(2)	129.0(2)
C(9´)—C(8´)—N(1)	110.2(2)	110.4(2)
C(8)—C(9)—C(10)	121.5(3)	122.0(2)
C(4´)—C(9´)—C(8´)	121.0(2)	121.0(2)
C(4´)—C(9´)—C(6)	130.0(2)	130.6(2)
C(8´)—C(9´)—C(6)	109.0(2)	108.3(2)
C(9)—C(10)—C(11)	121.9(2)	121.3(2)
C(10)—C(11)—C(12)	117.6(2)	118.2(2)
C(11)—C(12)—N(12)	129.1(2)	129.0(2)
C(11)—C(12)—C(13)	120.1(2)	119.7(2)
N(12)—C(12)—C(13)	110.7(2)	111.3(2)
N(7)—C(13)—C(8)	133.5(2)	133.7(2)
N(7)—C(13)—C(12)	104.4(2)	103.9(2)
C(8)—C(13)—C(12)	122.0(2)	122.4(2)
N(12)—C(14)—N(7)	113.2(2)	113.1(2)
N(12)—C(14)—C(15)	127.4(2)	127.5(2)
N(7)—C(14)—C(15)	119.4(2)	119.3(2)
C(1)—C(15)—C(5)	119.8(2)	120.6(2)
C(1)—C(15)—C(14)	122.7(2)	122.0(2)
C(5)—C(15)—C(14)	117.4(2)	117.4(2)

2-(2-Aminophenyl)benzimidazole and isatin were purchased from Lancaster. 5-Methylisatin[7] and 1-alkylisatins[8] were prepared according to standard procedures.

Synthesis of 5,6-dihydrospiro(benz[4,5]imidazo[1,2-*c*]quinazoline-6,3´-indolin)-2´-ones 4a and 4c (general procedure). A mixture of benzimidazole **1** (0.6 g, 2.87 mmol) and the corresponding isatin **2** (2.87 mmol) was refluxed in AcOH (4 mL) for 2 h. After 12 h, the precipitate that formed was filtered off and recrystallized from MeCN (**4a**) or MeOH (**4c**).

Synthesis of 5,6-dihydrospiro(benz[4,5]imidazo[1,2-*c*]quinazoline-6,3´-indolin)-2´-ones 4b and 4d (general procedure). A mixture of benzimidazole **1** (0.3 g, 1.44 mmol) and the corresponding isatin **2** (1.44 mmol) was refluxed in MeOH (5 mL) in the presence of AcOH (0.1 mL) for 5 h. After 12 h, the precipitate that formed was filtered off and dried at 80 °C.

5,6-Dihydrospiro(benz[4,5]imidazo[1,2-*c*]quinazoline-6,3´-indolin)-2´-one (4a). The yield was 0.35 g (73%), m.p. 208—210 °C. Found (%): C, 74.70; H, 4.27; N, 16.75. $C_{21}H_{14}N_4O$. Calculated (%): C, 74.54; H, 4.17; N, 16.56. ^{1}H NMR, δ: 6.10 (d, 1 H, H(8), *J* = 8.1 Hz); 6.82—7.00 (m, 3 H, H(2), H(4), H(10)); 7.08—7.22 (m, 3 H, H(5´), H(7´), H(9)); 7.29 (dd, 1 H, H(3), *J* = 7.8 Hz, *J* = 7.6 Hz); 7.50—7.60 (m, 2 H, H(4´), H(6´)); 7.68 (d, 1 H, H(11), *J* = 7.8 Hz); 7.81 (s, 1 H, N(5)H); 8.00 (d, 1 H, H(1), *J* = 7.6 Hz); 10.81 (br.s, 1 H, N(1´)H).

1´-Methyl-5,6-dihydrospiro(benz[4,5]imidazo[1,2-*c*]quinazoline-6,3´-indolin)-2´-one (4b). The yield was 0.41 g (81%), m.p. 192—194 °C. Found (%): C, 75.15; H, 4.67; N, 16.04. $C_{22}H_{16}N_4O$. Calculated (%): C, 74.98; H, 4.58; N, 15.90. ^{1}H NMR, δ: 3.18 (s, 3 H, N(1´)Me); 6.00 (d, 1 H, H(8), *J* = 8.1 Hz); 6.78—6.98 (m, 3 H, H(2), H(4), H(10)); 7.10—7.38 (m, 4 H, H(3), H(5´), H(7´), H(9)); 7.55—7.70 (m, 3 H, H(4´), H(6´), H(11)); 7.77 (s, 1 H, NH); 8.00 (d, 1 H, H(1), *J* = 7.8 Hz).

1´-Benzyl-5,6-dihydrospiro(benz[4,5]imidazo[1,2-*c*]quinazoline-6,3´-indolin)-2´-one (4c). The yield was 0.61 g (50%), m.p. 232—234 °C. Found (%): C, 78.68; H, 4.80; N, 13.23. $C_{28}H_{20}N_4O$. Calculated (%): C, 78.49; H, 4.70; N, 13.08. ^{1}H NMR, δ: 4.88 and 4.97 (both d, 1 H each, CH_2, *J* = 15.9 Hz); 5.92 (d, 1 H, H(8), *J* = 8.1 Hz); 6.81—6.97 (m, 3 H, H(2), H(4), H(10)); 7.12—7.43 (m, 7 H, Ar); 7.57 (dd, 1 H, H(6´), *J* = 7.1 Hz, *J* = 7.8 Hz); 7.62—7.73 (m, 2 H, H(4´), H(11)); 7.98 (s, 1 H, NH); 8.03 (d, 1 H, H(1), *J* = 7.8 Hz).

1´,5´-Dimethyl-5,6-dihydrospiro(benz[4,5]imidazo[1,2-*c*]quinazoline-6,3´-indolin)-2´-one (4d). The yield was 0.35 g (66%), m.p. 311—312 °C. Found (%): C, 75.56; H, 5.09; N, 15.46. $C_{23}H_{18}N_4O$. Calculated (%): C, 75.39; H, 4.95; N, 15.29. ^{1}H NMR, δ: 2.29 (s, 3 H, C(5´)H_3); 3.16 (s, 3 H, N(1´)Me); 6.05 (d, 1 H, H(8), *J* = 8.1 Hz); 6.83 (d, 1 H, H(4), *J* = 8.1 Hz); 6.85—6.98 (m, 2 H, H(2), H(10); 7.16 (dd, 1 H, H(9), *J* = 7.3 Hz, *J* = 8.1 Hz); 7.22 (d, 1 H, H(7´), *J* = 7.8 Hz); 7.29 (dd, 1 H, H(3), *J* = 7.3 Hz, *J* = 8.3 Hz); 7.38—7.48 (m, 2 H, H(4´), H(6´)); 7.67 (d, 1 H, H(11), *J* = 7.8 Hz); 7.74 (s, 1 H, NH); 8.00 (d, 1 H, H(1), *J* = 7.6 Hz).

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