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PREPARATION OF ISOINDOLO[2,1-*a*]QUINOXALINES BASED ON *N*-(2-AMINOPHENYL)ISOINDOLE DERIVATIVES

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A new method is proposed for the preparation of N-(2-aminophenyl)isoindoles by the reaction of o-(bromomethyl)benzophenones with 1,2-phenylenediamines. The reaction of N-(2-aminophenyl)isoindoles with Ac_2O leads to 1,N-diacetyl- or 1,N,N-triacetyl derivatives, whereas heating with formic acid or diethyl oxalate leads to cyclization with the formation of 11-arylisoindolo[2,1-a]quinoxaline derivatives. Salt formation in the 11-arylisoindolo[2,1-a]quin-oxaline series was studied.

Keywords: *N*-(2-aminophenyl)isoindole, *o*-(bromomethyl)benzophenone, isoindolo[2,1-*a*]quinoxaline, 1,2-phenylenediamine, acylation.

Polycyclic nitrogen-containing heterocyclic compounds with a flat structure are quite promising in the search for new chemotherapeutic medications [1]. Well-known antineoplastic chemotherapeutic medications characterized by flat polycyclic systems, such as anthracyclines, camptothecin, and amsacrine, are capable of inhibiting topoisomerases – enzymes that catalyze the transformation of one topological isomer of DNA to another. Here a triple complex, containing the drug, DNA, and the enzyme, is formed. Recent research into the biological activity of isoindolo[2,1-*a*]quinoxalines showed that these compounds have high cytotoxic activity against a wide range of human cancer cells and at the molecular level are inhibitors of tubulin polymerase and topoisomerase I. This confirms the prospects of using them as anticancer drugs [2, 3].

In all about 15 of isoindolo[2,1-*a*]quinoxaline derivatives have been described. Two methods have been used for construction of the heterosystem, i.e., building the isoindole onto the quinoxaline fragment [4, 5] or the quinoxaline onto the isoindole fragment [2, 3, 6]. In our opinion the second method [2, 3], which is based on the cyclization of *N*-(2-aminophenyl)isoindole derivatives, presents greater possibilities for functionalization of the system. However, the key compounds, 1-R-2-(2-aminophenyl)isoindoles of type **1**, are not readily obtainable, and methods for their synthesis are restricted to only two methods: reduction of isoindolo[2,1-*a*]benzimidazole derivatives [7, 8] and the Strecker reaction of 1,2-phenylenediamines with phthalaldehyde [2, 3, 9]. Convincing evidence for the structure of *N*-(2-aminophenyl)isoindole has only been presented in [2, 3, 9]. We are proposing another method for the preparation of *N*-(2-aminophenyl)isoindoles, involving the reaction of *o*-(bromomethyl)benzophenone derivatives **2** with 1,2-phenylenediamines.

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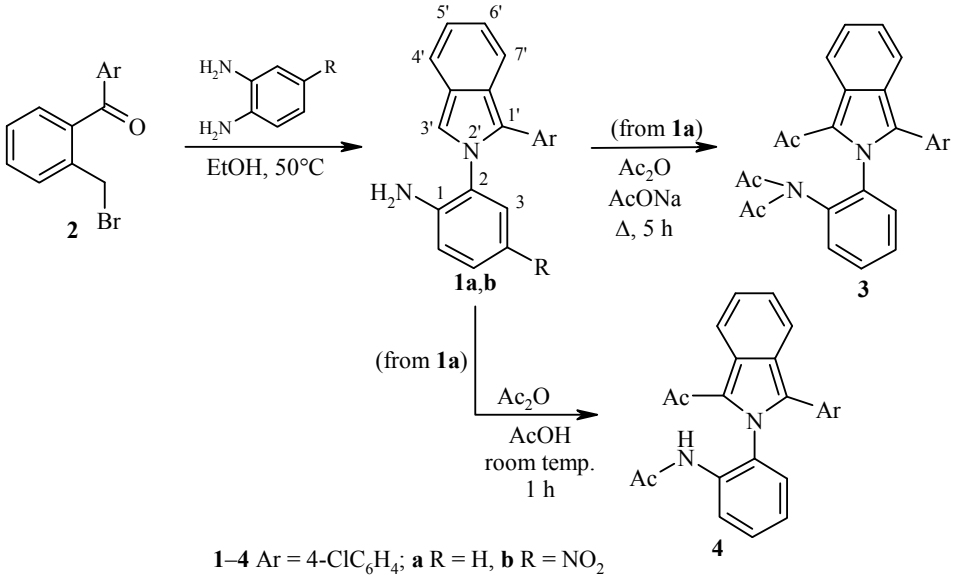
{2-[1-(4-Chlorophenyl)-2*H*-isoindol-2-yl]aryl}amines **1a**,**b** were obtained from [2-(bromomethyl)-phenyl](4-chlorophenyl)methanone (**2**) by reaction in ethanol at 50°C with a twofold excess of the amine under an inert atmosphere. The structure of the products was established on the basis of their spectral characteristics (^{1}H NMR, IR, UV), which agree with those of the 1,2-diarylisoindoles that we obtained earlier [10].



1–**4** Ar = 4-ClC$_6$H$_4$; **a** R = H, **b** R = NO$_2$

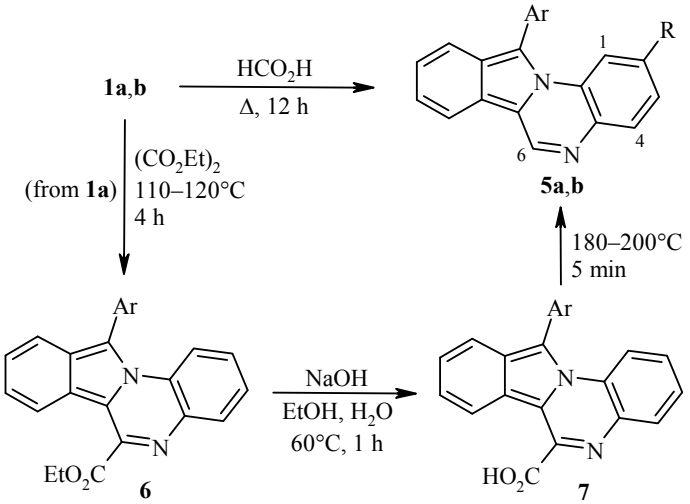
The formation of the *N*-(2-aminophenyl)isoindoles **1a**,**b** in the reaction is not an unambiguously predictable result. This reaction is unusual in that one of the amino groups is retained during the reaction of the dielectrophile with the dinucleophile (1,2-phenylenediamine). Usually all the reaction centers would react in such cases. For example, isoindolo[2,1-*a*]benzimidazole derivatives are formed in the reaction of 1,2-phenylenediamine with derivatives of phthalic acid, phthalaldehyde, *o*-acylbenzaldehyde, *o*-acylbenzoic acids, and *o*-halomethylbenzoic acid [11]. The same direction of reaction could also be expected in the case of the halide **2**, as occurs in the reactions of 1,2-phenylenediamine with α,β-unsaturated γ-halo ketones of the aliphatic series [12]. In practice, however, we observe similarity with the reaction of 1,2-phenylenediamine with γ-bromodypnone, when 2-(2,4-diphenyl-1*H*-pyrrol-1-yl)aniline is formed [13].

During a further study of the properties of compounds **1a**,**b** we started from known methods of building the pyrazine ring onto pyrrole, developed by Chessman and Tuck [14, 15] and used by us earlier in the synthesis of pyrrolo[1,2-*a*]quinoxaline derivatives [13]. Thus, with the aim of producing 6-methyl-isoindolo[2,1-*a*]quinoxaline, an attempt was made to synthesize the corresponding *N*-[(isoindolyl)-phenyl]acetamide by refluxing a solution of compound **1a** in Ac_2O in the presence of AcONa. In this case, however, acylation takes place not only at the amino group but also at the α-position of the isoindole fragment and leads to the triacyl derivative **3**, while in the absence of AcONa in reaction with Ac_2O in acetic acid at room temperature it leads to the diacyl derivative **4**. The position of the acetyl substituents in compound **4** is confirmed not only by the absence of a signal for the H-3' proton in the ^{1}H NMR spectrum (DMSO-d_6), but also by the presence of a broad signal for the protons of the NH group at 9.15 ppm, which exchange with D_2O. In the IR spectrum there are two narrow bands of medium intensity in the region of 3307 and 3287 cm^{-1}, the appearance of which results from amide-imide isomerism. This effect is also manifested by the broadening of the $\nu_{C=O}$ stretching vibration band of the acetamide group at 1623 cm^{-1}, while in the ^{1}H NMR spectrum it leads to a slight broadening of the signal for the methyl group protons of the NHAc substituent (singlet, 1.82 ppm in DMSO-d_6, 2.00 ppm in $CDCl_3$). In $CDCl_3$ solution the 2-phenyl and acetyl signal positions for the compound **4** are fixed in such conformation, where the effects of magnetically anisotropic groups are more pronounced. This leads to a shift of certain proton signals (H-3,6, CH_3 groups, the assignment of these signals was based on the

data from a ^1H–^1H COSY experiment) that do not agree fully with the change in the polarity of the solvent, compared to their position in the spectrum recorded in DMSO-d_6 solution. In the ^1H NMR spectrum (DMSO-d_6) of compound **3**, the greater steric hindrances to free rotation about the C–N single bonds lead to the appearance of two methyl proton signals of the NAc_2 group. The presence of an acetyl substituent at the α-position of the isoindole fragment of compounds **3** and **4** has yet another consequence – the appearance of atropisomers, which is typical for compounds of *N*-arylpyrrole type with bulky substituents in the *ortho* positions [16]. The 1-acetyl derivatives of 2-arylisoindole **3** and **4** also exist as mixtures of enantiomers. This is demonstrated by the data from the ^1H NMR spectrum of the sterically less crowded compound **3**, recorded in $CDCl_3$ solution in the presence of the optically active Eu(III) heptafluorobutyryloxymethylenecamphorate (Eu(HFBC)$_3$): splitting of the series of signals in a ratio of 1:1 is observed (the signals were not assigned).

In [3], the cyclization of the 1-cyano derivatives of *N*-(2-aminophenyl)isoindole was carried out by refluxing their solutions in acetic acid. It can be expected that the 1-acetyl derivatives will also be capable of cyclization under these conditions. In the case of compounds **3** and **4**, such a transformation must include a stage of hydrolysis of the acetamides. However, no appreciable changes in structure were observed when their solutions in acetic acid were refluxed (for more than 2 h), or heated in a solution of NaOH (10%). The desired result, i.e., intramolecular cyclization to derivatives of isoindolo[2,1-*a*]quinoxaline, was achieved under different conditions.

Thus, when solutions of compounds **1a**,**b** were refluxed in formic acid for 12 h, 11-(4-chlorophenyl)isoindolo[2,1-*a*]quinoxalines **5a**,**b** were obtained with yields of 81 and 61%. Heating of the compound **1a** mixture with an excess of diethyl oxalate leads to the 6-ethoxycarbonyl derivative **6**, which is readily transformed into the corresponding 6-carboxylic acid **7** upon hydrolysis in an aqueous-alcoholic solution of NaOH. The acid **7** proved unstable when heated above 180°C; it decomposed during an attempt to determine its melting point. The decarboxylation of the acid **7** with the formation of compound **5a** was achieved by heating for 5 min on an oil bath at 180-200°C. It was not possible to transform compound **1b** into an ester of type **6**, since its reaction with diethyl oxalate proceeded slower and was accompanied by the formation of a large amount of side products.



5–**7** Ar = 4-ClC_6H_4; **5 a** R = H, **b** R = NO_2

The structure of the isoindolo[2,1-*a*]quinoxalines **5-7** was established on the basis of data from chromato-mass spectroscopy and NMR spectroscopy. In the ^1H NMR spectra (DMSO-d_6) of compounds **5-7** there are doublets for the H-4,7 protons and singlets for the H-6 proton at $\delta > 8.0$ ppm (for compounds **5a**,**b**), the assignment of which was made according to the results of a NOE experiment. In the spectrum of the ester **6**, the signal of the H-7 proton is shifted upfield (at 8.06 ppm) in comparison with the corresponding signals for the unsubstituted derivatives **5a**,**b** and the acid **7** (8.41-8.55 ppm). We associate this effect with screening of the

H-7 proton by ethoxy group in the favoured conformation of the compound **6** in DMSO solution containing traces of water. This suggestion is supported by the NOE experiment data: during irradiation at the resonance frequency of the methylene group of the ethoxy fragment at 4.65 ppm the intensity of the aromatic proton doublet in the region of 8.07 ppm is increased, while from analysis of the compound **6** molecular model it follows that the H-7 proton is situated closest to the 6-CO_2Et substituent.

Final evidence for the structure of the reaction products **5-7** as derivatives of isoindolo[2,1-*a*]quinoxaline is provided by X-ray crystallographic analysis data for compound **5a** (Fig. 1). According to the obtained data, the tetracyclic fragment is planar within 0.009 Å. The aryl substituent in the molecule **5a** is twisted almost perpendicularly to the plane of the isoindoloquinoxaline fragment. (The dihedral angle N(12)–C(11)–C(13)–C(18) amounts to -86.1(1)°). Here a greatly shortened H(1A)···C(13) molecular contact of 2.47 Å is formed (sum of van der Waals radii 2.87 Å [17]). Since the hydrogen atom is directed towards the phenyl π-system of the aryl substituent, it can be assumed that this interaction is an intramolecular C–H···π hydrogen bond (the angle C(1)–H(1A)···C(13) is 128°). The hydrogen atom of the C(10)–H(10A) bond is similarly placed. However, the H(10A)···C(13) distance is much greater (3.00 Å), and the C(10)–H(10A)···C(13) angle is practically straight (94°), which precludes the interpretation of this interaction as a C–H···π hydrogen bond.

Quantum-chemical calculations [18] of the compound **5a** molecule by the M06-2X/6-311G(d,p) method indicated that the tetracyclic fragment in the crystal is planar due to intermolecular interactions. An isolated molecule is slightly twisted, and the angle between the terminal benzene rings is 12°. The rotation angle of the aryl substituent (54°) is slightly smaller than in a crystal. Here, however, the shortened intramolecular contact C(1)–H(1A)···C(13) of 2.43 Å is still retained. Analysis of the electron density distribution in terms of the Bader "atoms in molecules" theory [19] showed the presence of a critical point for the bond between the H(1A) and C(13) atoms, indicating the formation of a C–H···π hydrogen bond. At the same time, there is no critical point between the H(10A) atom and the carbon atoms of the aromatic ring, which confirms the idea about the absence of a second C–H···π hydrogen bond involving the given hydrogen atom.

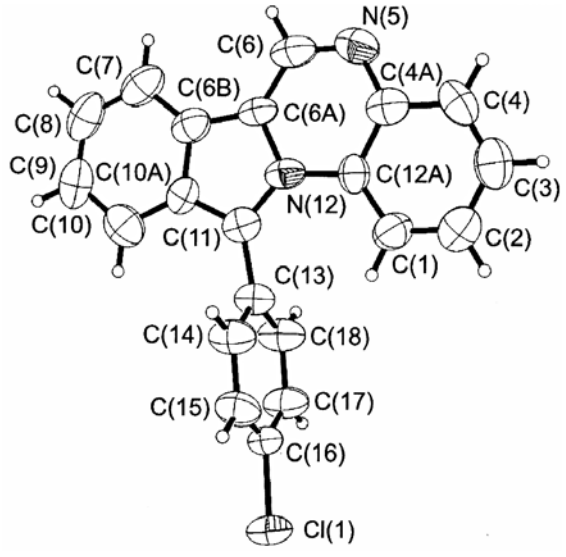
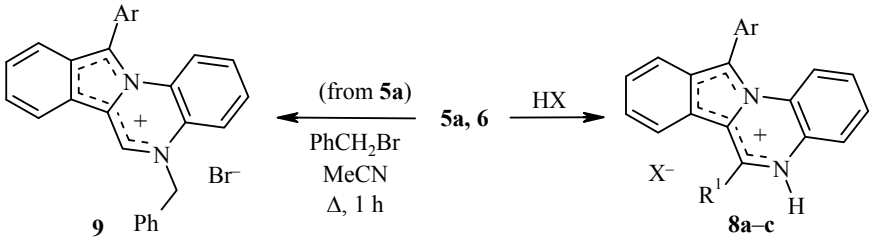


Fig. 1. The molecular structure of compound **5a** with the atoms represented by thermal vibration ellipsoids with 50% probability.

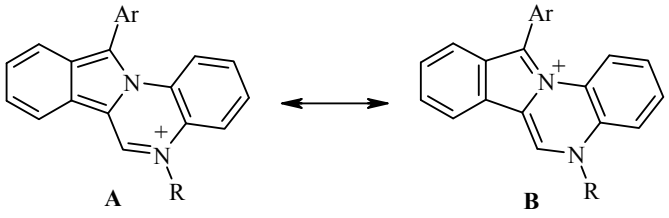
Compounds **5-7** are moderately soluble in polar solvents. Their solubility is higher in the presence of strong acids (HBr, HCl, trifluoroacetic acid (TFA)) due to the formation of protonated salts [6]. In the UV spectra of compounds **5a**, **6**, recorded in MeOH in the presence of hydrochloric acid, a bathochromic shift of the long-wave absorption maximum is observed (406 and 404 in MeOH, 437 and 472 nm in MeOH/HCl, respectively).

We isolated isoindoloquinoxaline bromide **8a** in the individual state, and by heating compound **5a** with benzyl bromide in acetonitrile we isolated a quaternary salt, the 5-benzyl derivative bromide **9**. By analysis of the ^{1}H and ^{13}C NMR spectra of compounds **5a**, **6**, and **9**, recorded in CF_3CO_2D solution, it was possible to reach certain conclusions concerning the structure of the isoindolo[2,1-*a*]quinoxalinium cation. An accurate assignment of the proton and carbon signals for the protonated salts, formed during dissolution of compounds **5a**, **6** in TFA (salts **8b**,**c**), and of compound **9** was made on the basis of COSY, NOESY, HMQC, and HMBC homo- and heteronuclear experiments.



8a–c, **9** Ar = 4-ClC_6H_4; **8 a** R^1 = H, X = Br; **b** R^1 = H, X = CF_3CO_2; **c** R^1 = CO_2Et, X = CF_3CO_2

It is difficult to reach a conclusion about the nature of the electron density distribution for the salts **8a-c** and **9** on the basis of existing data. To describe their structure in this case it is advantageous to consider their limiting resonance structures **A** and **B**, corresponding to the two tautomeric forms of isoindole – the *ortho*-quinoid structure and the isoindoline [20, 21]. In the studies [6, 22] such salts were assigned structures corresponding to the resonance structure **A**. However, in the ^{13}C NMR spectra (CF_3CO_2D) of the salts **8b**,**c**, **9** the signal of the carbon C-11 is observed in the downfield region (146.4-150.7 ppm) in comparison to that predicted for the structure **A**. The position of signals for C-6,6a,6b (upfield at 127-137 ppm) in relation to C-11 (in the most downfield region) also agrees with theoretical predictions for the spectrum of the corresponding structure **B**.



We obtained further evidence for the larger contribution from structure **B** for salts of the **8a-c**, **9** type during analysis of X-ray crystallographic analysis data (Fig. 2) for the previously obtained protonated isoindolo[2,1-*a*]quinoxalinium salt **10** [6], the uncondensed isoindole derivatives having *ortho*-quinoid structures (compound **11**) [10] or an isoindoline structure (compound **12**) [23], and the compound **5a** that we synthesized.

The bond length values in the pyrrole rings of the molecules of compounds **5a**, **10-12** indicate a substantial contribution from the resonance structure **B** to the electron density distribution in the cations of the isoindolo[2,1-*a*]quinoxalinium salts. Thus, whereas the lengths of the pyrrole ring C–N bonds in the molecules of compounds **5a** and **11** are close to the values typical of a C=N multiple bond in the aromatic system of pyrrole (1.38 Å [24]), in the molecules of compounds **10** and **12** one of the bonds corresponds in length to a C–N single bond (1.43-1.48 Å [24]), while the other corresponds to a C=N double bond (≤1.33 Å [24]). The increase in the C(4a)–N(5) and N(5)–C(6) bond lengths in the pyrazine ring in transition from the base **5a** to the salt **10**

also confirms our suggestion about the nature of electron density distribution changes in the isoindoloquinoxalinium cations.

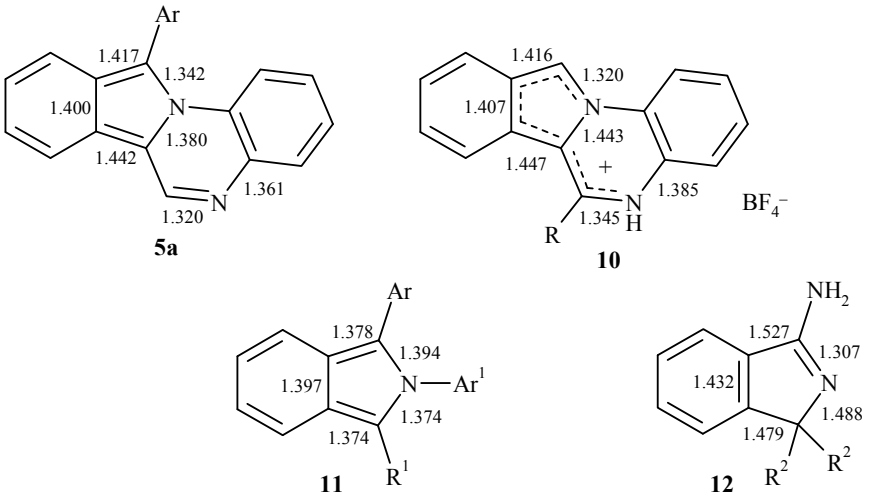


Fig. 2. The bond lengths in the molecules of 11-(4-chlorophenyl)isoindolo[2,1-*a*]quinoxaline (**5a**), 6-(5-methyl-2-furyl)isoindolo[2,1-*a*]quinoxalin-5-ium tetrafluoroborate (**10**), 3-[3-(4-chlorophenyl)-2-(4-fluorophenyl)-2*H*-isoindol-1-yl]-1-phenylpyrrolidine-2,5-dione (**11**), and 3,3'-(3-amino-1*H*-isoindol-1,1-diyl)bis(1-methylpyrrolidine-2,5-dione) (**12**). The data from X-ray crystallographic analysis were obtained from the Cambridge Structural Database (except for the synthesized compound **5a**). Deposit numbers: CCDC 138680 (compound **10**), CCDC 821341 (compound **11)**, CCDC 736675 (compound **12**).

Thus, the reaction of *o*-(bromomethyl)benzophenones with 1,2-phenylenediamines leads to the formation of *N*-(2-aminophenyl)isoindole derivatives – key compounds for further construction of condensed systems with an isoindole ring. When heated with formic acid or diethyl oxalate, the 1-aryl-2-(2-aminophenyl)isoindoles gave 11-arylisoindolo[2,1-*a*]quinoxaline derivatives, which are easily protonated and alkylated at the N(5) nitrogen atom with the formation of quaternary salts. The spectral and X-ray structural data of the isoindolo[2,1-*a*]quinoxalinium salts indicate that the greater contribution to the electron density distribution in them comes from the resonance structure corresponding to the isoindoline tautomer.

EXPERIMENTAL

The IR spectra were recorded in pellets with KBr on a Perkin Elmer Spectrum BX instrument. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance RX 500 instrument (500 and 125 MHz, respectively). The two-dimensional correlation spectroscopy experiments were carried out on a Varian Mercury 400 instrument (400 MHz for ^{1}H nuclei, 100 MHz for ^{13}C nuclei) with TMS as internal standard. The UV spectra were obtained in methanol on a Lambda 20 UV/VIS spectrometer. The elemental analyses were performed on a Vario MICRO Cube CHNS analyzer. The melting points were determined in a Thiele tube. The purity of the obtained compounds was monitored by HPLC mass spectroscopy on an Agilent 1100 Series instrument with an Agilent LC/MSDSL selective detector (gradient elution: phase A – H_2O + 0.1% HCO_2H, phase B – MeCN + 0.1% HCO_2H; ionization method – APCI, 400 V). [2-(Bromomethyl)phenyl](4-chlorophenyl)methanone (**2**) was obtained according to the procedure in [25].

2-[1-(4-Chlorophenyl)-2*H*-isoindol-2-yl]aniline (1a). [2-(Bromomethyl)phenyl](4-chlorophenyl)-methanone (**2**) (2.00 g, 6.46 mmol) was added to a solution of *o*-phenylenediamine (1.40 g, 12.92 mmol) in EtOH (30 ml). The reaction mixture was stirred at 50°C for 30 min and cooled to room temperature. After 30 min the precipitate was filtered off. Yield 1.76 g (85%); mp 187-189°C (PhMe–hexane, 1:1). IR spectrum, ν,

cm^{-1}: 3466 (NH_2), 3373 (NH_2), 3034, 1616, 1505, 1496, 1466, 1343, 1311, 1087, 826, 747. ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.62-7.61 (2H, m, H-4',7'); 7.38 (1H, s, H-3'); 7.32-7.31 (4H, m, H-2",3",5",6"); 7.13 (1H, t, ^3J = 8.0, H-5); 6.97-6.96 (3H, m, H-3,5',6'); 6.80 (1H, d, ^3J = 8.0, H-6); 6.58 (1H, t, ^3J = 8.0, H-4); 4.85 (2H, br. s, NH_2). UV spectrum, λ_{max}, nm (log ε): 246 (4.46), 286 (4.02), 304 (3.88), 354 (3.91). Found, %: C 75.23; H 4.79; N 8.83. $C_{20}H_{15}ClN_2$. Calculated, %: C 75.35; H 4.74; N 8.79.

2-[1-(4-Chlorophenyl)-2*H*-isoindol-2-yl]-4-nitroaniline (1b). A mixture of [2-(bromomethyl)phenyl]-(4-chlorophenyl)methanone (**2**) (2.00 g, 6.46 mmol) and 4-nitro-1,2-phenylenediamine (1.98 g, 12.92 mmol) in EtOH (20 ml) was stirred at 50°C for 3 h under an argon atmosphere. The precipitate was filtered off and washed with hexane. Yield 1.23 g (52%); mp 202-205°C (PhMe–hexane, 1:1). IR spectrum, ν, cm^{-1}: 3463 (NH_2), 3354 (NH_2), 1623, 1517 (NO_2), 1491, 1308 (br.), 835, 747. ^1H NMR spectrum (DMSO-d_6 + CCl_4), δ, ppm (*J*, Hz): 8.03 (1H, dd, ^3J = 9.2, ^4J = 2.4, H-5); 7.90 (1H, d, ^4J = 2.4, H-3); 7.59-7.58 (2H, m, H-4',7'); 7.46 (1H, s, H-3'); 7.33-7.32 (4H, m, H-2",3",5",6"); 6.98-6.99 (2H, m, H-5',6'); 6.81 (1H, d, ^3J = 9.2, H-6); 6.48 (2H, br. s, NH_2). UV spectrum, λ_{max}, nm (log ε): 244 (4.34), 356 (3.98). Found, %: C 65.96; H 3.82; N 11.49. $C_{20}H_{14}ClN_3O_2$. Calculated, %: C 66.03; H 3.88; N 11.55.

***N*-Acetyl-*N*-{2-[1-acetyl-3-(4-chlorophenyl)-2*H*-isoindol-2-yl]phenyl}acetamide (3).** AcONa (0.20 g, 2.4 mmol) was added to a solution of compound **1a** (0.32 g, 1.0 mmol) in Ac_2O (5 ml). The mixture was refluxed for 5 h. The excess of Ac_2O was evaporated under vacuum, and water (10 ml) was added to the residue. The precipitate was filtered off, washed with water and with 2-PrOH, and crystallized. Yield 0.18 g (40%); mp 220-221°C (DMF–EtOH, 1:1). IR spectrum, ν, cm^{-1}: 3044, 1711 (C=O), 1700 (C=O), 1620, 1610, 1499, 1401, 1362, 1179, 1013, 763. ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.11 (1H, d, ^3J = 9.2, H-7'); 7.87-7.86 (1H, m, H-6); 7.70-7.30 (9H, m, H Ar); 7.18 (1H, t, ^3J = 7.6, H-4); 2.32 (3H, s, 1'-$COCH_3$); 1.86 (3H, s, $NCOCH_3$); 1.38 (3H, s, $NCOCH_3$). Found, %: C 70.07; H 4.81; N 6.37. $C_{26}H_{21}ClN_2O_3$. Calculated, %: C 70.19; H 4.76; N 6.30.

***N*-{2-[1-Acetyl-3-(4-chlorophenyl)-2*H*-isoindol-2-yl]phenyl}acetamide (4).** Ac_2O (0.50 ml, 5.3 mmol) was added to a mixture of compound **1a** (0.32 g, 1.0 mmol) in AcOH (5 ml). The mixture was stirred at room temperature for 1 h. With cooling on an ice bath, H_2O (25 ml) was added to the mixture. After 30 min, the precipitate was filtered off and crystallized from EtOH. Yield 0.21 g (52%); mp 189-190°C (EtOH). IR spectrum, ν, cm^{-1}: 3287, 3307 (NH), 1703 (C=O), 1623 (C=O), 1527, 1450, 1408, 1331, 1297, 750. ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.15 (1H, br. s, NH); 8.20 (1H, d, ^3J = 7.6, H-7'); 7.81-7.80 (1H, m, H-6); 7.58 (1H, d, ^3J = 7.6, H-4'); 7.45-7.05 (9H, m, H Ar); 2.22 (3H, s, 1'-$COCH_3$); 1.82 (3H, s, $NCOCH_3$). ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.06 (1H, d, ^3J = 8.0, H-7'); 8.00 (1H, d, ^3J = 7.0, H-6); 7.71 (1H, d, ^3J = 8.0, H-4'); 7.47 (1H, t, ^3J = 8.0, H-6'); 7.39 (1H, t, ^3J = 7.5, H-5); 7.36 (1H, br. s, NH); 7.29-7.22 (3H, m, H-5',3",5"); 7.17 (2H, d, ^3J = 8.0, H-2",6"); 7.00 (1H, t, ^3J = 7.0, H-4); 6.76 (1H, d, ^3J = 7.0, H-3); 2.65 (3H, s, 1'-$COCH_3$); 2.00 (3H, s, $NCOCH_3$). Found, %: C 71.68; H 4.84; N 7.04. $C_{24}H_{19}ClN_2O_2$. Calculated, %: C 71.55; H 4.75; N 6.95.

11-(4-Chlorophenyl)isoindolo[2,1-*a*]quinoxaline (5a). A. Compound **1a** (0.5 g, 1.57 mmol) was dissolved with heating in HCOOH (10 ml). The mixture was refluxed for 12 h, the excess of the acid was evaporated, and the residue was crystallized from $MeNO_2$. Yield 0.42 g (81%); mp 237-238°C. IR spectrum, ν, cm^{-1}: 3044, 1577, 1459, 1320, 1219, 1087, 1013, 763, 740. ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.58 (1H, s, H-6); 8.46 (1H, d, ^3J = 8.0, H-7); 8.02 (1H, d, ^3J = 8.0, H-4); 7.73-7.71 (4H, m, H-2',3',5',6'); 7.60-7.36 (6H, m, H-1,2,3,8,9,10). When CF_3CO_2D was used as solvent for the NMR spectra, the spectra of the protonated form (**8b**) of the quinoxaline **5a** were obtained. **Compound 8b**. ^1H NMR spectrum (400 MHz, CF_3CO_2D), δ, ppm (*J*, Hz): 9.09 (1H, d, ^3J = 8.0, H-7); 7.92-7.91 (2H, m, H-4,8); 7.85 (1H, d, ^3J = 8.0, H-10); 7.81 (1H, d, ^3J = 8.8, H-1); 7.79-7.71 (4H, m, H-3,9,3',5'); 7.67 (2H, d, ^3J = 7.0, H-2',6'); 7.47 (1H, t, ^3J = 8.0, H-2). ^{13}C NMR spectrum (CF_3CO_2D), δ, ppm: 146.7 (C-11); 145.8 (C-4'); 138.3 (C-10a); 138.2 (C-8); 137.6 (2C, C-2',6'); 137.4 (2C, C-3',5'); 137.0 (C-3); 136.6 (C-6); 136.0 (C-9); 135.8 (C-6b); 135.2 (C-2); 134.7 (C-4a); 134.2 (C-1'); 132.6 (C-12a); 128.7 (C-10); 127.6 (C-4); 127.3 (C-6a); 126.5 (C-1); 125.2 (C-7). UV

spectrum (MeOH), λ_{max}, nm (log ε): 258 (5.32), 292 (5.04), 306 (4.94), 406 (5.04). UV spectrum (MeOH/HCl), λ_{max}, nm (log ε): 262 (5.35), 300 (5.06), 368 (4.71), 437 (5.14). Mass spectrum, *m*/*z* (I_{rel}, %): 329 $[M+H]^+$ (100), 331 $[M+H]^+$ (30). Found, %: C 76.84; H 4.06; N 8.41. $C_{21}H_{13}ClN_2$. Calculated, %: C 76.71; H 3.99; N 8.52.

B. Isoindolo[2,1-*a*]quinoxaline-6-carboxylic acid **7** (0.37 g, 1.0 mmol) was placed in a test tube of heat-resistant glass. With vigorous stirring, the mixture was heated on an oil bath at 180-200°C for 5 min. After cooling, the melt was dissolved in $MeNO_2$ with heating. The precipitate that separated after the solution had cooled was filtered off and washed with $MeNO_2$. Yield 0.16 g (50%). The physicochemical and spectral characteristics of the reaction product agreed with the data given for compound **5a** that was produced by method **A**.

11-(4-Chlorophenyl)-2-nitroisoindolo[2,1-*a*]quinoxaline (5b). The compound was obtained similarly to compound **5a** from compound **1b** (0.5 g, 1.37 mmol) and HCOOH (10 ml). Yield 0.31 g (61%); mp >300°C (DMF). IR spectrum, ν, cm^{-1}: 3121, 3059, 1592, 1517 (NO_2), 1468, 1339 (NO_2), 1323, 1305, 1217, 1197, 1145, 843, 729. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.73 (1H, s, H-6); 8.55 (1H, d, ^3J = 8.4, H-7); 8.50 (1H, d, ^4J = 2.4, H-1); 8.36 (1H, dd, ^3J = 9.2, ^4J = 2.4, H-3); 8.14 (1H, d, ^3J = 9.2, H-4); 7.81-7.79 (4H, m, H-2',3',5',6'); 7.67 (1H, d, ^3J = 8.0, H-10); 7.61 (1H, t, ^3J = 7.5, H-8); 7.52 (1H, t, ^3J = 7.5, H-9). UV spectrum, λ_{max}, nm (log ε): 209 (5.12), 252 (5.55), 277 (5.31), 309 (5.00), 403 (5.02). Mass spectrum, *m*/*z* (I_{rel}, %): 374 $[M+H]^+$ (100), 376 $[M+H]^+$ (30). Found, %: C 67.42; H 3.19; N 11.41. $C_{21}H_{12}ClN_3O_2$. Calculated, %: C 67.48; H 3.24; N 11.24.

Ethyl 11-(4-Chlorophenyl)isoindolo[2,1-*a*]quinoxaline-6-carboxylate (6). A mixture of compound **1a** (0.64 g, 2.0 mmol) and diethyl oxalate (1.20 g, 8.2 mmol) was heated on an oil bath at 110-120°C for 4 h. The reaction mixture was left at room temperature for 24 h, the precipitate was filtered off and washed with $MeNO_2$. Yield 0.41 g (51%); mp 186-187°C. IR spectrum, ν, cm^{-1}: 3070, 2982, 1726 (C=O), 1455, 1305, 1246, 1207 (C–O), 1088, 1016, 765, 739. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.07 (1H, d, ^3J = 8.0, H-7); 8.01 (1H, d, ^3J = 7.5, H-4); 7.71-7.89 (4H, m, H-2',3',5',6'); 7.56-7.34 (6H, m, H-1,2,3,8,9,10); 4.65 (2H, q, ^3J = 7.2, C<u>H</u>$_2$CH$_3$); 1.45 (3H, t, ^3J = 7.2, CH$_2$C<u>H</u>$_3$). When CF_3CO_2D was used as solvent for the NMR spectra the spectra of the protonated form (**8c**) of the quinoxaline **6** were obtained. **Compound (8c)**. ^{1}H NMR spectrum (400 MHz, CF_3CO_2D), δ, ppm (*J*, Hz): 9.14 (1H, d, ^3J = 8.0, H-7); 8.15-8.14 (2H, m, H-4,8); 8.06 (1H, d, ^3J = 7.5, H-10); 8.00 (1H, t, ^3J = 7.5, H-9); 7.91-7.90 (3H, m, H-3,3',5'); 7.83 (1H, d, ^3J = 9.0, H-1); 7.79 (2H, d, ^3J = 7.0, H-2',6'); 7.59 (1H, t, ^3J = 7.5, H-2); 5.05 (2H, q, ^3J = 7.0, C<u>H</u>$_2$CH$_3$); 1.80 (3H, t, ^3J = 7.0, CH$_2$C<u>H</u>$_3$). ^{13}C NMR spectrum (CF_3CO_2D), δ, ppm: 167.7 (C=O); 150.7 (C-11); 146.5 (C-4'); 139.7 (C-10a); 139.3 (C-8); 137.9 (C-6); 137.8 (C-3); 137.7 (2C, C-2',6'); 137.4 (2C, C-3',5'); 137.2 (C-9); 135.2 (C-2); 134.5 (C-6b); 134.1 (C-4a); 133.8 (C-1'); 131.7 (C-12a); 130.9 (C-7); 129.6 (C-10); 128.3 (C-6a); 127.8 (C-4); 126.9 (C-1); 73.6 (CH_2); 19.7 (CH_3). UV spectrum (MeOH), λ_{max}, nm (log ε): 209 (5.12), 252 (5.55), 277 (5.31), 310 (5.00), 404 (5.02). UV spectrum (MeOH/HCl), λ_{max}, nm (log ε): 280 (5.38), 320 (4.97), 472 (5.10). Mass spectrum, *m*/*z* (I_{rel}, %): 401 $[M+H]^+$ (100), 403 $[M+H]^+$ (30). Found, %: C 72.24; H 4.31; N 7.09. $C_{24}H_{17}ClN_2O_2$. Calculated, %: C 71.91; H 4.27; N 6.99.

11-(4-Chlorophenyl)isoindolo[2,1-*a*]quinoxaline-6-carboxylic Acid (7). NaOH (0.16 g, 4.0 mmol) was added to a solution of compound **6** (0.37 g, 1.0 mmol) in 50% EtOH (20 ml). The reaction mixture was heated at 60°C for 1 h, and the EtOH was distilled under vacuum. The solution was cooled and acidified with 1 M HCl. The precipitate was filtered off and washed with water. Yield 0.27 g (82%); mp >180°C (decomp., H_2O). IR spectrum, ν, cm^{-1}: 3439 (O–H), 3050, 2849, 1652 (C=O), 1613, 1598, 1528, 1448, 1407, 1356, 1212, 1088, 754. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.41 (1H, d, ^3J = 8.8, H-7); 8.07 (1H, d, ^3J = 8.0, H-4); 7.77-7.75 (4H, m, H-2',3',5',6'); 7.64-7.45 (6H, m, H-1,2,3,8,9,10). Found, %: C 70.81; H 3.56; N 7.58. $C_{22}H_{13}ClN_2O_2$. Calculated, %: C 70.88; H 3.51; N 7.51.

11-(4-Chlorophenyl)-5*H*-isoindolo[2,1-*a*]quinoxalin-12-ium Bromide (8a). Conc. HBr (1 ml) was added to a suspension of isoindolo[2,1-*a*]quinoxaline **5a** (0.33 g, 1.0 mmol) in MeCN (15 ml), and the mixture was heated until the isoindoloquinoxaline had completely dissolved. After cooling, the precipitate was filtered off and washed with EtOH. Yield 0.37 g (90%); mp >300°C (decomp., MeCN). IR spectrum, ν, cm^{-1}: 3426

(NH), 3044, 2579, 1641 (C=N$^+$), 1540, 1483, 1450, 1323, 763. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm (*J*, Hz): 10.27 (1H, s, H-6); 8.79 (1H, d, ^3J = 8.0, H-7); 8.22 (1H, d, ^3J = 8.0, H-4); 7.87-7.76 (7H, m, H Ar); 7.72-7.64 (2H, m, H Ar); 7.48 (1H, t, ^3J = 8.0, H-2). Mass spectrum, *m*/*z* (I_{rel}, %): 419 [M-Br]$^+$ (100), 421 [M-Br]$^+$ (30). Found, %: C 61.51; H 3.46; N 6.83. $C_{21}H_{14}BrClN_2$. Calculated, %: C 61.56; H 3.44; N 6.84.

5-Benzyl-11-(4-chlorophenyl)-5*H*-isoindolo[2,1-*a*]quinoxalin-12-ium Bromide (9). A mixture of isoindolo[2,1-*a*]quinoxaline **5a** (0.33 g, 1.0 mmol) and benzyl bromide (0.34 g, 2.0 mmol) in MeCN (15 ml) was refluxed for 1 h. After cooling, the precipitate was filtered off, washed with acetone, and crystallized from $MeNO_2$. Yield 0.38 g (85%); mp >300°C (decomp.). IR spectrum, ν, cm^{-1}: 3044, 2915, 1651, 1607, 1411, 1328, 1228, 1088, 763, 755. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm (*J*, Hz): 10.65 (1H, s, H-6); 8.70 (1H, d, ^3J = 8.0, H-7); 8.16 (1H, d, ^3J = 8.0, H-4); 7.96-7.70 (9H, m, H Ar); 7.56-7.54 (3H, m, H Ar); 7.43-7.30 (3H, m, H Ar); 6.09 (2H, s, NCH_2). ^{1}H NMR spectrum (CF_3CO_2D), δ, ppm (*J*, Hz): 9.34 (1H, s, H-6); 8.43 (1H, d, ^3J = 6.0, H-7); 8.05 (1H, d, ^3J = 7.0, H-4); 7.96-7.95 (2H, m, H-1,8); 7.89 (1H, d, ^3J = 7.0, H-10); 7.80-7.79 (3H, m, H-9,3',5'); 7.73-7.72 (3H, m, H-3,2',6'); 7.49-7.47 (6H, m, H-2, H Ph); 5.92 (2H, s, NCH_2). ^{13}C NMR spectrum (CF_3CO_2D), δ, ppm: 146.4 (C-11); 145.7 (C-4'); 140.9 (C-4"); 139.3 (C-4a); 138.2 (C-10a); 138.0 (C-8); 137.5 (2C, C-2',6'); 137.3 (2C, C-3',5'); 136.7 (C-3); 136.5 (2C, C-3",5"); 136.4 (C-6); 136.0 (C-9); 135.9 (C-1"); 135.6 (C-6b); 135.1 (C-2); 134.1 (C-1'); 133.9 (2C, C-2",6"); 133.4 (C-12a); 128.6 (C-10); 127.0 (2C, C-4,6a); 126.2 (C-1); 125.3 (C-7); 65.7 (CH_2). UV spectrum, λ_{max}, nm (log ε): 264 (5.23), 308 (4.98), 370 (4.73), 452 (5.34). Found, %: C 67.41; H 3.99; N 5.58. $C_{28}H_{20}BrClN_2$. Calculated, %: C 67.28; H 4.03; N 5.60.

X-Ray Crystallographic Investigation of Compound 5a. The crystals of compound **5a** are monoclinic, $C_{21}H_{13}ClN_2$, at 293 K: *a* 13.6687(9), *b* 12.7536(8), *c* 9.2145(6) Å; β 92.996(6)°; *V* 1604.12(18) Å^3; *Z* 4; space group $P2_{(1)}/c$; d_{calc} 1.361 mg/cm^3; μ(MoKα) 0.241 mm^{-1}; *F*(000) 680. The unit cell parameters and the intensities of 12039 reflections (2985 independent, R_{int} 0.049) were measured on an Xcalibur 3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω scanning, $2\theta_{max}$ 52°). The structure was solved by the direct method with SHELXTL software [26]. The positions of the hydrogen atoms were revealed from an electron density difference synthesis and refined by the "rider" model with $U_{iso} = 1.2U_{eq}$ for a non-hydrogen atom attached to a given hydrogen. The structure was refined by an F^2 full-matrix least-squares treatment for 2985 reflections in anisotropic approximation for the non-hydrogen atoms to wR_2 0.2180 (R_1 0.0775 in 2096 reflections with $I > 2\sigma(I)$, *GOOF* 1.035). The full crystallographic information was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 851257).

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