^{1}H AND ^{13}C NMR SPECTRAL ASSIGNMENTS AND X-RAY CRYSTALLOGRAPHY OF 4,5,8,12b-TETRAHYDRO-ISOINDOLO[1,2-*a*]ISOQUINOLINE AND DERIVATIVES

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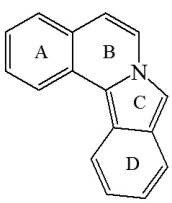
ABSTRACT

12b-Hydroxy-5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinolin-8-one (**4**), 5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinoline (**5**) and 12b-hydroxy-5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinoline (**6**) were obtained by reduction of 4,5,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinolin-8-one (**3**) with $LiAlH_4$/THF/N_2. The precursor and products were characterized by NMR spectroscopy and the X-ray crystal structure of **5** hydrochloride monohydrate (**5a**) was determined. ^{1}H and ^{13}C NMR spectra were completely assigned for compounds **3**, **4**, and **5a**, using two-dimensional experiments (H-H COSY, HMQC, HMBC and H-H NOESY).

INTRODUCTION

The isoindolo[1,2-*a*]isoquinoline structure (**1**) is a rigid tetracyclic ring system that has been poorly investigated. This system, as the 5,6-dihydro-8(12b*H*)one derivative, was first reported in 1968,[1] and later found in a natural product named nuevamine (**2**), isolated from an extract of *Berberis darwinii* Hook., native to south-central Chile and Argentina.[2,3] Several syntheses of **2** and, generally, the isoindolo[1,2-*a*]isoquinoline skeleton have been reported, but a systematic study of its analogues has been lacking in spite of the likelihood of some of these products having interesting pharmacological properties.[3-5]



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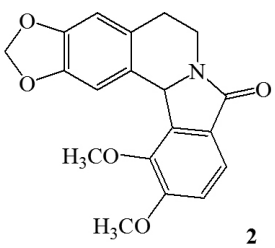

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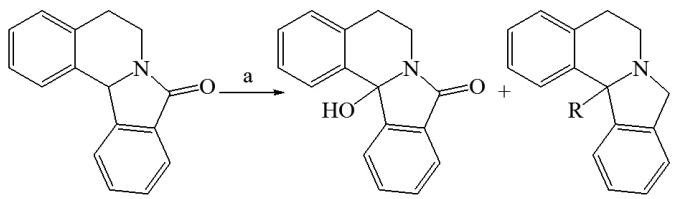
The synthesis of a series of (±)-5,6,8,12b-tetrahydroisoindolo[1,2-*a*] isoquinoline-8-ones (**3**) bearing one to three methoxyl groups, a methylenedioxy group, a methoxyl and a hydroxyl, or two hydroxyl groups on ring A was reported a couple of years ago,[4] following a general route that involved acid-catalyzed cyclization of the corresponding 3-hydroxy-2-(substituted phenyl)ethylisoindol-1-ones. The reactivity of these systems has been poorly investigated.[1] A particularly surprising observation was that attempts to obtain the corresponding tertiary amine (**5**) from **3** by treatment with $LiAlH_4$ in THF generated the 12b-hydroxy derivative (**4**) of **3** as the major product, plus a very low yield of **5** (Scheme 1).[6]

We have now confirmed that the $LiAlH_4$ reduction of lactam **3** generates the expected **5** and a high yield of **4**, together with the previously unreported **6**. In particular, we have provided convincing proof of the structure of **5** (as its hydrochloride monohydrate **5a**) based on a complete study of its ^{1}H and ^{13}C NMR spectra, those of **3** and **4**, and an X-ray crystallographic analysis of **5a**. In addition, **6** was found to participate in a ring-breaking tautomeric equilibrium that hindered its spectral assignments. Tertiary amines related to **5** and **6** have not been found in nature, and to the best of our knowledge only one direct synthesis of such compounds has been reported very recently.[7]



3 **4** (55%) **5** R= H (6%) **6** R= OH (3%)

Scheme 1. Reagents and conditions: a) $LiAlH_4$/THF, reflux, N_2, 72 h.

RESULTS AND DISCUSSION

Reduction of 4,5,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinolin-8one (**3**) with $LiAlH_4$/THF for 48 h under N_2 generated, in moderate yield, 12b-hydroxy-5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinolin-8-one (**4**, 55%), plus small amounts of 5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinoline (**5**, 6%) and a previously undocumented product,[6] 12b-hydroxy-5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinoline (**6**) in 3% yield. Walker and Kempton carried out this reduction under slightly different conditions, reporting 23% and 18% yields of **4** and **5**, respectively.[6] Compound **5** oxidizes rapidly in the presence of air, and therefore its hydrochloride **5a** was prepared and studied. The complete ^{1}H and ^{13}C NMR assignments of compounds **3-5a**, based on one- and two-dimensional NMR experiments (*e.g.* Figures 1 and 2; Figure 1 gives the atom numbering), are shown in Tables 1-3.

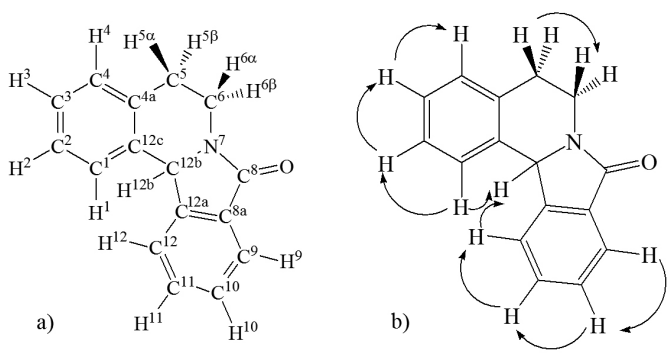


Figure 1. a) Numbering schemes of the 5,6,8,12b-tetrahydroisoindolo[1,2-*a*] isoquinolin-8-one skeleton and b) COSY correlations in **3**.

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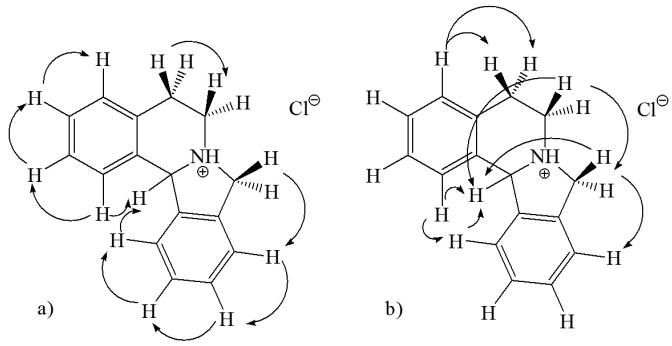

Figure 2. a) COSY and b) NOESY correlations for **5a**.

Table 1. ^{1}H chemical shifts (d) [H-X, multiplicity, *J*(H,H) (Hz)][a] and ^{13}C[a] chemical shifts (d) of 5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinolin-8-one (**3**).

	3				
Carbon	**δ ^{1}H**	**δ ^{13}C**	**HMBC[b]**	**COSY[c]**	**NOESY[d]**
1	7.75 [H-1, d, *J*(1,2) = 7.5]	125.7	3, 4a, 12b	2, 12b	12, 12b
2	7.28 [H-2, t, *J*(2,3) = *J*(2,1) = 7.5]	126.5	4, 12c	1, 3	-
3	7.22 [H-3, t, *J*(3,4) = *J*(3,2) = 7.5]	127.1	1, 4a	2, 4	-
4	7.19 [H-4, d, *J*(3,4) = 7.5]	129.1	2, 5, 12c	3	5 (both)
4a	-	134.4	1, 3, 6, 12b	-	-
5	2.83 [H-5α, m], 2.98 [H-5β, m]	28.79	4, 4a, 6, 12c	6α, 6β	4, 6 (both)
6	3.56 [H-6α, ddd, *J* = 12.9, 11.5, 4.5 Hz, 1H], 4.32 [H-6β, ddd, *J* = 13.0, 6.1, 2.2 Hz, 1H]	37.58	4a, 5, 8, 12b	6 (both), 5	5, 12b(α)
7	-	-	-	-	-
8	-	166.7	6, 9, 12b	-	-
8a	-	132.1	10, 12, 12b	-	-
9	7.67 [H-9, d, *J*(9,10) = 7.5]	131.7	8, 11, 12a	10	-
10	7.53 [H-10, t, *J*(10,9) = *J*(10,11) = 7.3]	128.5	8a, 12	9, 11	-
11	7.72 [H-11, t, *J*(11,10) = *J*(11,12) = 7.5]	122.9	9, 12a	10, 12	-
12	8.10 [H-12, d, *J*(12,11) = 7.6]	124.3	8a, 10, 12b	11,12b	1, 12b
12a	-	144.6	9, 11, 12b	-	-
12b	5.85 [H-12b, s]	58.48	1, 4a, 6, 8a, 12, 12a, 12c	1,12	1, 12
12c	-	134.5	2, 4, 5, 12b	-	-

[a] In ppm from TMS; [b] H,C HMBC, [c] H-H COSY and [d] H-H NOESY connectivities.

Table 2. ^{1}H chemical shifts (d) [H-X, multiplicity, *J*(H,H) (Hz)][a] and ^{13}C[a] chemical shifts (d) of 12b-hydroxy-5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinolin-8-one (**4**).

	4			
Carbon	**δ ^{1}H**	**δ ^{13}C**	**HMBC[b]**	**COSY[c]**
1	8.02 [H-1, d, *J*(1,2) = 7.6]	127.9	3, 4a, 12b	2
2	7.29 [H-2, t, *J*(2,3) = *J*(2,1) = 7.5]	126.4	4, 12c	1, 3
3	7.23 [H-3, t, *J*(3,4) = *J*(3,2) = 7.5]	128.0	1, 4a	2, 4
4	7.16 [H-4, d, *J*(3,4) = 7.5]	129.0	2, 5, 12c	3
4a	-	134.4	1, 3, 6	-
5	2.81 [H-5α], 2.96 [H-5β, m]	28.77	4, 4a, 6, 12c	6α, 6β
6	3.60 [H-6α, ddd, *J* = 13.0, 11.5, 4.5 Hz, 1H], 4.31 [H-6β, ddd, *J* = 13.0, 6.2, 2.3 Hz, 1H]	34.33	4a, 5, 8, 12b	6 (both), 5
7	-	-	-	-
8	-	166.0	6, 9	-
8a	-	130.5	10, 12	-
9	7.70 [H-9, d, *J*(9,10) = 8]	132.4	8, 11, 12a	10
10	7.53 [H-10, t, *J*(10,9) = *J*(10,11) = 7.2]	129.3	8a, 12	9, 11
11	7.63 [H-11, t, *J*(11,10) = *J*(11,12) = 7.6]	122.5	9, 12a	10, 12
12	8.17 [H-12, d, *J*(12,11) = 7.6]	124.0	8a, 10, 12b	11
12a	-	148.5	9, 11	-
12b	-	85.67	1, 6, 12	-
12c	-	137.4	2, 4, 5	-

[a] In ppm from TMS; [b] H,C HMBC and [c] H-H COSY connectivities.

Table 3. ^{1}H chemical shifts (d) [H-X, multiplicity, *J*(H,H) (Hz)][a] and ^{13}C[a] chemical shifts (d) of 5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinoline hydrochloride (**5a**).

	5a				
CN°	δ ^{1}**H**	**d** ^{13}**C**	**HMBC**[b]	**COSY**[c]	**NOESY**[c]
1	7.55 [H-1, d, *J*(1,2) = 7.6]	127.5	3, 4a, 12b	2, 12b	12, 12b
2	7.36 [H-2, t, *J*(2,3) = *J*(2,1) = 7.3]	127.6	4	1, 3	-
3	7.30 [H-3, t, *J*(3,4) = *J*(3,2) = 7.6]	128.3	1, 4a	2, 4	-
4	7.26 [H-4, d, *J*(3,4) = 7.6]	129.3	2, 5	3	5 (both)
4a	-	132.2	1, 3, 6, 12b	-	-
5	3.10 [H-5α, H-5β, m]	24.25	4, 4a, 6	6α, 6β	4
6	3.31 [H-6α, m], 3.59 [H-6β, m]	46.10	4a, 5, 8, 12b	6 (both), 5	8 (both), 12b(α)
7	-	-	-	-	-
8	4.82 [H-8α, d, *J* (a,b) = *J* (b,a) = 14.7], 4.67 [H-8β, d, *J* (a,b) = *J* (b,a) = 14.9]	56.70	6, 9, 12b	8 (both), 9	6 (both), 9, 12b(α)
8a	-	130.7	10, 12, 12b	-	-
9	7.45 [H-9, dd, *J* = 8.3, *J'*= 2.9]	124.2	8, 11, 12a	8 (both), 10	8 (both),
10	7.40 [H-10, t, *J*(10,9) = *J*(10,11) = 8.0]	129.3	8a, 12	9, 11	-
11	7.38 [H-11, t, *J*(11,10) = *J*(11,12) = 8.1]	128.0	9	10, 12	-
12	7.53 [H-12, dd, *J* = 8.3, *J'*=2.9]	124.1	8a, 10, 12b	11,12b	1, 12b
12a	-	137.6	9, 12b	-	-
12b	6.12 [H-12b, s]	64.52	1, 4a, 6, 8a, 12, 12a, 12c	1,12	1, 12
12c	-	134.1	12b	-	-

[a] In ppm from TMS; [b] H,C HMBC, [c] H-H COSY and [d] H-H NOESY connectivities.

The hydroxyl group on doubly benzylic carbon atom C12b of compounds **3** and **4** is associated with small downfield shifts of the H1 and H12 resonances. The same effect is seen for the signals of the C5 and C6 methylene protons. In contrast, the H11 resonance undergoes a slight upfield shift, and the remaining aromatic proton signals are practically unchanged.

In the ^{1}H NMR spectrum of **5a**, the H1 and H12 resonances appear at 7.55 and 7.53 ppm, respectively, suggesting that the molecule is considerably less planar than those of the lactams. The other ring A proton resonances are shifted downfield by almost 1 ppm, while the ring D proton signals appear further upfield due to the replacement of the C8 carbonyl by a methylene group. The positively charged nitrogen atom deshields H12b, but this effect is not manifest on H5, suggesting that in the cases of **3** and **4** the magnetic anisotropy of the C8 carbonyl group is dominant.

The ^{1}H NMR spectra of **3** and **4** are quite similar. In these, the H6a and H6b resonances appear at 3-55-3.53 and 4.32-4.31 ppm, respectively, with practically identical coupling constants for their doublets of doublets of doublets. H5a and –b resonate at 2.99-2.97 and 2.83-2.81 ppm, respectively, also with very similar coupling constants. This may be taken as an indication that both compounds have the same time-averaged conformation in spite of the conformational mobility inferred from the X-ray structures of different isoindolo[1,2-*a*]isoquinolin-8-ones (*vide infra*) and the possible steric bias due to the presence of the 12b-hydroxy group in **4**. In **5a** the pattern is rather different, with H6a and H6b as multiplets at 3.59 and 3.32, and H5a and H5b very poorly resolved and centred near 3.12 and 3.07 ppm. The lack of a downfield (i.e. 4.3 ppm) H6 resonance might be attributed to the absence of a carbonyl group at C8, although the change from an sp^2 lactam nitrogen to an sp^3 ammonium group might also be a determining factor. More significantly, the almost identical resonance frequencies of the H5 protons in **5a** suggests that the time-averaged conformation of this compound in solution bears both hydrogen atoms almost symmetrically with regard to ring A, while in the isoindolo[1,2-*a*] isoquinolin-8-ones the shielding of these atoms by the neighboring aromatic ring is quite different.

The ^{13}C NMR spectra of **3** and **4** only show significant differences for the unhydroxylated or hydroxylated C12b and the neighboring C12a and C12c. The ring A carbon resonances are very similar for all three compounds. Replacement of the C8 carbonyl group in **3** by an ammonium-substituted methylene group in **5a** leads to strong deshielding of the *para*-carbon atom and strong shielding of the *ortho* atoms in ring C.

Castro-Castillo *et al*.[4] recently reported the extremely facile and quantitative autoxidation of 4,5,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinolin-8-one (**3**) to its 12b-hydroxy derivative (**4**) and several analogous reactions, extending a report of a similar process undergone by 10,11-dimethoxy-4,5,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinolin-8-one.[1,8] The formation of **4** and its analogues is probably due to the doubly benzylic character of C12b which should therefore generate a highly stabilized free radical upon hydrogen abstraction. However, the strongly basic environment required suggests that the mechanism of autoxidation in this case might proceed *via* ionization to afford a carbanion capable of reducing molecular oxygen, and thus becoming oxidized to the stabilized free radical.[1]

The mass spectra of **3** and **4** are dominated by the ions presumably formed by loss of the hydrogen atom or the hydroxyl group, respectively, from C12b. The subsequent formation of a C=C double bond, necessarily at C5-C6, is another highly likely process, apparently followed in both cases by decarbonylation, generating a four-membered ring.

The crystal structure of **5a** was determined by single crystal X-ray diffraction. The asymmetric unit consists of 5,6,8,12b-tetrahydroisoindolo[1,2-*a*] isoquinoline hydrochloride and a solvent water molecule (Figure 3). The crystal contains a single enantiomer, as found previously by Wakchaure *et al.* for nuevamine (**2**),[9] and by us for 5,6,8,12b-tetrahydrodioxolo[4,5-*g*] isoindolo[1,2-*a*]isoquinolin-8-one,[10] indicating that these racemic synthetic compounds crystallize as conglomerates of both enantiomers.

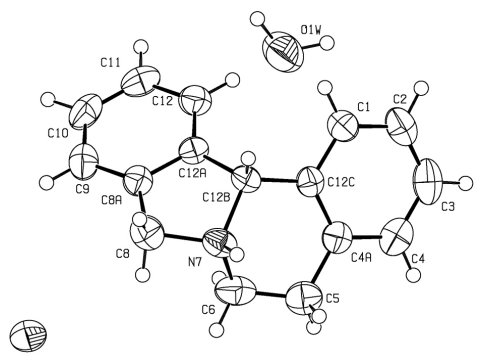

Figure 3. A view of the asymmetric unit of **5a,** showing the organic and solvent water molecules (atom numbering scheme) and the chloride ion. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radius.

Ring B (N7/C5-C6/C4a/C12B/C12C) has a distorted envelope conformation. Two sp^2 carbon atoms (C12C/C4a) of the benzene ring are almost coplanar with the base of the distorted envelope. The Cremer and Pople puckering parameters of ring B are QT = 0.477(3)Å, θ = 130.1(4)° and φ = 227.8(4)º.[11] The value of φ is appropriate for either an envelope or skew-boat.[12] Ring C (N7/C8/C8a/C12B/C12A) adopts an envelope conformation on N7 with puckering parameters q_2 = 0.323(3) Å and φ_2 = 178.1(4)º. The geometry at N7 is distorted pyramid (sp^3 hybridization). The sum of the three angles formed by N7, C6, C8 and H7N is 332.6º. Torsion angles C8-N7-C6-C5 and C12A-C12B-C12C-C1 are 178.5(2)º and 70.1(3)º, respectively. The C12a-C12b-C12C bond angle is 118.14(18)º.

Comparison of the crystal structure of **5a** with that of the related lactone 5,6,8,12b-tetrahydrodioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8-one ($C_{17}H_{13}NO_3$),[10] shows that the C12a-C12b-C12c angles of **5a** [118.15(18)º] and of the lactone [116.3(2)º] are very similar. However, the C8-N7-C6-C5 torsion angles are quite different [178.5(2)º and 100.3(4)º, respectively]. Nevertheless, this torsion angle in **5a** is similar to the corresponding angle in the synthetic intermediate iso - 12b-methoxycarbonyl-5,6,8,12b-tetrahydrodioxolo[4,5-*g*] isoindolo[1,2-*a*]isoquinolin-8-one.[9] This suggests that the latter ring is quite conformationally mobile and that the difference between ammonium salt **5a** and the corresponding lactone is largely dictated by crystal packing forces.

In the crystal of **5a**, molecules are linked by O1W—HW···Cl, N7—H7N···Cl, C—H···O1W and C—H···π intermolecular interactions forming a supramolecular network (Table 4). The solvent water molecule plays a dual role as both donor and acceptor in the hydrogen-bonding interactions, which consecutively generate the graph-set $R_4^2(8)$ and $R_2^1(6)$ motifs.[13] The H atoms of the water molecule (H1W and H2W) link each chloride anion forming a four-center $R_4^2(8)$ motif (Figure 4, top, Table 4).

Table 4. Hydrogen-bond and intermolecular contact interaction geometry of **5a** (Å, º).

D-X...A	d(D-X)	d(X...A)	d(D...A)	<(DXA)
O1W—H1W···Cl^{i}	0.97 (4)	2.26 (4)	3.222 (2)	176 (3)
O1W—H2W···Cl^{ii}	0.97 (1)	2.28 (1)	3.248 (2)	174 (3)
N7—H7N···Cl^{iii}	0.99 (1)	2.03 (1)	3.018 (2)	174 (2)
C1—H1···O1W	0.947 (19)	2.602 (19)	3.298 (4)	130.6 (15)
C9—H9···O1W^{ii}	0.94 (2)	2.51 (2)	3.430 (4)	164.5 (18)
C12B—H12B···O1W	0.974 (17)	2.572 (17)	3.351 (3)	137.0 (13)

Symmetry codes: (i) x, y, z+1; (ii) −x+1, −y, −z+1; (iii) x, −y+1/2, z+1/2.

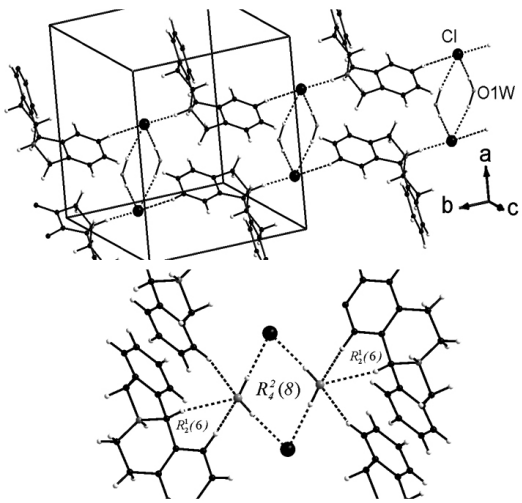

Figure 4. A partial packing scheme of **5a.** Top: A view of the hydrogen-bonded channels running parallel to the *ab* plane. Bottom: A view of the hydrogen bonds of the water molecules that are involved in the C1—H1···O1W and C12B—H12B···O1W centers. Dashed lines represent hydrogen bonds.

The molecules are linked *via* intermolecular N7—H7N···Cl^{iii} interactions [symmetry code: (iii) x, −y+1/2, z+1/2] between the chloride anions and the organic molecules (Table 4). Thus, the combination of O1W—HW···Cl and N—H···Cl hydrogen bonds leads to the formation of 3-dimensional channels running along the [010] direction (Figure 2, top). The hydrogen bonds of the water molecules that are involved in C1—H1···O1W and C12B—H12B···O1W generate two graph-set descriptor $R_2^1(6)$ motifs (Figure 2, bottom, Table 4). The packing structure contains an additional C9—H9···O1W^{ii} intermolecular contact [symmetry code: (ii) −x+1, −y, −z+1] with a bond distance of 2.51(2) Å and an angle of 164.5(18)º.

The hydrogen bond network is reinforced by two C—H···p interactions.[14] H8 on the five-membered ring is oriented toward the face of an aromatic ring of the neighboring molecule, leading to the formation of dimers (Figure 5). The C8—H8···*Cg1* distance is 2.81(2) Å and *Cg1* is the centroid of the C8a/C9-C12/C12a ring. The C6—H6B···*Cg2* distance is 2.83(3) Å and *Cg2* is the centroid of the C1-C4/C4a/C12c ring.

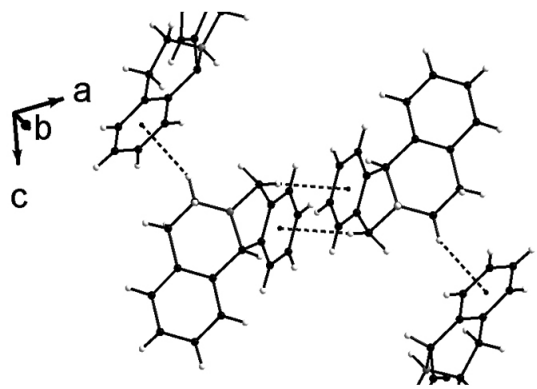

Figure 5. Part of the crystal structure of **5a**, showing the formation of the C—H···π intermolecular interactions built from C8—H8···*Cg1* [symmetry code: 1-x, −y, 1−z] and C6—H6B···*Cg2* [symmetry code: x, 1/2−y, -1/2+z]. Dashed lines represent intermolecular interactions.

The half-chair crystal conformations of ring B in nuevamine (**2**),[9] and 5,6,8,12b-tetrahydrodioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8-one ($C_{17}H_{13}NO_3$),[10] and the half-boat conformation of the corresponding ring in the crystals of 12b-methoxycarbonyl-5,6,8,12b-tetrahydrodioxolo[4,5-*g*] isoindolo[1,2-*a*]isoquinolin-8-one,[9] and now **5a**, reveal that the conformational difference between these pairs of compounds is unrelated to the sp^2 lactam or sp^3 tertiary ammonium character of the nitrogen atom. However, the presence of a large substituent at C12b in the 8-oxo compounds, as in 12b-methoxycarbonyl-5,6,8,12b-tetrahydrodioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8-one, might determine a preference for a half-boat conformation. In view of the flexibility of these molecules, the conformational data that can be gleaned from the ^{1}H NMR spectra cannot be related directly to either one of these basic X-ray conformational types, as both are presumably in equilibrium in solution.

As stated in the introduction, the isoindolo[1,2-*a*]isoquinoline scaffold is

of potential pharmacological interest, and it may be viewed as a "privileged" structure. Our results constitute the groundwork for a better understanding of the dynamics of this unusual system and for the interpretation of its interactions with proteins and/or nucleic acids. This is of particular interest in relation to the likely DNA interactions of the planar isoindolo[1,2-*a*]isoquinolin-8-ones and the effect of unprecedented tertiary amines like **5** on enzymes, receptors, structural or transporter proteins. We have now proved beyond all doubt the identity of the latter compound, whose structure has only been reported with some uncertainty in the older literature,[6] and which holds much promise for future elaboration.

EXPERIMENTAL SECTION

General Procedures. Commercially available, laboratory grade reagents were used without further purification. Melting points were determined on a Reichert Galen III hot plate with a DUAL JTEK Dig – Sense thermocouple thermometer, and are uncorrected. Analytical TLC was performed on Merck silica gel 60 F_{254} chromatofoils.

The synthesis of **3** has been reported,[1] based on the partial reduction with $NaBH_4$ of *N*-(2-phenylethyl)phthalimide to 3-hydroxy-2-(2-phenylethyl) isoindolin-1-one and the cyclization of this compound in 37% HCl.

3-Hydroxy-2-(2-phenylethyl)isoindolin-1-one. Colorless needles from MeOH (96 %), mp 170-172 °C (lit.[4] 170-172 °C). ^{1}H NMR: δ 2.98 (m, 2H, CH_2), 3.63 (m, 2H, CH_2), 5.52 (s, 1H, CH), 6.43 (s, 1H, OH) 7.22 (m, 5H, ArH), 7.60 (m, 4H, ArH).

5,6,8,12b-Tetrahydroisoindolo[1,2-*a*]isoquinolin-8-one (3). Colorless plates from EtOAc (77%), mp 115-117 °C (lit.[1,4,6,8] 114-116, 115-117, 116-118, 114-116 °C), HREIMS *m/z* 235.0605 (calcd for $C_{16}H_{13}NO$, 235.0997), EIMS *m/z* (rel. int.) 235.10 (19 %), 234.06 (85 %), 232.05 (100 %), 204.06 (31 %).

12b-Hydroxy-5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinolin-8-one (4), 5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinoline hydrochloride (5a) and 12b-hydroxy-5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinoline (6). A suspension of 5.0 g $LiAlH_4$ in 250 mL anhydrous THF was placed under an inert atmosphere (dry N_2) and stirred. A solution of **2** (5.0 g, 21.2 mmol) in THF (15 mL) was added dropwise and the reaction mixture was maintained at reflux for 48 h. After returning to room temperature, the excess hydride was destroyed by adding water-THF (1:1, 20 mL) followed by 15 % NaOH (15 mL) and then again water (10 mL). The solids were removed by filtration and washed with additional THF. The combined filtrate and washes were stripped of solvent under vacuum, and the residue was chromatographed on silica gel (EtOAc) to afford **4** (2.9 g, 55 %) as colorless prisms from MeOH, **5** (yellow oil, 297 mg, 6%) and **6** (yellow oil, 154 mg, 3%). Mp (**4**) 197-198 °C (lit.[4,6] mp 197-198, 200-203 °C), HREIMS *m/z* (**4**) 251.0756 (calcd for $C_{16}H_{13}NO_2$, 251.0946), EIMS *m/z* (rel. int.) 251.07 (16 %), 234.07 (100 %), 232.05 (88 %), 204.06 (31 %). Mp (**5a**) 219-221 °C (lit.[6] mp 221-225 °C), HREIMS *m/z* (**5a**) 221.1016 (calcd for $C_{16}H_{15}N$, 221.1205). ^{1}H NMR (**6**) (400 MHz): δ 3.27 (t, *J* = 7.4 Hz, 2H, CH_2), 3.83 (s, 2H, CH_2), 4.34 (s, 2H, CH_2), 7.21 (d, *J* = 7.8 Hz, 1H, ArH), 7.26 (d, *J* = 7.6 Hz, 1H, ArH), 7.32 (t, *J* = 7.5 Hz, 1H, ArH), 7.35 (m, 3H, ArH), 7.60 (t, *J* = 7.5 Hz, 1H, ArH), 7.63 (t, *J* = 7.6 Hz, 1H, ArH). ^{13}C NMR (**6**) (400 MHz): δ 24.46 (CH_2), 45.88 (CH_2), 56.35 (CH_2), 83.02 (C), 123.48 (C), 123.83 (CH), 126.75 (CH), 126.89 (C), 127.27 (CH), 127.57 (CH), 127.86 (CH), 129.31 (CH), 131.81 (CH), 136.75 (CH), 138.22 (C), 139.02 (C), HREIMS *m/z* (**6**) 237.1096 (calcd for $C_{16}H_{15}NO$, 237.1154).

NMR studies. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance 400 spectrometer with a Bruker inverse 5 mm Z gradient probe operating at 400.13 MHz and 100.62 MHz, respectively. All experiments were carried out at a probe temperature of 300 K, using solutions in DMSO-d_6 containing tetramethylsilane as an internal standard. Proton spectra were obtained with a spectral width of 5 kHz, a 30° flip angle (9.20 ms) and 1.0 s relaxation delay in 32 scans. ^{13}C spectra were recorded with a spectral width of 20 kHz with 256 ns between transients, and the 30° flip angle pulse lasted 13.50 ms.

The homonuclear ^{1}H-^{1}H shift-correlated 2D spectra were acquired with spectral widths of 5 kHz using the cosygpqf pulse sequence in the Bruker software. The spectra were collected with 1024 ´ 256 data points. Other parameters were the following: number of increments in t_1, 3 ms; number of scans, 4; relaxation delay, 1.0 s. The HSQC spectra were recorded using the invietgpsi pulse sequence in Bruker software with 1024 x 256 data points. The spectral widths were 5 and 17 Hz in the F_2 (^{1}H) and F_1 (^{13}C) domains, respectively, with 4 scans x F_2 and 3 ms increments in t_1. The data were processed using Qsine functions for weighting in both dimensions. The HMBC spectra were obtained using the inv4gplrndqf pulse sequence in Bruker software with 1024 ´ 128 data points, acquiring 16 scans ´ F_2 and 3 ms increments in t_1. They were acquired with spectral widths of 5 (F_2) and 17 kHz (F_1), and the delays D_1 and D_2 were 3.5 and 65 ms, respectively.

X-ray Crystallography

Single crystal analysis data were collected on a Bruker SMART CCD diffractometer with Mo*Ka* radiation. Data collection: Bruker *SMART* (BRUKER 1996); cell refinement: Bruker SAINTPLUS V6.02 (BRUKER 1997); data reduction: Bruker *SHELXTL* V6.10 (BRUKER 2000); program used to solve structure: *SHELXS97* (Sheldrick, 1990); program used to refine structure: *SHELXL97* (Sheldrick, 1997).[15,16] Molecular graphics: *DIAMOND* (Brandenburg, 1999); software used to prepare material for publication: *PLATON* (Spek, 2003).[17,18] Crystal dimensions of $C_{16}H_{16}N.H_2O.Cl$ 0.26×0.21×0.06 mm; *Mr* = 275.76; Monoclinic $P2_1/c$; a = 11.3465 (14) Å; b = 11.0603(14) Å; c = 11.3638 (14) Å;b = 94.698 (2)°; V = 1421.3 (3) Å^3; Z = 4; m = 0.26 mm^{-1}. 9997/1568 measured/unique reflections with I > 2s(I) [R_{int} = 0.070]; R [(F^2> 2*s* (F^2)] = 0.044; *w*R(F^2) = 0.086; *S* = 1.08; 244 parameters; Dr_{max} =0.40 e Å^{-3} and Dr_{mim} = -0.15 e Å^{-3}. All H atoms were located in difference maps and their positions and isotropic displacement parameters were refined freely. Supplementary information: crystallographic data (excluding structure factors) for the structural analysis have been deposited in the Cambridge Crystallographic Data Centre, CCDC 802469. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre; Postal Address: CCDC, 12 Union Road, Cambridge CB21EZ, UK, Telephone: (44) 01223 762910, Fax: (44) 01223 336033, e-mail: deposit@ccdc.cam.ac.uk.

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