Tetrahedron 66 (2010) 508–512

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The Curtin–Hammett principle in action: 1-amino-3*H*-isoindole in cycloaddition reactions

Igor V. Levkov [a], Oleksandr V. Turov [a], Oleg V. Shishkin [b], Svetlana V. Shishkina [b], Zoia V. Voitenko [a,*]

[a] *Kiev National Taras Shevchenko University, 64 Str Volodymyrska, 01033 Kiev, Ukraine*
[b] *STC 'Institute for Single Crystals' NASU, 60 Lenina ave, 61001 Kharkiv, Ukraine*

ARTICLE INFO

Article history:
Received 18 August 2009
Received in revised form
21 October 2009
Accepted 5 November 2009
Available online 15 November 2009

ABSTRACT

Based on the spectral studies of 1-aminoisoindole we have observed that in solution the isoindolenine tautomer predominates. In spite of this fact but, taking into account the Curtin–Hammett principle, we undertaken the first study of the Diels–Alder reaction for 1-aminoisoindole as a typical representative of simple isoindoles in isoindoline form. We have studied the interaction of 1-aminoisoindole with maleimide derivates and demonstrated that the products are rearranged 1:2 composition adducts. We have proposed a rearrangement mechanism, detected and identified the intermediate Diels–Alder products containing both *endo*- and *exo* adducts.

1. Introduction

Isoindoles are promising active biological materials[1,2] with interesting spectral properties and are the subject of study for important theoretical questions, such as: aromaticity, tautomerism[3–8] and represent the important source of the reactive compounds and synthons used for cycloaddition reactions,[9–14] the study of the organic reactions mechanisms, new rearrangements[15–21] and the creation of new colouring agents.[22–24]

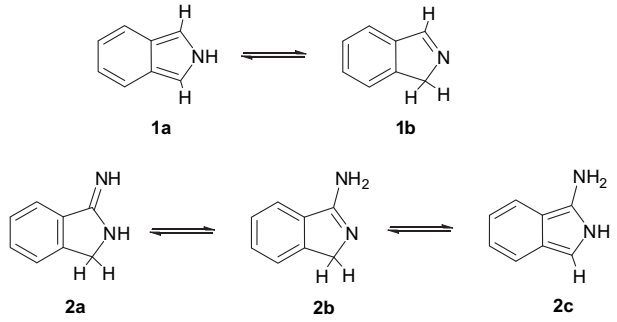
The most typical reaction for simple isoindole systems is the Diels–Alder reaction but previously this reaction was associated only with isoindoles prevalently in the isoindole tautomeric form.

Our previous researches in the chemistry of the simple isoindoles[9] have shown that the main products in the reaction with maleimide derivates are the Diels–Alder adducts. In some cases the rearrangement with the formation of naphthalene derivate is possible. For condensed azolo and azinoisoindoles[21] have been found three types of rearrangements, that are uncharacteristic for the simple isoindoles. In order to study these features we have chosen 1-aminoisoindole as the object of our researches. It is the basic elementary structural fragment, that enters into the structure of condensed azolo and azinoisoindoles.

Based on the study of electronic spectrums we were able to prove the existence of a tautomeric equilibrium for 1-amonoisoindole in spite of the fact, that is, oindole tautomer is the prevailing form here. Based on the Curtin–Hammett principle[25] we first examined reactions typical only for the isoindole tautomer and chose an isoindole, which was prevalently in the isoindolenine tautomeric form. In this work therefore, we have investigated the interaction between 1-aminoisoindole and maleimide derivates.

2. Results and discussion

One of the most interesting properties of the parent isoindole **1a** is the rapid tautomeric equilibrium with isoindolenine **1b**[26,27](Scheme 1).



Scheme 1. Tautomerism of unsubstituted isoindole **1** and 1-aminoisoindole **2**.

The percentage content of the isoindole form can be increased or reduced by adding substituents to the simple isoindole framework. For isoindoles in the *ortho*-quinoid system, i.e., type **1** composition, the most studied process is the Diels–Alder reaction which has been studied in the case of maleic acid derivates as dienophiles. If isoindoles isolation is complicated through their

* Corresponding author. Tel.: +38 096 449 2900; fax: +38 044 235 1273.
E-mail address: z_voitenko@mail.univ.kiev.ua (Z.V. Voitenko).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.11.031

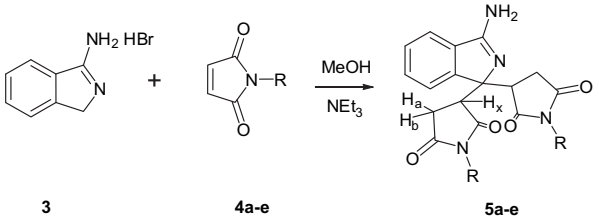
instability, their adducts are often identified by reactions with either maleic anhydride or *N*-phenylmaleimide.

We were interested to see if we could extend the boundaries of the synthetic use of the isoindoles in the isoindolenine form in cycloaddition reactions. To answer this question we need to perform a detailed study of the tautomerism of this type of compounds. The object of the study was 1-aminoisoindole. 1-Aminoisoindole has three theoretically possible tautomeric forms—**2a**, **2b** and **2c**. But only one of them—**2c**—can theoretically enter into the Diels–Alder reaction as it contains an *ortho*-quinoid diene fragment.

According to the IR-spectral data[27] 1-aminoisoindole in solid state and in solution prevalently exists in the **2b** form. The position of aminoisoindole characteristic frequencies depends on the solvent nature and concentration as these are the factors, which determine the degree of association.

According to our UV-spectral data a small amount of the isoindole tautomeric form is present in equilibrium and it can be measured. This enabled us to use the Curtin–Hammett principle and study the reaction between 1-aminoisoindole and maleimide derivates as active dienophiles.

First we tried to perform the reaction between 1-aminoisoindole **3** bromide and maleimides **4a**–**e** in 1:1 and 1:2 ratios in methanol with presence of triethylamine, at room temperature (25 °C). Irrespective of the compound ratio, in all cases we obtained product **5a**–**e** (Scheme 2), which was confirmed by spectral study.



3 **4a-e** **5a-e**

Maleimide	Product	R	Yield (%)
4a	**5a**	H	36
4b	**5b**	4-CH_3O-C_6H_4	77
4c	**5c**	C_6H_5	81
4d	**5d**	4-CH_3-C_6H_4	84
4e	**5e**	CH_3	39

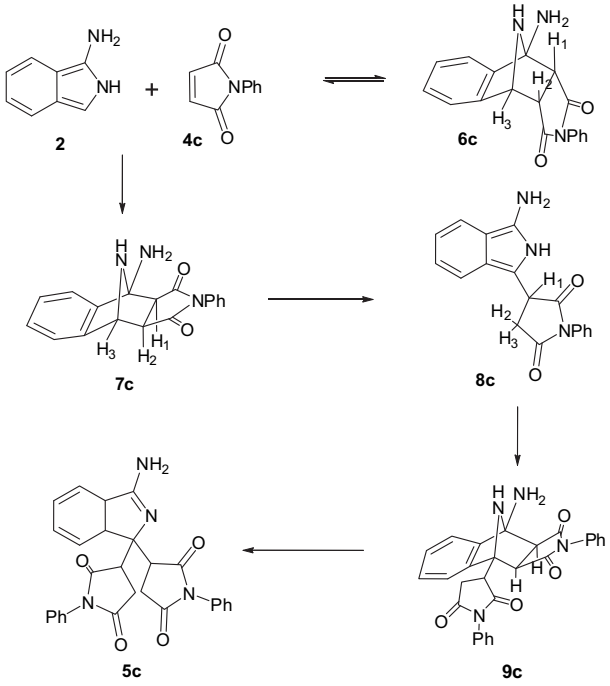
Scheme 2. Interaction of hydrobromide of 1-aminoisoindole **3** with maleimides **4a**–**e** in the ratio 1:2.

The yields of the obtained products strongly depend on the substituent R. In the case of aromatic substituents the yields were higher. We were unable to obtain the final adducts with some other maleimide derivates, in particular with *ortho*- and *meta*-substituted *N*-phenylmaleimides.

It was also interesting that we could not perform the reaction between 1-aminoisoindole and 3-methyl-*N*-phenylmaleimide, which can presumably be explained by the steric complications considering the common synchronous [4+2]-cycloaddition mechanism. This may mean that the reaction goes not under a Michael addition mechanism but through the formation of the Diels–Alder adduct.

To probe this statement we tried to obtain the cycloaddition adduct. Selecting the solvent for this reaction was extremely important. First, we need the solvent to shift the equilibrium towards the formation of the isoindole tautomeric form. Secondly, the solvent had to be aprotonic as the cycloaddition adducts for 1-aminoisoindole readily and easily rearrange to Michael adducts. Diethyl ether was an ideal choice as it perfectly met all these requirements.

An equimolar quantity of *N*-phenylmaleinimide was added to the aetheric solution of 1-aminoisoindole cooled to −10 °C. After several minutes, we observed a yellow residue of the Diels–Alder cycloaddition adduct, which could be described as *endo*-adduct **6c** (Scheme 3) considering the previously determined by NMR-spectroscopy[6,10] structure of *endo*- and *exo*-isomers of 7-azabenzonorbornens. After gentle heating or dissolution of the *endo*-adduct in different solvents, it rearranged to *exo*-adduct **7c** with subsequent rearrangement to the Michael adduct **8c**. It was easy to follow this process visually as with the formation of adduct **8c** the reaction mixture had become light pink (a colour typical for isoindole structures). The *endo*-adduct then transforms to *exo*-adduct through a Diels–Alder retro-reaction with the formation of a more thermodynamically stable isomer. We have proved this fact via a chemical trap method: several drops of acetylenedicarboxylic acid methylic ether (DMAD) were added to the solution of *endo*-adduct, which made the mixture turn bright red in colour typical for interaction with 1-amonoisoindole. Similarly, we determined the mechanism of transformation of *endo*-adducts to *exo*-adducts for the reaction between *N*-methylisoindole quinazolone and maleimide derivates.[21] Acetylenedicarboxylic acid ethers mixed with this compound form Michael adducts that are red in colour. All intermediate adducts are unstable and are quickly decomposed even in solid state.



2 **4c** **6c** **7c** **8c** **5c** **9c**

Compound	Yield (%)
6c	67
7c	43
8c	73
9c	-
5c	81

Scheme 3. Mechanism of interaction of 1-aminoisoindole **2** with maleimide **4c**.

Adduct **8c** further easily enters the next cycloaddition with another maleimide molecule. After the next rearrangement, we obtained Michael bis-adduct **5c**. We were unable to obtain intermediate **9c**.

All intermediate adducts are unstable and are quickly destroyed even in solid state, for this reason we were only able to identify

their structure by qa rapid measurment of their ^{1}H NMR spectra. *endo*- and *exo*-adducts configuration was proved in view of the previously determined criteria.

We have proved the rearranged structure of the type **5** adducts both by ^{1}H NMR spectrums and by two-dimensional spectroscopy. The ^{1}H NMR spectrum of the compound **5e** corresponds the formula where two succinimide fragments are combined with atom C(8) of 1-aminoisodole fragment. The aromatic protons of the isoindole fragment appear at the low field (7–7.8 ppm), the protons of the amino group can be observed at 6.59 ppm, the protons of succinimide fragments give two well-resolved AMX spin systems and the protons of the methyl groups give singlets at 2.81 and 2.78 ppm. Two succinimide fragments are not equivalent because of the atropoisomerism that leads to the existence of two not equivalent AMX spin systems. It was a bit unexpected to observe the signals of one of the protons of the methylene group of both succinimide fragments at such strong field as 0.88 and 1.02 ppm. The signals of the second protons of these methylene groups have no anomalies in chemical shifts and they can be observed at 2.50 and 2.25 ppm.

As proton magnetic resonance spectrum of the obtained product has a number of peculiarities, in order to ensure further confirmation of the compound structure we measured its spectrum on nuclei ^{13}C and made experiments on ^{1}H–^{13}C heteronuclear correlation through one chemical bond (HMQC) and 2–3 chemical bonds (HMBC). The coordinates of the cross-peaks found in the two-dimensional spectrums are given in Table 1.

Table 1
Coordinates of the crosspeaks in spectrums HMQC and HMBC for the compound **5c**

Coordinate ^{1}H, δ, ppm	Coordinate ^{13}C, δ, ppm	
	HMQC	HMBC
7.81	121.6	165.3; 149.8; 130.3; 122.0
7.44	129.4	137.4; 122.0
7.40	130.3	149.8; 121.6; 76.8
7.08	122.0	149.8; 137.4; 129.4; 121.6; 76.8
6.96	—	137.4
4.60	43.2	76.8; 179.3; 149.8
4.43	42.6	76.8; 178.9
2.81	25.0	178.9; 176.9
2.78	24.8	179.3; 176.6
2.50	31.1	76.8; 41.2
2.25	31.3	76.8; 42.6
1.02	31.1	76.8; 41.2; 179.3; 176.6
0.88	31.3	76.8; 42.6; 178.9; 176.9

These experiments enabled to assign the signals in the carbon spectrum of the compound and to make a number of conclusions about its structure. The protonated carbon atoms are easily assigned on the basis of the correlations existing in the HMQC spectrum, while the quaternary carbon atoms are assigned by the correlations through 2–3 chemical bonds in HMBC spectrum. The signal assignments are shown in Figure 1.

The key aspect in determining the molecular structure is the presence of a quaternary carbon atom C(8) in the isoindole fragment with a chemical shift of 76.8 ppm. The HMBC spectrum has the relevant signal correlations expected for the proton signals of the CH and CH_2 groups of succinimide fragments. This confirms that both of the residues are bound with atom C(8). The molecular location of this atom is proved by the correlation with the signal of one of the aromatic protons with chemical shift of 7.08 ppm (proton H-4).

The correlations in the HMBC spectrum also enable conclusions on the mutual orientation of the protons in the synthesised product molecule. One of the signals of the CH proton of the succinimide fragments (with a chemical shift of 4.60 ppm) has intensive correlation via three bonds with the C(7) signal absorbing at

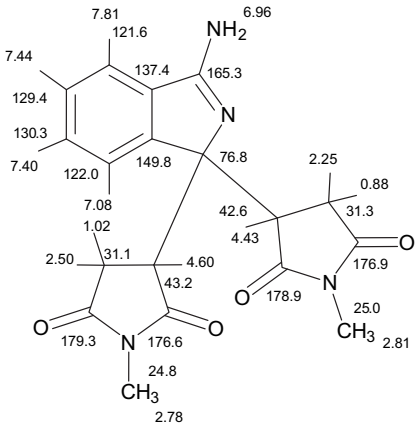


Figure 1. Coordinations of signals ^{13}C and ^{1}H NMR for compound **5e**.

149.8 ppm, while the other signal of this proton absorbing at 4.43 ppm has no such correlation. This indicates different sizes for the torsion angle between bond C(7)-C(8) of isoindole nucleus and bond of C–H methine proton of succinimide fragments. The absence of the named correlation means that ^3J (C, H) is approximate to zero, which is possible if the torsion angle is approximate to 90°. This is the situation which is observed for one of the succinimide residues.

The fact of the anomalously strong field position of the signals of one of the methylene protons of succinimide fragment also needs to be explained. Most likely this is because one of the methylene protons of succinimide fragments gets into the anisotropic magnetic field of C=N double bond of the isoindole fragment.

The structure of the rearrangement adducts has been confirmed by X-ray diffraction analysis (Fig. 2).

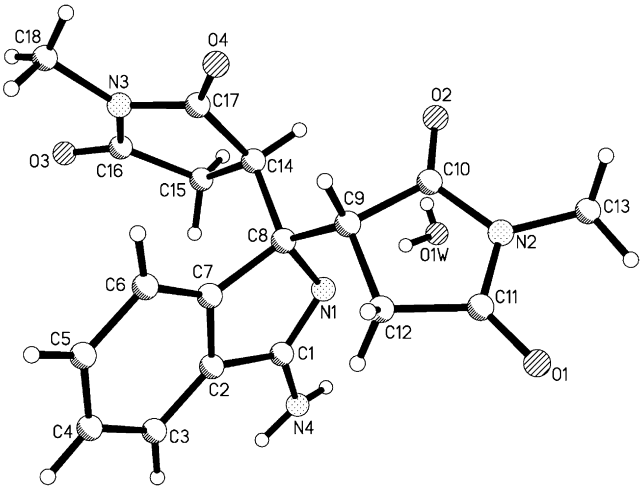


Figure 2. X-ray diffraction analysis of the compound **5e**.

According to the X-ray diffraction study compound **5e** exists in the crystal phase as monohydrate. Two succinimidyl substituents have similar orientation with respect to the aminoisoindole fragment (the C(2)-C(7)-C(8)-C(9) and C(2)-C(7)-C(8)-C(14) torsion angles are −120.0(2)° and 113.9(2)°, respectively). Such arrangement of the substituents is stabilised additionally by the weak intramolecular hydrogen bond C(14)-H(14)···O(2) (H···O 2.39 Å C–H···O 131°). Steric repulsion between atoms of the C(14)-C(15)-C(16)-N(3)-C(17) heterocycle and aminoisoindole fragment (the shortened intramolecular contacts: H(6)···C(17) 2.81 Å (van der Waals radii sum[28] is 2.87 Å), H(15a)···N(1) 2.63 Å (2.67 Å), H(15a)···

C(1) 2.70 Å (2.87 Å), H(15a)···C(7) 2.80 Å (2.87 Å)) is considerably stronger as compared to steric interactions between the C(9)-C(10)-N(2)-C(11)-C(12) ring and the bicyclic fragment where only one shortened intramolecular contact (the H(12a)···C(7) 2.67 Å) is observed. The difference in the degree of the repulsion between succinimidyl substituents and the bicyclic fragment results, evidently, in a slightly different conformation of the five-membered heterocycles: the C(9)···C(12), N(2) ring is a planar within 0.01 Å while the C(14)···C(17), N(3) ring adopts the envelope conformation where the deviation of the C(14) atom from the mean plane of the remaining atoms of the ring is 0.13 Å. The nitrogen atom of the amino group has the pyramidal configuration (the sum of bond angles centred at the N(4) atom is 352°).

3. Conclusions

We have discovered a new transformation on the basis of the reactions between 1-aminoisoindole and maleimide derivates in a 1:2 ratio leading to formation of Michael bis-adducts. The following intermediates reactions have been defined: Diels–Alder adducts in 1:1 composition. We have also proposed the mechanism for the formation of rearrangement products and transformation of *endo*-isomers to *exo*-isomers. The structure of all the obtained substances has been studied by spectral methods including two-dimensional NMR spectroscopy and X-ray diffraction analysis.

4. Experimental section

4.1. General

The ^{1}H NMR spectra (400.396 MHz) were recorded with a Varian Mercury 400 with TMS as internal standard. The UV-spectra were recorded on Specord M400. The IR-spectra were recorded on Specord M82. The chromatomass-spectra were recorded on Agilent 1100 Series with selective detector Agilent LC/MSD SL. Elemental analysis was realised with a Carlo Erba Strumenization analyser.

*4.1.1. endo-Adduct of 1-aminoisoindole with N-phenilmaleimide (**6c**).* To a solution of 1-aminoisoindole hydrobromide[29] **3** (1.07 g, 5 mmol) in water (10 mL) was added saturated NaOH water solution (10 mL). 1-aminoisoindole was extracted by diethyl ether (20 mL). The ether extracts were dried over anhydrous Na_2SO_4. The solution was cooled to −10 °C and *N*-phenylmaleimide **4c** (0.87 g, 5 mmol) was added. The reaction was performed for 5 h at −10 °C. The residue was filtered and washed with absolute ether and gave the *title compound* **6c** (1.02 g, 67%) as a light yellow solid. δ_H (400 MHz, DMSO-d_6) 4.15 (1H, dd, *J* 2.3, 8.0 Hz), 4.44 (1H, dd, *J* 6.0, 8.0 Hz), 5.72 (1H, dd, *J* 2.3, 6.0 Hz), 6.99–7.93 (9H, m), 10.2 (3H, s, N*H*, NH_2).

*4.1.2. exo-Adduct of 1-aminoisoindole with N-phenilmaleimide (**7c**).* To a solution of 1-aminoisoindole hydrobromide[29] **3** (1.07 g, 5 mmol) in water (10 mL) was added saturated NaOH water solution (10 mL). 1-aminoisoindole was extracted by diethyl ether (20 mL). The ether extracts were dried over anhydrous Na_2SO_4. To a solution was added isopropyl alcohol and then *N*-phenylmaleimide **4c** (0.87 g, 5 mmol) at room temperature. After 30 min the residue was filtered and washed with isopropyl alcohol and absolute ether and gave the *title compound* **7c** (0.66 g, 43%) as a light yellow solid. δ_H (400 MHz, DMSO-d_6) 4.09 (1H, d, *J* 7.8 Hz), 4.37 (1H, d, *J* 7.8 Hz), 5.70 (1H, s), 7.00–8.04 (9H, m), 10.2 (3H, s, N*H*, NH_2).

*4.1.3. 3-(2,5-pyrrolidinone-1-phenil)-3H-1-aminoisoindole (**8c**).* To a solution of *exo*- **6c** or *endo*-adduct **7c** or their mixtures (0.61 g, 2 mmol) in methanol (10 mL) were added 5 drops of triethylamine and the solution was boiled for 15 min in inert atmosphere. After cooling, the water (30 mL) was added. The residue was filtered and washed with isopropyl alcohol and gave the *title compound* **8c** (0.45 g, 73%) as a light pink solid. δ_H (400 MHz, DMSO-d_6) 2.91 (1H, dd, *J* 9.2, 18.0 Hz), 3.20 (1H, d, *J* 4.8, 18.0 Hz), 3.96 (1H, d, *J* 4.8, 9.2 Hz), 6.92–7.77 (9H, m), 8.89 (3H, s, N*H*, NH_2).

4.2. Common procedure for reaction of 1-aminoisoindole with maleimides (5a–e)

To a solution of 1-aminoisoindole hydrobromide[29] **3** (0.43 g, 2 mmol) in absolute methanol (5 mL) was added the relevant maleimide **4a**–**e** (4.2 mmol) with heating until dissolved. It was added triethylamine (1 mL) and the flask was closed tightly. After a while the mixture produced white plate-formed crystals. The residue was filtered and washed with methanol. The filtrate was left until the precipitate stopped form.

*4.2.1. 3,3-Bis-(2,5-pyrrolidinone-1H)-1-aminoisoindole (**5a**).* 0.23 g, 36%, white solid, mp 270 °C; [Found: C, 58.89; H, 4.32; N, 17.17. $C_{16}H_{14}N_4O_4$ requires C, 58.81; H, 4.41; N, 17.25]; υ_{max}(KBr) 3456, 3368, 3236, 3068, 2725, 1708, 1636, 1556, 1344, 1172, 768 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.99 (2H, dd, *J* 6.0, 18.8 Hz), 2.65 (2H, dd, *J* 9.2, 18.8 Hz), 3.85 (2H dd, *J* 6.0, 9.2 Hz), 6.90 (2H, s, NH_2), 7.21 (1H, d), 7.38–7.40 (2H, m), 7.71 (1H, d), 11.00 (2H, s, 2 N*H*); δ_H (400 MHz, CF_3COOD) 2.80 (2H, dd, *J* 6.0, 18.8 Hz), 3.42 (2H, dd, *J* 9.2, 18.8 Hz), 4.62 (2H, dd, *J* 6.0, 9.2 Hz), 7.72 (1H, d), 7.9 (1H, t), 8.0 (1H, t), 8.31 (1H, d); δ_C (100.7 MHz, DMSO-d_6) 33.0, 46.7, 75.7, 121.1, 122.4, 128.5, 129.5, 137.4, 150.5, 164.9, 178.2, 179.1; HRMS (EI): M$^+$, found 327.3. $C_{16}H_{14}N_4O_4$ requires 327.3.

*4.2.2. 3,3-Bis-(2,5-pyrrolidinone-1-(4-methoxyphenil))-1-aminoisoindole (**5b**).* 0.83 g, 77%, white solid, mp 285 °C; [Found: C, 66.91; H, 4.87; N, 10.40. $C_{30}H_{26}N_4O_6$ requires C, 66.95; H, 4.93; N, 10.51]; υ_{max}(KBr) 3424, 3072, 2992, 2936, 2836, 1708, 1644, 1508, 1248, 1184, 832 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.08 (1H, dd, *J* 6.0, 18.8 Hz), 1.26 (1H, dd, *J* 6.0, 18.8 Hz), 2.47 (1H, dd, *J* 9.2, 18.8 Hz), 2.67 (1H, dd, *J* 9.2, 18.8 Hz), 3.79 (6H, s), 4.53 (1H dd, *J* 6.0, 9.2 Hz), 4.68 (1H dd, *J* 6.0, 9.2 Hz), 7.00–7.18 (10H, m), 7.30 (1H, d), 7.53–7.55 (2H, m), 7.89 (1H, d); δ_H (400 MHz, CF_3COOD) 2.27 (1H, dd, *J* 6.0, 18.8 Hz), 2.46 (1H, dd, *J* 6.0, 18.8 Hz), 2.97 (1H, dd, *J* 9.2, 18.8 Hz), 3.40 (1H, dd, *J* 9.2, 18.8 Hz), 4.06 (6H, s), 5.36 (2H, dd, *J* 6.0, 9.2 Hz), 7.25 (8H, m), 7.86 (1H, d), 8.00 (1H, t), 8.15 (1H, t), 8.48 (1H, d); δ_C (100.7 MHz, DMSO-d_6) 31.4, 31.7, 42.9, 43.2, 56.1, 77.3, 114.8, 115.0, 121.8, 122.4, 125.4, 125.8, 129.0, 129.1, 129.6, 130.4, 137.6, 149.8, 159.5, 159.7, 165.4, 176.0, 176.3, 178.3, 178.5; HRMS (EI): M$^+$, found 539.6. $C_{30}H_{26}N_4O_6$ requires 539.6.

*4.2.3. 3,3-Bis-(2,5-pyrrolidinone-1-phenil)-1-aminoisoindole (**5c**).* 0.77 g, 81%, white solid, mp 282 °C; [Found: C, 70.28; H, 4.63; N, 11.71. $C_{28}H_{22}N_4O_4$ requires C, 70.21; H, 4.74; N, 11.67]; υ_{max}(KBr) 3424, 3100, 3064, 1704, 1644, 1564, 1496, 1384, 1184, 700 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.17 (1H, dd, *J* 6.0, 18.8 Hz), 1.33 (1H, dd, *J* 6.0, 18.8 Hz), 2.42 (1H, dd, *J* 9.2, 18.8 Hz), 2.65 (1H, dd, *J* 9.2, 18.8 Hz), 4.61 (1H dd, *J* 6.0, 9.2 Hz), 4.77 (1H dd, *J* 6.0, 9.2 Hz), 6.93 (2H, s, NH_2), 7.11–7.54 (13H, m), 7.90 (1H, d); δ_H (400 MHz, CF_3COOD) 2.26 (1H, dd, *J* 6.0, 18.8 Hz), 2.45 (1H, dd, *J* 6.0, 18.8 Hz), 2.95 (1H, dd, *J* 9.2, 18.8 Hz), 3.39 (1H, dd, *J* 9.2, 18.8 Hz), 5.36 (2H, dd, *J* 6.0, 9.2 Hz), 7.24–7.61 (10H, m), 7.85 (1H, d), 7.98 (1H, t), 8.14 (1H, t), 8.46 (1H, d); δ_C (100.7 MHz, DMSO-d_6) 31.5, 31.8, 43.1, 43.3, 77.4, 121.8, 122.5, 127.8, 128.0, 129.0, 129.2, 129.5, 129.7, 129.8, 130.4, 132.9, 133.3, 137.6, 149.8, 165.4, 175.8, 176.1, 178.1, 178.2; HRMS (EI): M$^+$, found 479.5. $C_{28}H_{22}N_4O_4$ requires 479.5.

*4.2.4. 3,3-Bis-(2,5-pyrrolidinone-1-tolyl)-1-aminoisoindole (**5d**).* 0.85 g, 84%, white solid, mp 283 °C; [Found: C, 71.08; H, 5.17;

N, 11.06. $C_{30}H_{26}N_4O_4$ requires C, 71.15; H, 5.22; N, 11.01]; υ_{max}(KBr) 3424, 3064, 2920, 1700, 1644, 1508, 1384, 1180, 720 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.15 (1H, dd, *J* 6.0, 18.8 Hz), 1.36 (1H, dd, *J* 6.0, 18.8 Hz), 2.37 (1H, dd, *J* 9.2, 18.8 Hz), 2.45 (6H, s), 2.56 (1H, dd, *J* 9.2, 18.8 Hz), 4.59 (1H dd, *J* 6.0, 9.2 Hz), 4.76 (1H dd, *J* 6.0, 9.2 Hz), 6.92 (2H, s, NH_2), 7.14–7.52 (11H, m), 7.90 (1H, d); δ_H (400 MHz, CF_3COOD) 2.23 (1H, dd, *J* 6.0, 18.8 Hz), 2.44 (1H, dd, *J* 6.0, 18.8 Hz), 2.46 (6H, s), 2.94 (1H, dd, *J* 9.2, 18.8 Hz), 3.38 (1H, dd, *J* 9.2, 18.8 Hz), 5.36 (2H, dd, *J* 6.0, 9.2 Hz), 7.07 (2H, d), 7.12 (2H, d), 7.38 (4H, d), 7.86 (1H, d), 7.98 (1H, t), 8.13 (1H, t), 8.46 (1H, d); δ_C (100.7 MHz, DMSO-d_6) 17.7, 17.9, 31.4, 31.7, 42.9, 43.2, 77.3, 121.8, 122.4, 125.4, 125.8, 128.0, 128.1, 129.6, 130.4, 132.7, 137.6, 138.7, 149.8, 159.5, 159.7, 165.4, 176.0, 176.3, 178.3, 178.5; HRMS (EI): M^+, found 507.6. $C_{30}H_{26}N_4O_4$ requires 507.6.

*4.2.5. 3,3-Bis-(2,5-pyrrolidinone-1-methyl)-1-aminoisoindole (**5e**).* 0.28 g, 39%, white solid, mp 273 °C; [Found: C, 61.01; H, 5.12; N, 15.81. $C_{18}H_{18}N_4O_4$ requires C, 61.13; H, 5.07; N, 15.78]; υ_{max}(KBr) 3440, 3108, 3068, 2948, 1688, 1648, 1432, 1380, 1276, 1120, 688 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 0.87 (1H, dd, *J* 6.0, 18.8 Hz), 1.02 (1H, dd, *J* 6.0, 18.8 Hz), 2.25 (1H, dd, *J* 9.2, 18.8 Hz), 2.50 (1H, dd, *J* 9.2, 18.8 Hz), 2.79 (6H, s), 4.42 (1H dd, *J* 6.0, 9.2 Hz), 4.60 (1H dd, *J* 6.0, 9.2 Hz), 6.96 (2H, s, NH_2), 7.08 (1H, d), 7.40 (1H, t), 7.46 (1H, t), 7.80 (1H, d); δ_H (400 MHz, CF_3COOD) 2.00 (1H, dd, *J* 6.0, 18.8 Hz), 2.20 (1H, dd, *J* 6.0, 18.8 Hz), 2.79 (1H, dd, *J* 9.2, 18.8 Hz), 3.20 (7H, m), 5.10 (2H, dd, *J* 6.0, 9.2 Hz), 7.61 (1H, d), 7.90 (1H, t), 8.00 (1H, t), 8.36 (1H, d); δ_C (100.7 MHz, DMSO-d_6) 24.8, 25.0, 31.1, 31.3, 42.6, 43.2, 76.8, 121.6, 122.0, 129.4, 130.3, 137.4, 149.8, 165.3, 176.6, 176.9, 178.9, 179.6; HRMS (EI): M^+, found 355.4. $C_{18}H_{18}N_4O_4$ requires 355.4.

4.3. X-ray diffraction study

The colourless crystals of **5e** ($C_{18}H_{20}N_4O_5$) are orthorhombic. At 100 K a=11.815(2), b=14.054(2), c=21.508(6) Å, V=3571(1) $Å^3$, M_r=372.38, Z=8, space group Pbca, d_{calcd}=1.385 g/cm^3, μ(MoKα)=0.103 mm^{-1}, F(000)=1568. Intensities of 19434, reflections (5199 independent, R_{int}=0.105) were measured on the 'Xcalibur-3' diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scaning, $2\Theta_{max}$=60°). The structure was solved by direct method using SHELXTL package.[30] Positions of the hydrogen atoms of water molecule were located from electron density difference maps and refined using 'riding' model with U_{iso}=1.5U_{eq} of the carrier atom. All hydrogen atoms in molecule **5e** are refined in isotropic approximation. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 5175 reflections was converged to wR_2=0.109 (R_1=0.060 for 2394 reflections with $F>4\sigma(F)$, S=0.860). The final atomic coordinates, and crystallographic data for molecule **5e** have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033,; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 736675.

References and notes

1. Toja, E.; Omodei-Sale, A.; Favara, D.; Cattaneo, C.; Gallico, L.; Galliani, G. *Arzneim.-Forsch.* **1983**, *33*, 1222.
2. Lerner, L. J. *J. Reprod. Fertil. Suppl.* **1989**, *39*, 251.
3. Bonnett, R.; North, S. A. *Adv. Heterocycl. Chem.* **1981**, *29*, 341.
4. Kreher, R.; Herd, K.-J. *Chem. Ztg.* **1982**, *106*, 305.
5. Kreher, R. P.; Kohl, N. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 517.
6. Kovtunenko, V. A.; Voitenko, Z. V.; Sheptun, V. L.; Tyltin, A. K.; Chernega, I.; Struchkov, Y. T.; Babichev, F. S. *Chem. Heterocycl. Comp.* **1984**, *20*, 1235.
7. Kreher, R. P.; Use, G. *Chem. Ber.* **1988**, *121*, 927.
8. Bonnett, R.; North, S. A.; Newton, R. F.; Scopes, D. I. *Tetrahedron* **1983**, *39*, 1401.
9. Kovtunenko, V. A.; Voitenko, Z. V. *Russ. Chem. Rev.* **1994**, *63*, 997.
10. Kovtunenko, V. A.; Voitenko, Z. V.; Tyltin, A. K.; Turov, A. V.; Babichev, F. S. *Ukr. Khim. Zh.* **1983**, *49*, 1287.
11. Kreher, R. P.; Feldhoff, U.; Seubert, J.; Schmitt, D. *Chem. Ztg.* **1987**, *111*, 155.
12. Orti, E.; Bredas, J. L. *J. Chem. Phys.* **1988**, *89*, 1009.
13. Kreher, R. P.; Seubert, J.; Schmitt, D.; Use, G.; Kohl, N.; Muleta, T. *Chem. Ber.* **1990**, *123*, 381.
14. Zhou, Z.; Parr, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 7371.
15. Kovtunenko, V. A.; Voitenko, Z. V.; Kucherenko, T. T.; Turov, A. V.; Tyltin, A. K.; Babichev, F. S. *Chem. Heterocycl. Comp.* **1990**, *26*, 161.
16. Troll, T.; Ollmann, G. W. *Tetrahedron Lett.* **1981**, *22*, 3497.
17. Voitenko, Z. V.; Samoilenko, V. P.; Kovtunenko, V. A.; Gurkevich, V. Y.; Tyltin, A. K.; Shcherbakov, M. V.; Shishkin, O. V. *Chem. Heterocycl. Comp.* **1999**, *35*, 600.
18. Voitenko, Z. V.; Pokholenko, A. A.; Shkarov, O. O.; Kovtunenko, V. A.; Babichev, F. S. *Chem. Heterocycl. Comp.* **2002**, *38*, 190.
19. Voitenko, Z. V.; Pokholenko, A. A.; Ilkun, O. T.; Mazieres, M. R.; Wolf, J. G. C. R. *Chima.* **2006**, *9*, 1482.
20. Voitenko, Z.; Lyaskovskyy, V.; Wolf, J. G.; Jaud, J. *ARKIVOC* **2007**, *15*, 90.
21. Pokholenko, A. A.; Voitenko, Z. V.; Kovtunenko, V. A. *Russ. Chem. Rev.* **2004**, *73*, 771.
22. Voitenko, Z. V.; Kysil', A.; Wolf, J. G. *Dyes and Pigment* **2007**, *74*, 477.
23. Voitenko, Z. V.; Yegorova, T. V.; Kysil', A. I.; Andre, C.; Wolf, J. G. *Tetrahedron* **2004**, *60*, 195.
24. Voitenko, Z. V.; Yegorova, T. V.; Kovtunenko, V. A.; Zubatyuk, R. I.; Shishkina, S. V.; Shishkin, O. V.; Tsapko, M. D.; Turov, A. V. *J. Mol. Struct.* **2004**, *707*, 193.
25. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part A: Structure and Mechanisms - 4th ed.*; 2000; pp 215–261.
26. Veber, D. F.; Lwowski, W. *J. Am. Chem. Soc.* **1963**, *85*, 646.
27. Sieveking, H. U.; Luttke, W. *Annalen* **1977**, *2*, 189.
28. ZefirovYu, V. *Kristallografiya* **1997**, *42*, 936.
29. Ussr, P. 1166476 *Byull. Izobret.* **1983**, *46*, 68.
30. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112.