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INVESTIGATIONS IN THE FIELD OF BENZOXAZINES. 15*. TANDEM HETEROCYCLIZATIONS WITH THE PARTICIPION OF 2-FORMYLBENZOIC ACID. THE SYNTHESIS OF ISOINDOLO[1,2-*b*][1,3]- AND -[2,1-*a*][3,1]BENZOXAZINONES

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Single stage reactions of 2-formylbenzoic acids with substituted 2-(1-aminoalkyl)phenols and 2-aminophenylcarbinols give a novel series of isomeric isoindolobenzoxazinones. X-ray analysis was used to study the molecular structure of 9-bromo-5,5-diphenyl-5H-isoindolo[2,1-a][3,1]benzoxazin-11(6aH)-one and 2-bromo-8,10-dimethyl-10H-isoindolo[1,2-b][1,3]-benzoxazin-12(4bH)-one.

Keywords: 2-(1-aminoalkyl)phenols, 2-aminophenylcarbinols, 10H-isoindolo[1,2-*b*][1,3]benzoxazin-12(4*b*H)-ones, 5H-isoindolo[2,1-*a*][3,1]benzoxazin-11(6*a*H)-ones, 2-formylbenzoic acids.

Tetracyclic condensed structures containing an annelated isoindole fragment are widely distributed in nature and have a broad spectrum of biological activity that is well reflected in recent reviews [2, 3]. Hence there is much interest in developing new routes for their synthesis. The isoindolo[2,1-*a*][3,1]benzoxazine system has been described in the literature, however, most data concerns isoindolo[2,1-*a*][3,1]benzoxazine-5,11-diones [4-7], while the synthesis of derivatives of 5,6*a*-dihydroisoindolo[2,1-*a*][3,1]benzoxazin-11-ones has been reported in only one publication [8] to our knowledge. The authors of this article used the 2-amino ketone phthalimides **A** as starting compounds, and these were converted to the respective structures **B** through a simple sequence of reactions.

Despite the simplicity of the scheme, this method still has an important drawback, since the use of asymmetrically substituted phthalic anhydrides in the synthesis of the phthalimides **A** should lead to a mixture of isomeric alcohols **C**. To avoid this difficulty, derivatives of 2-formylbenzoic acid can be used. It is well known that 2-formylbenzoic acids can react with binucleophiles containing at least one primary amino group to give annelated isoindolinones [9-12].

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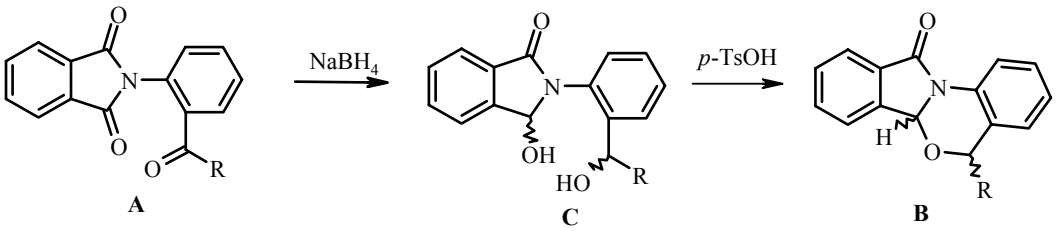
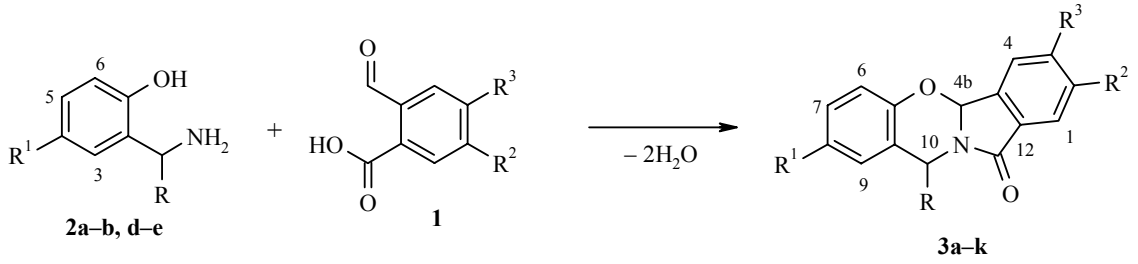


The aim of our work was to develop a versatile, preparative method leading not only to isoindolo-[2,1-*a*][3,1]benzoxazines (for which only two of the compounds of type **B** given above have been reported [8]) but also to related isoindolo[1,2-*b*][1,3]benzoxazines [12].

We have used the 2-(aminoalkyl)phenols **2** (obtained by a standard method [14]) as binucleophiles in reaction with the 2-formylbenzoic acids **1** [13]. Reaction of equimolar amounts of reagents **1** and **2** in refluxing toluene with a catalytic amount of *p*-toluenesulfonic acid and azeotropic distillation of water gave the tetracyclic 10H-isoindolo[1,2-*b*][1,3]benzoxazin-12H(4*b*H)-ones **3**.



a R = R^3 = H, R^1 = R^3 = Cl; **b–k** R = Me, **b–f** R^3 = H, **b** R^1 = Me, R^2 = Br; **c** R^1 = Me, R^2 = Cl; **d** R^1 = Cl, R^2 = Br; **e** R^1 = OMe, R^2 = Cl; **f** R^1 = R^2 = Cl; **g** R^1 = OMe, R^2 = NO_2, R^3 = Cl; **h** R^1 = Me, R^2 = NO_2, R^3 = Cl; **i** R^1 = R^3 = Cl, R^2 = NO_2; **j** R^1 = Cl, R^2 = R^3 = OMe; **k** R^1 = R^2 = R^3 = OMe

The synthesis reaction time is virtually independent of the nature of the substituent in the 2-(1-amino-alkyl)phenol molecules **2** but it does depend markedly on the type of substituent in the formylbenzoic acid. Acceptor substituents (NO_2 or two halogen) shorten the reaction time to 40-60 min while electron donors (methoxy groups) increase the time for reaction completion to 10-12 h. Evidently this is connected with the change in electrophilicity of the formyl carbon atom and, possibly, the carbon atom of the azomethine group of the Schiff base formed in the first stage of the reaction. The fact that a Schiff base is actually an intermediate in the complex sequence of reactions is indirectly indicated by a change in the color of the reaction mixture during the synthesis. Initially colorless it takes on a strong yellow color and this disappears when the reaction is complete. TLC also indicates the appearance and disappearance of a strongly colored reaction intermediate. An azomethine is the only intermediate product of those possible.

The isoindolobenzoxazinones **3a-k** are colorless, crystalline substances readily soluble in most organic solvents (Table 1). The IR spectra of compounds **3** show characteristic stretching absorptions for a lactam carbonyl group at 1645-1700 cm^{-1}. The compound **3a** molecule has one chiral center at atom 4*b* and this is clearly revealed in the ^{1}H NMR spectrum. The diastereotopic protons of the 10-CH_2 function absorb as a pair of doublets with a geminal spin-spin coupling of J = 17.1 Hz (Table 2). Compounds **3b-k** have two chiral centers at atoms 4*b* and 10 and can, in principle, exist as two pairs of enantiomers. The ^{1}H NMR spectra of these substances show only one set of signals, typical of which are a three-proton doublet at high field and a one-proton quartet at medium field for the A_3X system formed by the H-10 and CH_3 group protons and also a sharp

TABLE 1. Physicochemical Characteristics for the Isoindolobenzoxazinones **3a-k** and **5a-k**

Compound*	Empirical formula	Found, % / Calculated, %			mp, °C	R_f (Silufol UV-254)	Yield, %
		C	H	N			
3a	$C_{15}H_9Cl_2NO_2$	59.11 / 58.82	2.51 / 2.94	4.35 / 4.58	208-210	0.58	60
3b	$C_{17}H_{14}BrNO_2$	59.66 / 59.30	4.35 / 4.07	4.25 / 4.07	149-150	0.52	65
3c	$C_{17}H_{14}ClNO_2$	68.62 / 68.11	4.32 / 4.67	4.35 / 4.67	132-133	0.60	68
3d	$C_{16}H_{11}BrClNO_2$	52.50 / 52.67	3.15 / 3.02	3.96 / 3.84	151-152	0.62	65
3e	$C_{17}H_{14}ClNO_3$	64.42 / 64.66	4.58 / 4.44	4.32 / 4.44	147-148	0.37	58
3f	$C_{16}H_{11}Cl_2NO_2$	60.35 / 60.00	3.27 / 3.44	4.52 / 4.38	180-181	0.65	70
3g	$C_{17}H_{13}ClN_2O_5$	56.71 / 56.59	3.53 / 3.61	7.90 / 7.77	179-180	0.50	65
3h	$C_{17}H_{13}ClN_2O_4$	59.41 / 59.22	3.92 / 3.77	8.01 / 8.13	183-185	0.60	65
3i	$C_{16}H_{10}Cl_2N_2O_4$	52.91 / 52.60	2.61 / 2.74	7.42 / 7.67	199-200	0.55	67
3j	$C_{18}H_{16}ClNO_4$	62.32 / 62.52	4.61 / 4.63	4.30 / 4.05	181-182	0.25	62
3k	$C_{19}H_{19}NO_5$	67.03 / 66.86	5.85 / 5.57	4.29 / 4.31	151-152	0.20	65
5a	$C_{15}H_{10}N_2O_4$	63.62 / 63.83	3.80 / 3.55	9.71 / 9.93	112-113	0.67	75
5b	$C_{15}H_{10}ClNO_2$	66.48 / 66.30	3.51 / 3.68	5.32 / 5.16	115-116	0.78	72
5c	$C_{15}H_{10}BrNO_2$	56.72 / 56.96	3.30 / 3.16	4.71 / 4.43	141-142	0.86	70
5d	$C_{19}H_{19}NO_2$	77.60 / 77.81	6.33 / 6.48	4.92 / 4.78	100-122	0.38	75
5e	$C_{27}H_{19}NO_2$	83.41 / 83.29	4.56 / 4.88	3.85 / 3.60	210-211	0.59	77
5f	$C_{19}H_{18}N_2O_4$	67.65 / 67.46	5.21 / 5.33	8.42 / 8.28	160-161	0.46	80
5g	$C_{27}H_{18}N_2O_4$	74.41 / 74.65	4.02 / 4.15	6.63 / 6.45	>250	0.65	75
5h	$C_{21}H_{23}NO_4$	71.58 / 71.39	6.41 / 6.52	4.08 / 3.97	171-172	0.31	75
5i	$C_{29}H_{23}NO_4$	77.38 / 77.51	5.21 / 5.12	3.35 / 3.12	>230	0.46	65
5j	$C_{19}H_{18}BrNO_2$	61.51 / 61.29	4.70 / 4.84	3.88 / 3.76	147-149	0.78	70
5k	$C_{27}H_{18}BrNO_2$	69.45 / 69.23	4.02 / 3.85	3.15 / 2.99	236-238	0.85	75

* Mass spectra, *m/z* of isotopes ^{35}Cl; ^{79}Br; **5b** = 271 $[M]^+$; **5c** = 315 $[M]^+$; **5h** = 353 $[M]^+$; **5j** = 371 $[M]^+$; **5k** = 467 $[M]^+$

one-proton singlet for the H-4*b* proton at 5.85-6.30 ppm. The absence of a long range stereospecific constant for the H-4b and H-10 protons supports a structure with a transoid orientation of these hydrogen atoms relative to the oxazine ring (an *R*,*S*-*S*,*R* enantiomeric pair), i.e. a stereochemical control of the sequence of cyclization reactions.

X-ray analytical data for compound **3b** is fully in agreement with this proposal. The crystal actually contains one pair of enantiomers while in the unit cell each enantiomer is present as two conformational isomers (see Fig. 1 for the two independent molecules **E** and **F** with the same 4*bR*,10*S*-configuration). The

molecules **E** and **F** differ only in the conformation of the oxazine ring. In both cases it has the form of a *half chair* with a plane based on the five atoms N(1)–C(16)–C(15)–C(10)–O(1) (plane 1, mean deviation of the atoms from the plane for molecule **E** being 0.0123 Å and for **F** 0.0208 Å). The angle between plane 1 and the N(1)–C(9)–O(1) plane (plane 2) is 132.4º in **E** and 136.8º in **F**.

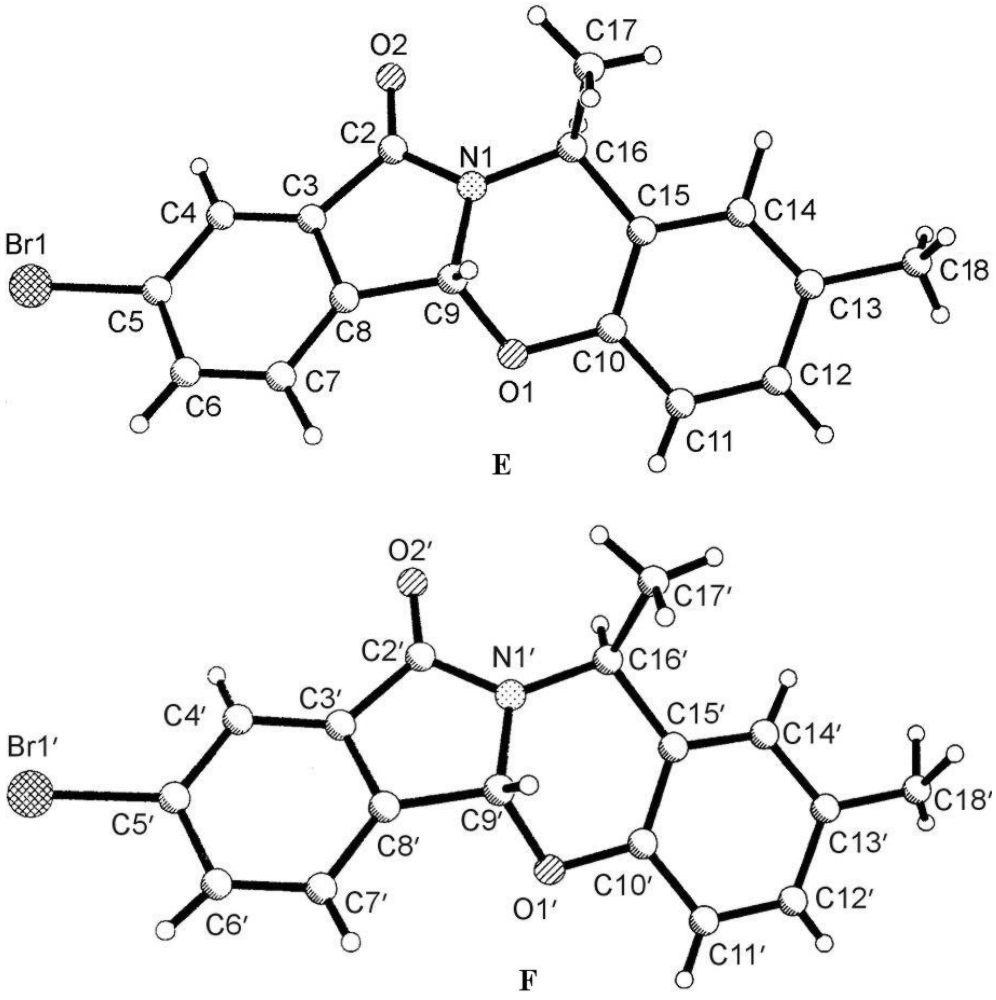


Fig. 1. Projection of the steric model for the conformational isomers of (4*bR*, 10*S*)-2-bromo-8,10-dimethyl-10H-isoindolo[1,2-*b*][1,3]benzoxazin-12(4*b*H)-one (**3b**) in the crystal.

Otherwise independent molecules are virtually identical. The plane of the benzene ring C(10)···C(15) deviates from plane 1 by 2.9 and 3.1º and the isoindole fragment plane is twisted relative to plane 2 by 60.4 and 60.5º for the molecules **E** and **F** respectively. As regards the planar-trigonal geometry of the N(1) atom: the sums of the valence angles at this nitrogen atom are 359.9 and 359.7º for molecules **E** and **F** respectively.

The reaction of equimolar amounts of the formylbenzoic acids **1** and 2-aminophenylcarbinols **4a-c** in acetic acid [15, 16] give the isoindolobenzoxazinones **5** in a single stage without separation of intermediate products. The reaction also occurs readily in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid but, in this case, an additional operations is needed for neutralization of the catalyst and removal of solvent. In the previous case the separation of the product just needs dilution of the reaction mixture with water.

TABLE 2. IR and ^{1}H NMR Spectra of Compounds **3a-k** and **5a-k**

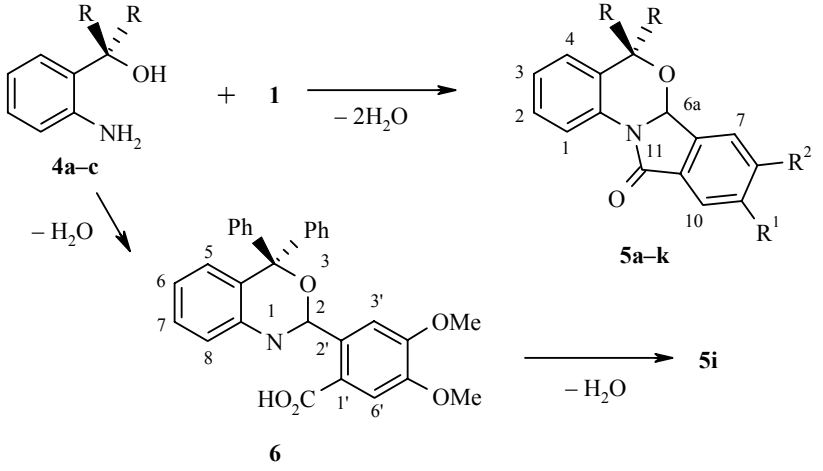
Com-pound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum*	
		Chemical shifts, δ, ppm	SSCC, *J*, Hz
1	2	3	4
3a	1700 (C=O)	4.53 (1H, d, H-10*a*); 5.14 (1H, d, H-10*e*); 5.93 (1H, s, H-4*b*); 6.93 (1H, d, H-6); 7.20 (2H, m, H arom); 7.65 (1H, m, H arom); 7 .85 (1H, s, H-1)	$^2J_{10a,e}$ = 17.1, $^3J_{6,7}$ = 9.3
3b	1690 (C=O)	1.66 (3H, d, 10-CH_3); 2.33 (3H, s, 8-CH_3); 5.30 (1H, q, H-10); 5.95 (1H, s, H-4*b*); 6.86 (1H, d, H-6); 7.01 (2H, m, H-7,9); 7.65 (1H, d, H-4); 7.77 (1H, dd, H-3); 8.00 (1H, d, H-1)	$^3J_{CH_3,H}$ = 6.7, $^3J_{6,7}$ = 8.9, $^3J_{3,4}$ = 8.0, $^4J_{3,1}$ = 1.5
3c	1690 (C=O)	1.66 (3H, d, 10-CH_3); 2.33 (3H, s, 8-CH_3); 5.29 (1H, q, H-10); 5.95 (1H, s, H-4*b*); 6.86 (1H, d, H-6); 7.02 (2H, m, H-7 + H-9); 7.61 (1H, dd, H-3); 7.71 (1H, d, H-4); 7.85 (1H, d, H-1)	$^3J_{CH_3,H}$ = 6.7, $^3J_{6,7}$ = 8.8, $^3J_{3,4}$ = 8.0, $^4J_{3,1}$ = 1.6
3d	1645 (C=O)	1.66 (3H, d, 10-CH_3); 5.31 (1H, q, H-10); 5.91 (1H, s, H-4*b*); 6.91 (1H, d, H-6); 7.17 (1H, d, H-7); 7.22 (1H, s, H-9); 7.63 (1H, d, H-4); 7.78 (1H, dd, H-3); 8.00 (1H, d, H-1)	$^3J_{CH_3,H}$ = 6.7, $^3J_{6,7}$ = 8.7, $^3J_{3,4}$ = 7.9, $^4J_{3,1}$ = 1.4
3e	1690 (C=O)	1.67 (3H, d, 10-CH_3); 3.80 (3H, s, OCH_3); 5.30 (1H, q, H-10); 5.95 (1H, s, H-4*b*); 6.75 (1H, d, H-9); 6.79 (1H, dd, H-7); 6.91 (1H, d, H-6); 7.60 (1H, dd, H-3); 7.68 (1H, d, H-4); 7.84 (1H, d, H-1)	$^3J_{CH_3,H}$ = 6.8, $^4J_{7,9}$ = 2.8, $^3J_{6,7}$ = 8.8, $^3J_{3,4}$ = 8.0, $^4J_{1,3}$ = 1.5
3f	1680 (C=O)	1.66 (3H, d, 10-CH_3); 5.31 (1H, q, H-10); 5.98 (1H, s, H-4*b*); 6.91 (1H, d, H-6); 7.18 (1H, d, H-7); 7.21 (1H, s, H-9); 7.62 (1H, d, H-4); 7.69 (1H, d, H-3); 7.85 (1H, s, H-1)	$^3J_{CH_3,H}$ = 6.7, $^3J_{6,7}$ = 8.6, $^3J_{3,4}$ = 7.8
3g	1670 (C=O), 1335, 1520 (NO_2)	1.69 (3H, d, 10-CH_3); 3.81 (3H, s, OCH_3); 5.32 (1H, q, H-10); 6.02 (1H, s, H-4*b*); 6.75 (1H, d, H-9); 6.81 (1H, dd, H-7); 6.92 (1H, d, H-6); 7.96 (1H, s, H-4); 8.28 (1H, s, H-1)	$^3J_{CH_3,H}$ = 6.7, $^4J_{7,9}$ = 2.7, $^3J_{6,7}$ = 8.9
3h	1680 (C=O), 1320, 1510 (NO_2)	1.68 (3H, d, 10-CH_3); 2.34 (3H, s, 8-CH_3); 5.31 (1H, q, H-10); 6.04 (1H, s, H-4*b*); 6.88 (1H, d, H-6); 7.04 (2H, m, H-7,9); 7.97 (1H, s, H-4); 8.28 (1H, s, H-1)	$^3J_{CH_3,H}$ = 6.7, $^3J_{6,7}$ = 8.9
3i	1700 (C=O), 1330, 1510 (NO_2)	1.69 (3H, d, 10-CH_3); 5.33 (1H, q, H-10); 6.06 (1H, s, H-4*b*); 6.93 (1H, d, H-6); 7.21 (1H, d, H-7); 7.25 (1H, s, H-9); 7.97 (1H, s, H-4); 8.28 (1H, s, H-1)	$^3J_{CH_3,H}$ = 6.7, $^3J_{6,7}$ = 8.5
3j	1700 (C=O)	1.62 (3H, d, 10-CH_3); 3.94 and 4.00 (6H, two s, $(OCH_3)_2$); 5.26 (1H, q, H-10); 5.89 (1H, s, H-4*b*); 6.88 (1H, d, H-6); 7.13 (1H, dd, H-7); 7.19 (1H, d, H-9); 7.21 (1H, s, H-4); 7.32 (1H, s, H-1)	$^3J_{CH_3,H}$ = 6.6, $^3J_{6,7}$ = 8.8, $^4J_{7,9}$ = 2.2
3k	1690 (C=O)	1.62 (3H, d, 10-CH_3); 3.76 (3H, s, 8-OCH_3); 3.93 and 3.98 (6H, two s, $(OCH_3)_2$); 5.25 (1H, q, H-10); 5.85 (1H, s, H-4*b*); 6.72 (1H, dd, H-7); 6.75 (1H, d, H-9); 6.88 (1H, d, H-6); 7.20 (1H, s, H-4); 7.31 (1H, s, H-1)	$^3J_{CH_3,H}$ = 6.6, $^3J_{6,7}$ = 7.8, $^4J_{7,9}$ = 2.9
5a	1670 (C=O), 1490, 1320 (NO_2)	5.09 (1H, d, H-5*a*); 5.30 (1H, d, H-5*e*); 5.99 (1H, s, H-6*a*); 7.26 (3H, m, H-2,3,4); 7.84 (1H, d, H-1); 8.38 (1H, d, H-7); 8.49 (1H, d, H-8); 8.69 (1H, s, H-10)	$^2J_{5a,e}$ = 14.8, $^3J_{7,8}$ = 7.6, $^3J_{1,2}$ = 6.9

TABLE 2 (continued)

1	2	3	4
5b	1690 (C=O)	5.10 (1H, d, H-5*a*); 5.30 (1H, d, H-5*e*); 6.23 (1H, s, H-6*a*); 7.20 (1H, dd, H-3); 7.27 (1H, d, H-4); 7.38 (1H, dd, H-2); 7.82 (2H, m, H-7,8); 7.90 (1H, s, H-10); 8.25 (1H, d, H-1)	$^2J_{5a,e}$ = 15.2, $^3J_{2,3}$ = 7.0, $^3J_{2,1}$ = 8.2; $^3J_{4,3}$ = 8.5
5c	1680 (C=O)	5.10 (1H, d, H-5*a*); 5.30 (1H, d, H-5*e*); 6.22 (1H, s, H-6*a*); 7.20 (1H, dd, H-3); 7.25 (1H, d, H-4); 7.39 (1H, dd, H-2); 7.75 (1H, d, H-7); 7.95 (1H, dd, H-8); 8.00 (1H, d, H-10); 8.23 (1H, d, H-1)	$^2J_{5a,e}$ = 15.2, $^3J_{2,1}$ = 8.2, $^3J_{2,3}$ = 7.0, $^3J_{7,8}$ = 8.0, $J_{3,4}$ = 8.0, $^4J_{8,10}$ = 2.7
5d	1685 (C=O)	0.55 and 1.18 (6H, two t, $(CH_3)_2$); 2.05 (4H, m, $(CH_2)_2$); 5.97 (1H, s, H-6*a*); 7.19 (2H, m, H-3,4); 7.34 (1H, dd, H-2); 7.61 (3H, m, H-7,8,9); 7.92 (1H, d, H-10); 8.35 (1H, d, H-1)	$^3J_{CH_3CH_2}$ = 7.2, $^3J_{2,1}$ = 8.2, $^3J_{2,3}$ = 6.5, $^3J_{9,10}$ = 6.9
5e	1680 (C=O)	5.88 (1H, s, H-6*a*); 6.90 (1H, d, H-4); 7.07 (1H, dd, H-3); 7.40 (14H, m, H arom); 7.95 (1H, d, H-10); 8.58 (1H, d, H-1)	$^3J_{4,3}$ = 7.8, $^3J_{3,2}$ = 7.2, $^3J_{2,1}$ = 8.2, $^3J_{9,10}$ = 8.6
5f	1690 (C=O), 1510, 1320 (NO_2)	0.53 and 1.18 (6H, two t, $(CH_3)_2$), 2.00 (4H, m, $(CH_2)_2$); 6.06 (1H, s, H-6*a*); 7.27 (3H, m, H arom); 7.83 (1H, d, H-7); 8.31 (1H, d, H-8); 8.52 (1H, d, H-1); 8.73 (1H, s, H-10)	$^3J_{CH_3CH_2}$ = 7.3, $^3J_{1,2}$ = 8.1, $^3J_{7,8}$ = 8.2
5g	1680 (C=O), 1500, 1320 (NO_2)	5.94 (1H, s, H-6*a*); 6.92 (1H, d, H-4); 7.33 (12H, m, $(C_6H_5)_2$, H-2,3); 7.73 (1H, d, H-7); 8.48 (1H, d, H-8); 8.55 (1H, d, H-1); 8.76 (1H, s, H-10)	$^3J_{4,3}$ = 7.8, $^3J_{7,8}$ = 8.3, $^3J_{1,2}$ = 8.6
5h	1690 (C=O)	0.40 and 1.10 (6H, two t, $(CH_3)_2$); 1.92 (2H, dq, CH-2*a*); 2.15 (2H, dq, CH-2*e*); 3.85 and 3.90 (6H, two s, $(OCH_3)_2$); 6.08 (1H, s, H-6*a*); 7.14 (1H, dd, H-3); 7.92 (1H, s, H-7); 7.55 (2H, m, H arom); 7.60 (1H, s, H-10); 8.10 (1H, d, H-1)	$^3J_{CH_3CH_2}$ = 7.2, $^3J_{1,2}$ = 8.2, $^3J_{3,4}$ = 8.5, $^3J_{2,3}$ = 8.6, $^2J_{H,Ha}$ = 6.0, $^2J_{H,He}$ = 18.5
5i	1670 (C=O)	3.96 (3H, s, OCH_3); 3.98 (3H, s, OCH_3); 5.78 (1H, s, H-6*a*); 6.87 (1H, d, H-4); 6.96 (1H, s, H-7); 7.03 (1H, dd, H-3); 7.35 (12H, m, $(C_6H_5)_2$, H-2 ,10); 8.55 (1H, d, H-1)	$^3J_{4,3}$ = 7.8, $^3J_{2,1}$ = 8.0, $^3J_{2,3}$ = 7.5
5j	1690 (C=O)	0.40 and 1.10 (6H, two t, $(CH_3)_2$); 1.85 (2H, dq, H-2*a*); 2.12 (2H, dq, H-2*e*); 6.18 (1H, s, H-6*a*); 7.20 (1H, dd, H-2); 7.32 (1H, d, H-4); 7.36 (1H, dd, H-3); 7.70 (1H, d, H-7); 7.94 (1H, d, H-8); 8.00 (1H, s, H-10); 8.15 (1H, d, H-1)	$^3J_{CH_3CH_2}$ = 7.2, $^3J_{2,1}$ = 8.0, $^3J_{4,3}$ = 8.2, $^3J_{2,3}$ = 7.9, $^3J_{7,8}$ = 9.0, $^2J_{H,Ha}$ = 7.5, $^2J_{H,He}$ = 16.0
5k	1675 (C=O)	5.85 (1H, s, H-6*a*); 6.90 (1H, d, H-4); 7.04 (1H, dd, H-2); 7.16 (1H, dd, H-3); 7.50 (10H, m, $(C_6H_5)_2$); 7.68 (1H, d, H-7); 7.92 (1H, d, H-8); 8.05 (1H, s, H-10); 8.40 (1H, d, H-1)	$^3J_{2,1}$ = 8.5, $^3J_{3,4}$ = 9.0, $^3J_{2,3}$ = 8.2, $^3J_{7,8}$ = 9.5

* Solvent: $CDCl_3$ for compounds **3a-k, 5a,d-g,i** and DMSO-d_6 for compounds **5b,s,h,j,k**.

In the two successive heterocyclization reactions the first is closure of the oxazine ring and this is confirmed by the structure of the intermediate compound **6** obtained as 4,5-dimethoxy-2-(4,4-diphenyl-1,4-dihydro-2H-3,1-benzoxazin-2-yl)benzoic acid. It can be converted to the corresponding isoindolobenzoxazinone **5i** in almost quantitative yield by short heating in acetic acid (see Experimental).



4a R = H, **b** R = Et, **c** R = Ph; **5a–g** R^2 = H, **a** R = H, R^1 = NO_2; **b** R = H, R^1 = Cl; **c** R = H, R^1 = Br; **d** R = Et, R^1 = H; **e** R = Ph, R^1 = H; **f** R = Et, R^1 = NO_2; **g** R = Ph, R^1 = NO_2; **h** R = Et, R^1 = R^2 = OMe; **i** R = Ph, R^1 = R^2 = OMe; **j** R = Et, R^1 = Br, R^2 = H; **k** R = Ph, R^1 = Br, R^2 = H

On a qualitative level the results of the experimental studies showed that acceptor substituents in the formylbenzoic acids **1** (NO_2, Cl, Br) and donor substituents in the aminophenylcarbinol **4b** shortened the reaction time for the synthesis of compounds **5**. Thus the syntheses of isoindolobenzoxazinones **5a-d,f,j** were complete and in quite high yields after 30-45 min while in the preparation of compounds **5e,g-i,k** it was expedient to carry out the reaction at 45-50ºC for 1-1.5 h.

The isoindolobenzoxazinones of formula **5** are colorless crystals, the physicochemical parameters of which are reported in Table 1. The IR spectra of benzoxazinones **5**, as in the case of the spectra of compounds **3**, show an absorption stretching band for the lactam carbonyl at 1645-1700 cm^{-1} (Table 2). The molecules of compound **5** have one chiral center at the 6*a* atom and this results in the prochiral 5-CH_2 methylene hydrogen atoms in molecules **5a-c** becoming diastereotopic and resonating in the ^{1}H NMR spectra as a pair of doublets with a geminal constant of J = 14.8 to 15.2 Hz (Table 2). A similar situation occurs in molecules **5d,f,h,j** which have two prochiral methylene units in the ethyl substituents at the C(5) atom. The protons of these methylene units absorb as two doublets of quartets but with different geminal constants of about 6-8 and 16-18 Hz (Table 2).

An unambiguous confirmation of the structure of the isoindolobenzoxazines **5** was carried out by the X-ray analysis of a single crystal of compound **5k**. The projection of the steric model for this molecule is given in Fig. 2. The interatomic distances and valence angles are close to standard values.

The determination of the conformation of the oxazine ring was performed from the experimental values of six dihedral angles using the RICONF software package [17]. The folding parameters found were: S = 0.866, θ = 30.66º, and ψ (2) = 7.78º and according to data in [18] this would indicate a slightly distorted *chair* conformation. Its base at atoms C(1), N(1), C(9), C(14), and C(15) forms plane 1 (mean deviation of the atoms from the mean-square plane 1 is 0.0355 Å). The O(1) oxygen atom deviates from this plane by 0.6336 Å and, with atoms C(10) and C(15) forms the *chair* back which deviates from plane 1 by 127º. In its turn, the *chair* base plane deviates from the plane of benzene ring **A** by 3.7º.

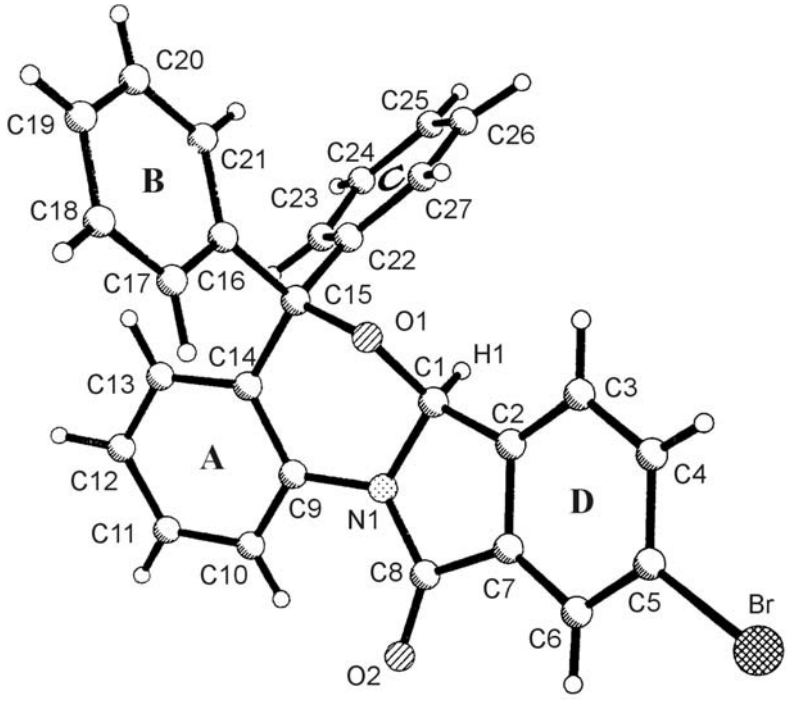
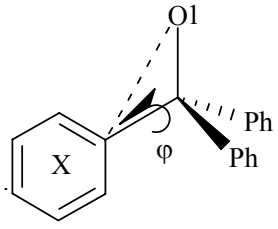


Fig. 2. Projection of the steric model for the molecule of 9-bromo-5,5-diphenyl-5H-isoindolo-[2,1-*a*][3,1]benzoxazin-11(6*a*H)-one (**5k**) from X-ray structural data and the atomic numbering (the number of the hydrogen atoms corresponds to the numbering of the carbon atoms).

In general, the isoindolone fragment in the molecule is not totally planar. The angle between the planes of the benzene ring **D** and the mean square plane of the lactam ring (average deviation of planar atoms 0.0193 Å) is 176.2º. None the less, if the isoindolone fragment is considered as a plane (plane 2, mean deviation of the atoms 0.0355 Å) the angle between planes 1 and 2 is 155.8º. Evidently such a powerful twist in the molecule along the C(1)–N(1) bond is due to the sp^3-hybridization of the C(1) atom.



X = **A**, **B** or **C**

Fig. 3. Twist of the phenyl substituent relative to the plane of the three atoms – oxazine oxygen, methine carbon, and the carbon atom of the phenyl substituent bonded to the methine carbon.

The mutual arrangement of the phenyl substituents **A**, **B**, and **C** at atom C(15) can be considered as a nonsymmetrical propeller in which each of the rings is turned to the same side relatively to the corresponding plane of three atoms O(1), C(15), and the aromatic ring added to the latter by the corresponding angles (Fig. 3): $\varphi_A = 29.5$, $\varphi_B = 54.6$, and $\varphi_C = 35.4$º.

As is evident, the aromatic ring **A** bound to atom C(15) (with a further three atom link) has the smallest rotation angle φ. Practically, the same nonsymmetrical propeller conformation occurs in triphenylmethane crystals [19] but, of course, with other phenyl substituent rotation angles.

In conclusion it should be noted that 2-formylbenzoic acids can be used as specific structural units for the construction of an isoindolone fragment in tandem heterocyclization reactions and in reactions with other N,O- N,N- and N,S-binucleophiles for synthesizing aza- and thiaaza heterocyclic systems and this will be revealed in subsequent publications.

EXPERIMENTAL

IR spectra were recorded in vaseline oil on a Specord IR-71 instrument. ^{1}H NMR spectra were taken on Bruker AC-200 (200 MHz), WM-250 (250 MHz), AM-300 (300 MHz), and DR-500 (500 MHz) instruments with TMS as internal standard. Mass spectra were recorded on a Varian CH-6 instrument using a direct introduction method of the sample into the ion source at a temperature of 50-180ºC and an electron ionization energy of 70 eV. TLC was carried out for compounds **5a-k** and **3a-k** on Silufol UV-254 plates in the systems benzene–acetone (4:1 and 2:1 respectively) and revealed using iodine vapor.

X-ray Study of Compounds 3b and 5k. Colorless monoclinic crystals of 2-bromo-8,10-dimethyl-10H-isoindolo[1,2-*b*][1,3]benzoxazin-12(4*b*H)-one (**3b**) were grown by crystallization from ethanol: a = 12.949(3), b = 8.438(2), c = 27.120(3) Å, α = γ = 90, β = 91.29(1)º, V = 2962(1) Å^3, d = 1.543 g/cm^3. Space group $P2(1)/c$, Z = 8. X-ray analysis was carried out on a CAD 4 circle automatic diffractometer (graphite monochromator, MoKα radiation, θ/2θ scanning 1.5 to θ_{max} = 22.98º). Crystal size 0.40×0.32×0.25 mm.

4112 Reflections with $I > 3\sigma(I)$ were obtained. The structure was solved by a direct method using the SHELXTL program package [20] and refined in the anisotropic approximation (isotropic for hydrogen atoms) to divergence factors of R = 0.0389 and wR = 0.0925. The atomic coordinates have been placed in the Cambridge Structural Database (reference CCDC 720446).

Colorless monoclinic crystals of 9-bromo-5,5-diphenyl-5H-isonidolo[2,1-*a*][3,1]benzoxazin-11(6*a*H)-one (**5k**) were grown by crystallization from ethanol: a = 11.805(2), b = 12.717(3), c = 14.603(3) Å, α = γ = 90, β = 107.61(3)º, V = 2089.5(7) Å^3, d = 1.489 g/cm^3. Space group $P2(1)/n$, Z = 4. X-ray analysis was carried out on the CAD 4 circle automatic diffractometer (graphite monochromator, MoKα radiation, θ/2θ scanning 1.95 to θ_{max} = 24.98º). Crystal size 0.24×0.16×0.15 mm. 3667 Reflections were obtained with $I > 3\sigma(I)$. The structure was solved by a direct method using the SHELXTL program package [20] and refined in the anisotropic approximation (isotropic for hydrogen atoms) to divergence factors of R = 0.0370 and wR = 0.0781. The atomic coordinates have been placed in the Cambridge structural database (reference CCDC 710445).

4,5-Dimethoxy-2-(4,4-diphenyl-1,4-dihydro-2H-3,1-benzoxazin-2-yl)benzoic Acid (6). 2-Formyl-4,5-dimethoxybenzoic acid (1.05 g, 5 mmol) was added to a solution of 2-aminophenyldiphenylcarbinol (**4c**) (1.38 g, 5 mmol) in glacial acetic acid (5 ml) cooled to 0ºC. The mixture was stirred with cooling (ice bath) for 30 min. The precipitate formed was filtered off and recrystallized from benzene to give compound **6** (1.63 g, 70%) with mp > 250ºC and R_f 0.20 (benzene–acetone, 4:1). IR spectrum, ν, cm^{-1}: 3560-3500 (COOH), 3370 (NH). ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: 3.81 (3H, s, OCH$_3$); 3.85 (1H, s, H-2); 3.90 (3H, s, OCH$_3$); 6.23 (1H, s, H-3'); 7.00 (15H, m, 14 H arom + NH); 7.60 (1H, s, H-6'); 12.60 (1H, br. s, COOH). Found, %: C 74.68; H 5.27; N 2.91. $C_{29}H_{25}NO_5$. Calculated, %: C 74.52; H 5.35; N 3.00.

8,9-Dimethoxy-5,5-diphenyl-5H-isoindolo[2,1-*a*][3,1]benzoxazin-11(6*a*H)-one (5i). A. A mixture of carbinol **4c** (1.38 g, 5 mmol) and 2-formyl-4,5-dimethoxybenzoic acid (1.05 g, 5 mmol) in glacial acetic acid (10 ml) was stirred at room temperature for 5-10 min, heated to 45-50ºC, and stirred for a further 1 h. At the end of the reaction (TLC monitoring) the precipitate formed was filtered and a further portion of precipitate was separated from the filtrate using an aqueous alcohol mixture (7:3). The precipitates were combined and recrystallized from an alcohol–benzene mixture (4:1). Yield 1.46 g (65%).

B. A solution of the amino acid **6** (2.34 g, 5 mmol) and glacial acetic acid (10 ml) was stirred for 30 min at a temperature not exceeding 50ºC. Separation was carried out as in procedure A. Yield 2.02 g (90%).

Benzoxazines 5e,g,h,k were prepared similarly (method A).

5,5-Diethyl-9-nitro-5H-isoindolo[2,1-*a*][3,1]benzoxazin-11(6*a*H)-one (5f). A mixture of the 2-aminophenyldiethylcarbinol **4b** (0.89 g, 5 mmol) and 2-formyl-5-nitrobenzoic acid (0.97 g, 5 mmol) in glacial acetic acid (10 ml) was stirred for 45 min at room temperature. At the end of the reaction (TLC monitoring) compound **5f** was precipitated from the reaction mixture by addition of an aqueous alcohol mixture (7:3). The precipitate was filtered off and recrystallized from an alcohol–benzene mixture (4:1). Yield 1.35 g (80%).

Benzoxazines 5a-d,j were prepared similarly.

2-chloro-8,10-dimethyl-10H-isoindolo[1,2-*b*][1,3]benzoxazin-12(4*b*H)-one (3c). A mixture of 2-(1-aminoethyl)-4-methylphenol **2b** (0.75 g, 5 mmol) and 5-chloro-2-formylbenzoic acid (0.76 g, 5 mmol) in absolute toluene (50 ml) and a catalytic amount of *p*-toluenesulfonic acid was refluxed for 1-3 h with azeotropic distillation of alcohol until the calculated amount had separated. Solvent was evaporated and the residue was purified by column chromatography on KSK silica gel (5-40 μm fraction) using benzene-petroleum ether (1: 4) as eluent. Yield 0.92 g (60%).

Compounds 3a-b,d-k were prepared similarly. The synthesis of the isoindolobenzoxazinones **3j-k** was carried out for 10-12 h.

2-Aminophenylcarbinols 4b,c were prepared by treating methyl anthranilate with the corresponding alkylmagnesium halides [1, 15].

2-(Aminoalkyl)phenols 2a-b,d-e (Table 3) were prepared using method [14].

The synthesis of the formylbenzoic acids **1** has been reported in [13].

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