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Unexpected Formation of 6,7-Dihydrobenzo[4′,5′]imidazo-[1′,2′:1,6]pyrimido[5,4-*a*]indolizine Derivative in the Alkylation of 2-Amino-1-(benzimidazol-2-yl)-3-(4-methoxybenzoyl)indolizine

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Abstract—An attempt to effect exhaustive alkylation of 2-amino-1-(benzimidazol-2-yl)-3-(4-methoxybenzoyl) indolizine with alkyl iodides in boiling acetone led to the formation of 6,6-dimethyl-8-(4-methoxybenzoyl)-6,7-dihydrobenzo[4′,5′]imidazo[1′,2′:1,6]pyrimido[5,4-*a*]indolizine instead of expected *N*-alkyl derivatives. The product structure was proved by X-ray analysis.

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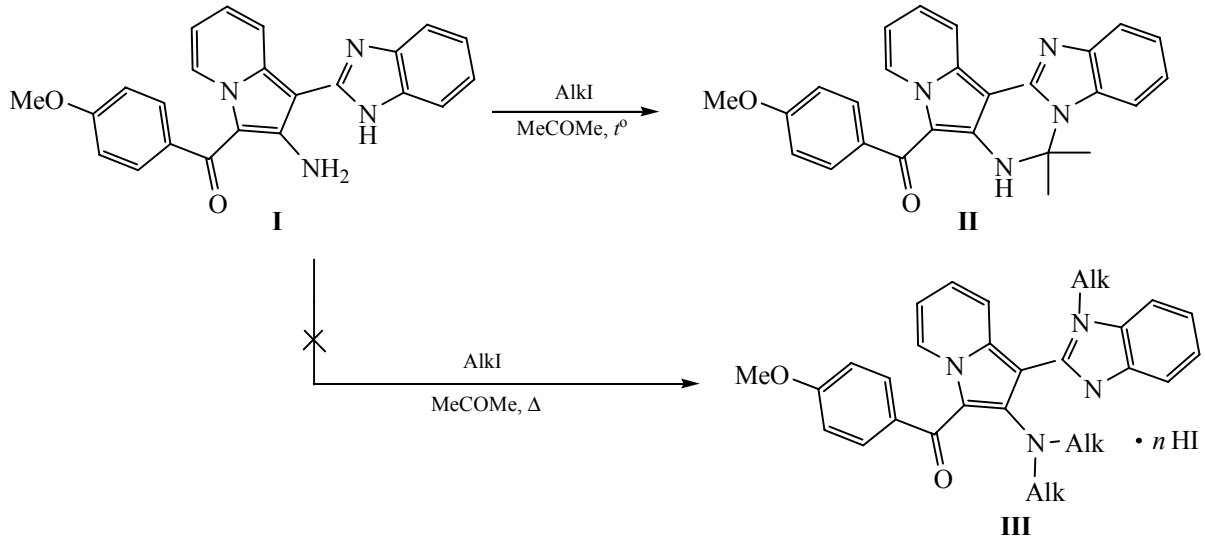
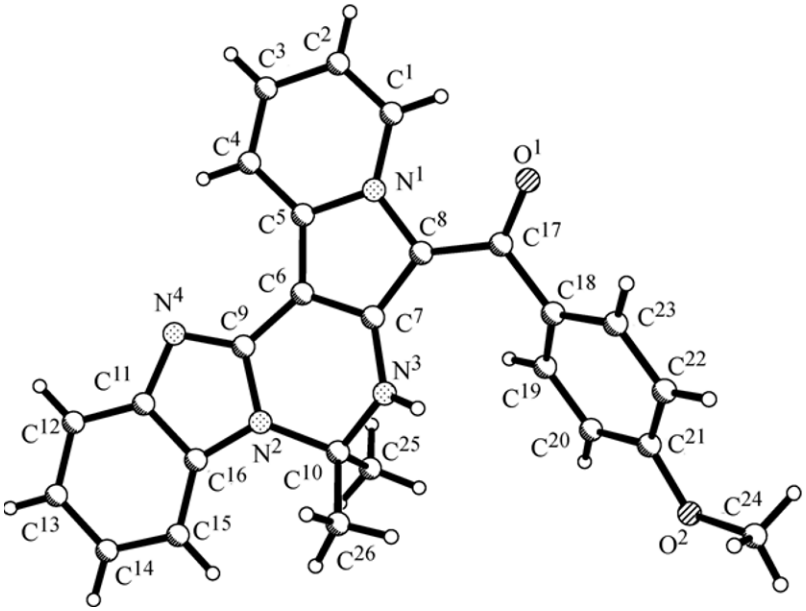
2-Amino-3-aroyl-1-(benzimidazol-2-yl)indolizines are convenient reagents for the synthesis of fused pyrimidine derivatives [1, 2] which attract interest as potential pharmacologically active compounds [3–9]. We made an attempt to effect exhaustive alkylation of indolizine **I** [1] with methyl or ethyl iodide in acetone. However, in both cases, the product was 8-(4-methoxybenzoyl)-6,6-dimethyl-6,7-dihydrobenzo-[4′,5′]imidazo[1′,2′:1,6]pyrimido[5,4-*a*]indolizine (**II**) rather than expected salt **III**. The structure of **II** was proved by spectral data and X-ray analysis.

Taking into account that no base was added to the reaction mixture to bind liberated HI, the latter was likely to catalyze the reaction with acetone. We failed to obtain compound **II** by prolonged heating



I **II** **III**

Alk = Me, Et.



Structure of the molecule of 8-(4-methoxybenzoyl)-6,6-dimethyl-6,7-dihydrobenzo[4′,5′]imidazo[1′,2′:1,6]pyrimido[5,4-*a*]indolizine (**II**) according to the X-ray diffraction data.

of indolizine **I** in acetone in the absence of alkyl iodide.

The structure of **II** was unambiguously proved by X-ray analysis (see figure; Tables 1, 2). The dihydropyrimidine ring in molecule **II** adopts a *half-chair* conformation with almost planar $C^7C^6C^9N^2$ fragment [torsion angle 5.86(18)°]. The N^3 and C^{10} atoms deviate from that plane by –0.167(2) and 0.243 Å, respectively. The formation of intramolecular hydrogen bond C^1–$H^1\cdots O^1$ (H···O 2.29, ∠CHO 119°) is accompanied by a small rotation of the carbonyl group with respect to the polycyclic fragment [torsion angle $N^1C^8C^{17}O^1$ 16.0(2)°]. In addition, the C^{18}–C^{23} benzene ring is slightly turned relative to the carbonyl group [torsion angle $O^1C^{17}C^{18}C^{23}$ 33.3(2)°], which may also be induced by steric factors (shortened intramolecular contact $N^3\cdots C^{19}$ 2.97 Å; the sum of the corresponding van der Waals radii is 3.21 Å [10]). Despite the presence in molecule **II** of proton-donor (N^3) and two acceptor centers (O^1, O^2), no intermolecular hydrogen bonds were found in crystal. Among specific intermolecular interactions we can note only stacking of the indolizine fragments related to each other through the symmetry operation [1 – *x*, 1 – *y*, –*z*] (the planes of these fragments are rigorously parallel, and the distances $N^1\cdots Cg^1$ and $C^2\cdots Cg^2$ are 3.42 and 3.40Å, where Cg^1 and Cg^2 are the gravity centers of the six- and five-membered rings, respectively). Also, weak intermolecular hydrogen bonds C–H···π between the phenyl substituent and indolizine and benzimidazole fragments of the two neighboring molecules were observed (C^{23}–$H^{23}\cdots Cg^2$: H···Cg 2.74 Å, ÐCHCg 123°; C^{20}–$H^{20}\cdots C^{16}$: H···C 2.88 Å, ∠CHC 137°).

Table 1. Bond lengths (*d*, Å) in structure **II**

Bond	*d*, Å	Bond	*d*, Å
O^1–C^{17}	1.2355(16)	C^6–C^9	1.4230(17)
O^2–C^{21}	1.3608(16)	C^7–C^8	1.4085(18)
O^2–C^{24}	1.419(2)	C^8–C^{17}	1.4382(19)
N^1–C^1	1.3694(15)	C^{10}–C^{26}	1.5118(19)
N^1–C^5	1.3865(17)	C^{10}–C^{25}	1.516(2)
N^1–C^8	1.4122(16)	C^{11}–C^{12}	1.3856(19)
N^2–C^9	1.3819(14)	C^{11}–C^{16}	1.4064(18)
N^2–C^{16}	1.3876(16)	C^{12}–C^{13}	1.370(2)
N^2–C^{10}	1.4858(17)	C^{13}–C^{14}	1.386(2)
N^3–C^7	1.3729(16)	C^{14}–C^{15}	1.380(2)
N^3–C^{10}	1.4563(17)	C^{15}–C^{16}	1.3928(18)
N^4–C^9	1.3178(16)	C^{17}–C^{18}	1.4884(19)
N^4–C^{11}	1.3847(16)	C^{18}–C^{23}	1.385(2)
C^1–C^2	1.352(2)	C^{18}–C^{19}	1.3913(19)
C^2–C^3	1.403(2)	C^{19}–C^{20}	1.3757(19)
C^3–C^4	1.3614(18)	C^{20}–C^{21}	1.391(2)
C^4–C^5	1.3988(17)	C^{21}–C^{22}	1.382(2)
C^5–C^6	1.3968(16)	C^{22}–C^{23}	1.3749(19)
C^6–C^7	1.3899(17)		

Table 2. Bond angles (ω, deg) in structure **II**

Angle	ω, deg	Angle	ω, deg
$C^{21}O^{2}C^{24}$	117.74(12)	$N^{3}C^{10}C^{26}$	106.67(12)
$C^{1}N^{1}C^{5}$	120.46(11)	$N^{2}C^{10}C^{26}$	111.45(12)
$C^{1}N^{1}C^{8}$	129.24(12)	$N^{3}C^{10}C^{25}$	109.60(12)
$C^{5}N^{1}C^{8}$	110.29(10)	$N^{2}C^{10}C^{25}$	108.13(11)
$C^{9}N^{2}C^{16}$	105.62(10)	$C^{26}C^{10}C^{25}$	112.15(13)
$C^{9}N^{2}C^{10}$	124.15(10)	$N^{4}C^{11}C^{12}$	128.63(12)
$C^{16}N^{2}C^{10}$	129.40(10)	$N^{4}C^{11}C^{16}$	110.68(11)
$C^{7}N^{3}C^{10}$	121.19(12)	$C^{12}C^{11}C^{16}$	120.68(12)
$C^{9}N^{4}C^{11}$	104.26(10)	$C^{13}C^{12}C^{11}$	118.36(14)
$C^{2}C^{1}N^{1}$	119.89(14)	$C^{12}N^{13}C^{14}$	120.91(14)
$C^{1}C^{2}C^{3}$	120.89(13)	$C^{15}C^{14}C^{13}$	122.17(13)
$C^{4}C^{3}C^{2}$	119.63(13)	$C^{14}C^{15}C^{16}$	117.14(14)
$C^{3}C^{4}C^{5}$	119.60(13)	$N^{2}C^{16}C^{15}$	133.91(13)
$N^{1}C^{5}C^{6}$	107.00(11)	$N^{2}C^{16}C^{11}$	105.37(10)
$N^{1}C^{5}C^{4}$	119.50(11)	$C^{15}C^{16}C^{11}$	120.72(13)
$C^{6}C^{5}C^{4}$	133.47(12)	$O^{1}C^{17}C^{8}$	121.68(13)
$C^{7}C^{6}C^{5}$	108.21(11)	$O^{1}C^{17}C^{18}$	119.61(13)
$C^{7}C^{6}C^{9}$	120.18(11)	$C^{8}C^{17}C^{18}$	118.70(11)
$C^{5}C^{6}C^{9}$	131.26(12)	$C^{23}C^{18}C^{19}$	118.00(13)
$N^{3}C^{7}C^{6}$	120.03(12)	$C^{23}C^{18}C^{17}$	118.82(13)
$N^{3}C^{7}C^{8}$	130.06(12)	$C^{19}C^{18}C^{17}$	123.17(13)
$C^{6}C^{7}C^{8}$	109.48(10)	$C^{20}C^{19}C^{18}$	120.89(13)
$C^{7}C^{8}N^{1}$	104.91(11)	$C^{19}C^{20}C^{21}$	119.91(13)
$C^{7}C^{8}C^{17}$	132.27(12)	$O^{2}C^{21}C^{22}$	124.75(13)
$N^{1}C^{8}C^{17}$	122.54(11)	$O^{2}C^{21}C^{20}$	115.52(13)
$N^{4}C^{9}N^{2}$	113.98(11)	$C^{22}C^{21}C^{20}$	119.73(13)
$N^{4}C^{9}C^{6}$	128.65(11)	$C^{23}C^{22}C^{21}$	119.48(14)
$N^{2}C^{9}C^{6}$	117.37(11)	$C^{22}C^{23}C^{18}$	121.71(14)
$N^{3}C^{10}N^{2}$	108.78(10)		

EXPERIMENTAL

The IR spectra were recorded in KBr on a Perkin–Elmer Spectrum One spectrometer. The ^{1}H NMR spectra were measured on a Bruker DRX-200 (200 MHz) and Bruker Avance II-400 (400 MHz) instruments using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on MKh-1321 and Varian 1200 L spectrometers with direct sample admission into the ion source. The melting points were determined on a Kofler hot stage. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using acetone–hexane (3 : 5) as eluent; the chromatograms were developed by treatment with iodine vapor or under UV light.

2-Amino-1-(benzimidazol-2-yl)-3-(4-methoxybenzoyl)indolizine (**I**) was synthesized according to the procedure described in [1].

8-(4-Methoxybenzoyl)-6,6-dimethyl-6,7-dihydrobenzo[4′,5′]imidazo[1′,2′ : 1,6]pyrimido[5,4-*a*]indolizine (II). Indolizine **I**, 1 mmol, was dispersed in 15 ml of acetone, 3.0 mmol of methyl or ethyl iodide was added, and the mixture was heated for 8 h under reflux. After 24 h, the precipitate was filtered off and washed with acetone. Yield 0.281 g (67%, MeI), 0.320 g (76%, EtI), yellow powder, mp 240°C (from EtOH). IR spectrum, ν, cm^{-1}: 3410 (NH), 1644 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.80 s (6H, Me), 3.86 s (3H, OMe), 5.46 s (1H, NH), 6.96 t (1H, 11-H, J = 6.94 Hz), 7.01–7.31 m (4H, 4-H, 1-H, *m*-H), 7.46 t (1H, 12-H, J = 7.59 Hz), 7.54–7.64 m (2H, 3-H, 2-H), 7.70 d (2H, *o*-H, J = 8.70 Hz), 8.08 d (1H, 13-H, J = 8.53 Hz), 9.30 d (1H, 10-H, J = 7.02 Hz). Mass spectrum, m/z (I_{rel}, %): 422 (82) $[M]^+$, 407 (95.5) $[M - CH_3]^+$. Found, %: C 73.90; H 5.28; N 13.22. $C_{26}H_{22}N_4O_2$. Calculated, %: C 73.92; H 5.25; N 13.26.

X-Ray diffraction data for compound **II**. Monoclinic crystals, $C_{26}H_{22}N_4O_2$; unit cell parameters (298 K): a = 10.1901(3), b = 8.5336(3), c = 24.0462(7) Å; β = 94.562(3)°; V = 2084.41(11) Å^3; M_r = 422.48; Z = 4; space group $P2_1/c$; d_{calc} = 1.346 g/cm^3; μ(MoK_α) = 0.088 mm^{-1}; F(000) = 888. The unit cell parameters and intensities of 23244 reflections (7001 independent reflections, R_{int} = 0.026) were measured on an Xcalibur 3 automatic four-circle diffractometer (MoK_α irradiation, graphite monochromator, CCD detector, ω-scanning, $2\theta_{max}$ = 65.06°). The structure was solved by the direct method using SHELX-97 software package [11]. The positions of hydrogen atoms attached to carbon atoms were calculated on the basis of geometry considerations and were refined according to the *riding* model ($U_{iso} = nU_{eq}$; n = 1.5 for methyl groups, and n = 1.2 for aromatic carbon atoms). The position of the hydrogen atom on N^3 was refined independently in isotropic approximation. The structure was refined by F^2 using the full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atoms; wR_2 = 0.139 for 7001 reflections and R_1 = 0.053 for 3967 reflections with $F > 4\sigma(F)$; s = 1.00. The bond lengths and bond angles in molecule **II** are given in Tables 1 and 2, respectively. The complete set of crystallographic parameters, coordinates of atoms, and all bond lengths and bond angles were deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 771465).

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