SYNTHESIS OF 1-SUBSTITUTED 3,4-DIARYLISOQUINOLINE DERIVATIVES

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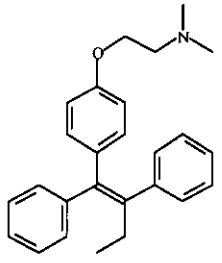
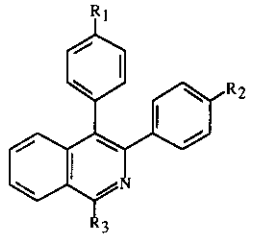
Abstract - 3,4-Diaryl-*2H*-isoquinolin-1-ones and corresponding 1-chloro derivatives were easily prepared in a way involving i) condensation of 2-aroylbenzyl chlorides with arylmethylamines ; ii) treatment of the resulting 1-aryl-*N*-1-hydroxyarylmethylisoindol-3-ones with LDA leading to an opening reaction and subsequent ring closure ; iii) dehydration in boiling formic acid which generally provided the expected isoquinolones in good yields.; iv) chlorination of the *2H*-isoquinolin-1-ones by phosphorous oxychloride.
In the cases of unsymmetrical 4-hydroxy-3-(4-methoxyphenyl)-4-phenyl- and 4-hydroxy-4-(4-methoxyphenyl)-3-phenyl-1, 2, 3, 4-tetrahydroisoquinolin-1-ones a partial and unexpected double aryl migrations (3 → 4) and (4 → 3) were observed.

In view to study biological properties of 3,4-diarylisoquinolines bearing a dialkylamino-alkylamino side chain at their 1 position, especially by comparison with triarylethylenes and tamoxifen-like compounds, [1] we were interested in the synthesis of variously substituted 1-chloro-3,4-diarylisoquinolines. Thus our project was to make these key intermediates from 2-aroylbenzoyl chlorides (**1**) and arylmethylamines (**2**), in which lithium diisopropylamide (LDA) deprotonation and subsequent transformation of the expected compounds (**3**) were supposed to successively provide **6** and **7**.



TAMOXIFEN



3.4-DIARYL ISOQUINOLINES

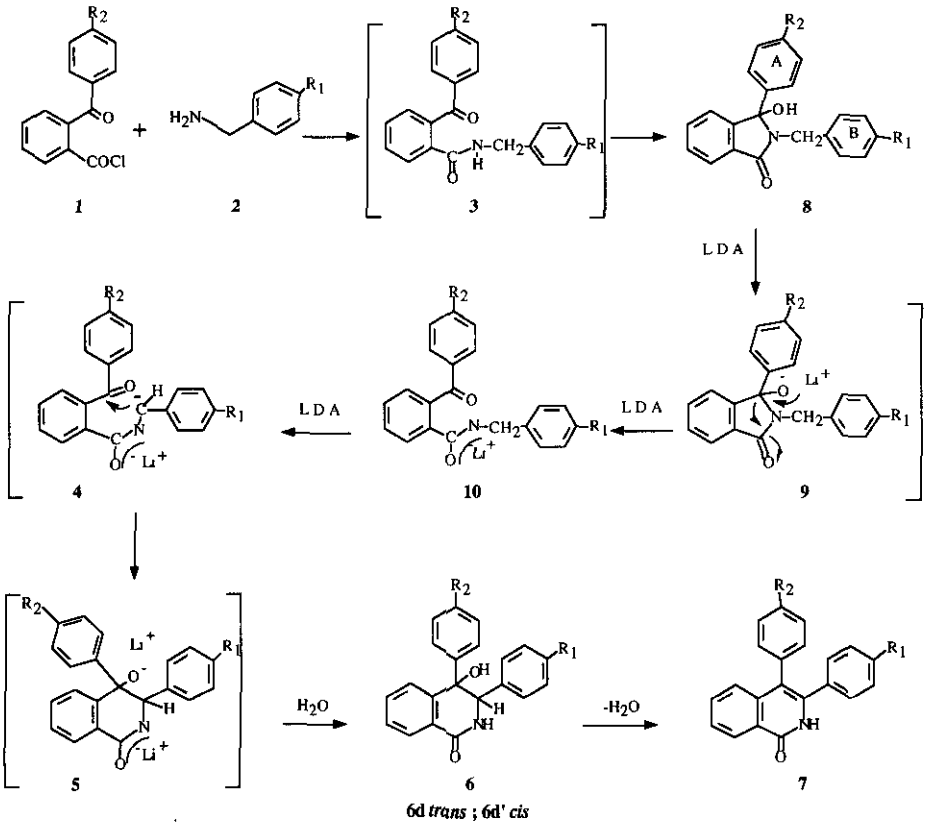
As a matter of fact, the reaction of 2-aroylbenzoyl chlorides (**1**) [2] with benzylamines (**2**) led to 1-aryl-*N*-arylmethyl-1-hydroxyisoindol-3-ones (**8**) whose structures were established on the basis of ^{1}H nmr spectra. Thus, ^{1}H nmr shows the lack of N<u>H</u>-C<u>H</u>$_2$ coupling, two nonequivalent protons at 4.04 and 4.72

ppm ($C\underline{H}_2$; doublet with J = 15 Hz) and a high field shift of an exchangeable proton at 3.13 ppm characteristic of a hydroxyl group. Moreover, ^{13}C nmr spectrum displays a signal for CO group at 167.16 ppm and the presence of a quaternary carbon bearing a OH group at 91.6 ppm. These data are fully in agreement with the assigned structures (**8**).

However, treatment of compounds (**8**) with an excess of LDA generated compounds (**6**), probably through the ring opening of **9** and then transformation into intermediates (**10**, **4**, and **5**) as summarised in Scheme 1.

Though the observed reaction led to 3,4-diaryl-4-hydroxyisoquinolin-1-ones which are fully different from the compounds arising from N-CH_2-CO-R substituted phtalimide rearrangement, namely 3-acyl (or 3-alkyloxycarbonyl)-4-hydroxyquinolin-1-ones, this ring extension is obviously related to the Gabriel Colman ring enlargment. [3]

Scheme 1



a : R_1=R_2=H ; b : R_1=H ; R_2=OCH_3 ; c : R_1=OCH_3 ; R_2=H ; d : R_1=R_2=OCH_3

Whereas mixtures of 3,4-*trans* and 3,4-*cis* diastereoisomers were expected for each compound (**6**),[4] only a single one (for **6a-c**) was isolated in 74-87 % yields. Examination of ^1H nmr did not allow us to assign the *trans* or *cis* geometry to these 3,4-diaryl-4-hydroxytetrahydroisoquinolin-1-ones. Starting from **8d**,

however, two products were obtained. Pure **6d** was isolated by crystallisation and **6d'**was purified by silica gel column chromatography of the mother liquors. They gave different melting points and Rfs values on tlc. ^{1}H Nmr spectra showed close similarities except for the signals of the 4-methoxyphenyl group of one isomer. Thus, in the case of **6d'**, the more soluble compound, a completely degenerated AA'BB' system was observed for one of the two 4-methoxyphenyl groups, while in the less soluble product (**6d**) the systems were completely resolved for both aromatic residues. Assignments of signals in ^{1}H and ^{13}C nmr spectra of the major component (**6d**) were fully performed. These inspection was confirmed by the combined use of 2D ^{1}H-^{1}H and ^{13}C nmr correlation experiments (reverse detection for HMQC and HMBC), [5] and NOE difference spectroscopy.

First, unambiguous assignment of signals for 2,6-H Ar-A and 2,6-H Ar-B was performed by using hetero long-range coupling between C3, C4 and 2,6 protons of each phenyl group. The degenerated AA'BB' system was attributed to Ar-B, which was confirmed by an NOE measurement between 4-O<u>H</u>, 3-<u>H</u> and 2,6-<u>H</u> of Ar-A and Ar-B.

The NOE allows us to point out differences between the two molecules. At first, in the less soluble isomer (**6d**), 4-O<u>H</u> and 3-<u>H</u>, and each with both p-anisyl groups (A and B) show NOE response, whereas in the more soluble one (**6d'**), a positive response was observed for the protons of only one p-anisyl group (Table 1).

Table 1 : NOE intensities for **6d** and **6d'** isomers.

	The less soluble compound **6d**					The more soluble compound **6d'**				
	4-OH	**3-H**	**2,6-H-Ar A**	**2,6-H-Ar B**	**NH**	**4-OH**	**3-H**	**2,6-H-Ar A**	**2,6-H-Ar B**	**NH**
4-OH		1.5	4.3	4.6*			1	1.5		
3-H	1.5		9*	9	10	1			5	10
2,6-H-Ar A									3*	
2,6-H-Ar B								3*		
NH		10		3.5			10		1.5	

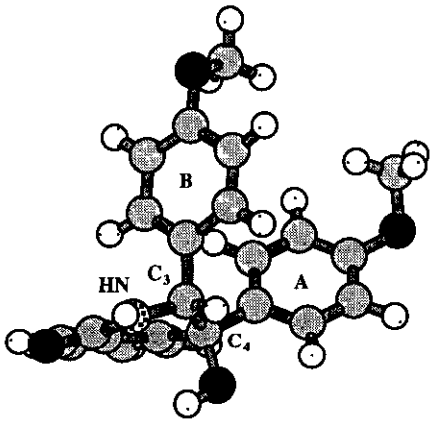
NOE response (relative intensities (%) of cross peaks in the NOESY map for a mixing time of 1 sec.)
* Compound specific response.

Secondly, *p*-anisyl groups A and B of compound (**6d'**) are "dipolarly" connected (NOE) contrary to what we observed for **6d** isomer. These results agree with those obtained by measuring the distances between each group implicated in the NOE for the four forms modelised and minimised by computer modeling.[6] So, according to these confrontations, we assign the *trans* conformation for the less soluble compound (**6d**) and the *cis* one for the more soluble and minor isomer (**6d'**).

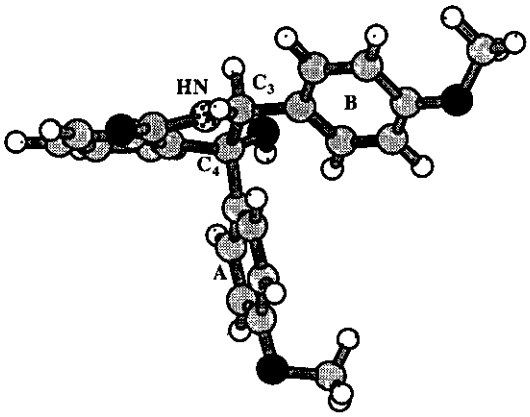
Furthermore, the absence of NOE between N<u>H</u> and 2,6-<u>H</u> of Ar-A in the two isomers should indicate a *trans* equatorial-equatorial configuration of the *p*-anisyl group for **6d** (*trans* 1) and a *cis* equatorial-axial

configuration for its **6d'** (*cis* 2) isomer. According to various possible conformation shown on Figure 1, we should have an NOE in the two other cases (Figure 1).

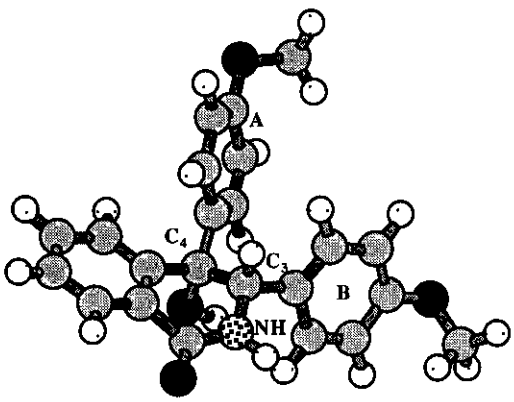
Figure 1



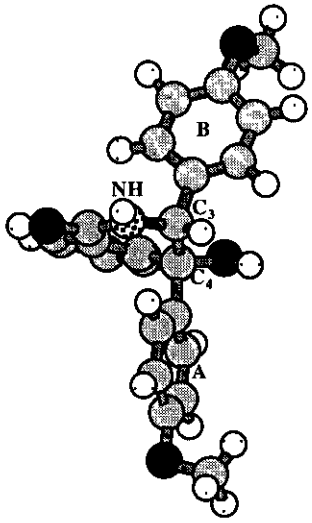
***cis*-1 (A axial, B equatorial)**



***cis*-2 (A equatorial, B axial)**



***trans*-1 (A and B equatorial)**



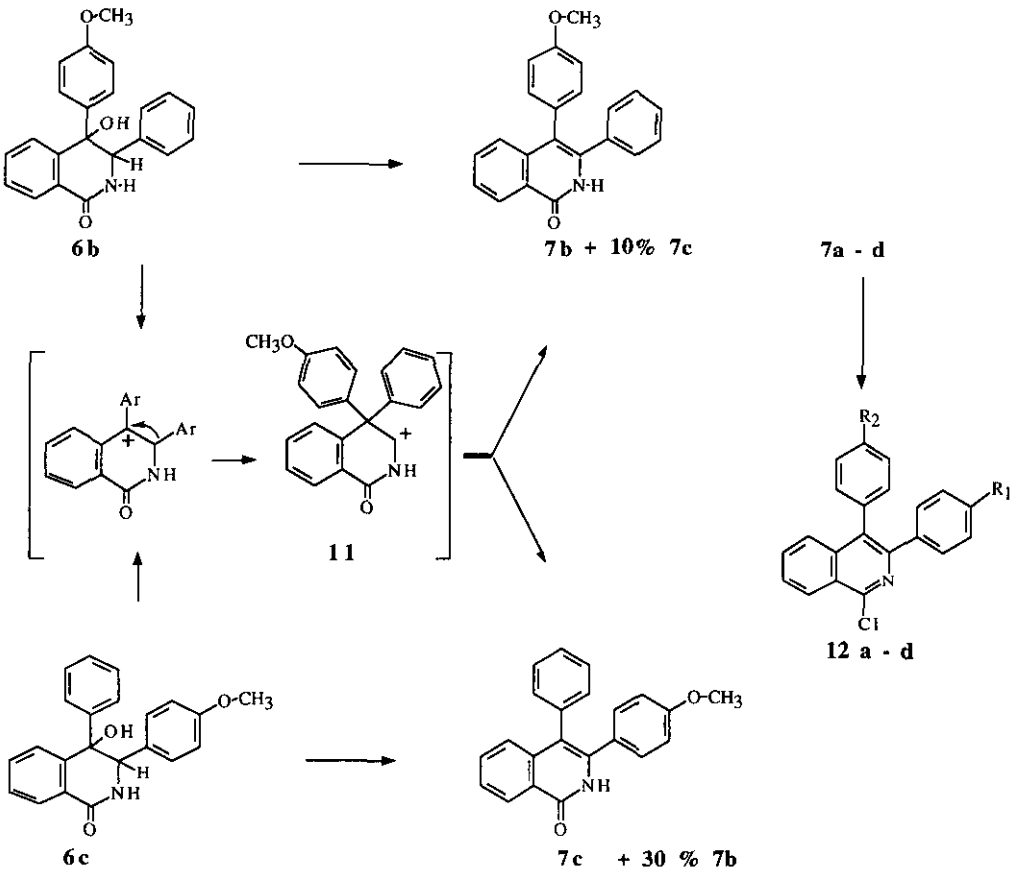
***trans*-2 (A and B axial)**

These results are in agreement with ^{1}H nmr data recently reported for tetrahydro-3,4-diaryl-2-methyl-isoquinolin-4-ols [7] from which it appeared likely that ^{1}H nmr spectra of **6a-c** and the major compound (**6d**) obtained from **8d** corresponded to the 3,4-*trans*-diaryl-4-hydroxy-1,2,3,4-tetrahydroisoquinolin-1-one diastereoisomers. This observation was also in agreement with the results generally obtained for tetrahydroisoquinolines. [8]

By performing dehydration of 3,4-diarylisoquinolin-4-ols, (**6a**), (**6d**) and (**6d'**) (where $R_1 = R_2$), in boiling formic acid, corresponding 3,4-diaryl-2*H*-isoquinolin-1-ones (**7a**) and (**7d**) were obtained in nearly quantitative yields.

In the cases of **6b** and **6c**, dehydration mainly led to the corresponding expected compounds (**7b**) and (**7c**) but ^{1}H nmr spectra showed the presence of the unexpected isomers (**7b** from **6c** and **7c** from **6b**). From these mixtures (95 % yield) only **7b** was obtained in a pure form. This allowed us to perform a detailed ^{1}H nmr study. On the basis of NOE measurement between protons of the NH and 2,6-H unsubstituted phenyl group the assigned structure was confirmed .

Scheme 2



These results clearly show that besides the normal dehydration of 3,4-diaryl-4-hydroxy-1,2,3,4-tetrahydro-isoquinolin-1-ones which gave the expected compound, double aryl migrations (3 → 4 and 4 → 3) took place (Scheme 2).

Examples of 3 → 4 aryl migration in dehydration of a 3-aryl-4-hydroxyisoquinoline have been already described. [9] In the present case, the established double aryl migrations probably involve the intermediate carbocations drawn on Scheme 2 which account for the observed isomerization.

However, as exemplified in an old deamination study of 1,2,2-triarylethylamines [10] the markedly superior migration aptitude of *p*-anisyl versus phenyl in carbocation reactions [11] involving concomitent competitive aryl migration could account for our result.

Treatment of **7** with boiling phosphorous oxychloride gave the corresponding pure chloro compounds (**12**) in which **12b** was obtained by separation using column chromatography of a mixture of **12b** and **12c** prepared from a mixture of **7b** and **7c**.

In conclusion, various 3,4-diaryl-*2H*-isoquinolin-1-ones and corresponding 1-chloro-derivatives are easily prepared through a 3-4 step sequence from available substituted benzylamines and 2-benzoylbenzoyl chlorides. In the case of unsymmetrical 3,4-diaryl substituted derivatives, unexpected rearranged compounds arising from dehydration and concomitant double aryl migrations (4 → 3 and 3 → 4) can yet result.

EXPERIMENTAL PART

Melting points were determined on Reichert hot stage microscope and are uncorrected. Microanalytical results were obtained from C.N.R.S. Institut des Substances Naturelles, Gif sur Yvette. ^{1}H and ^{13}C Nmr spectra were recorded in a Brucker 200 AC (200 MHz). Chemical shifts are given in ppm relative to internal TMS (δ scale).

Physical data for compounds (**6-8** and **12**) are listed in Table 2.

General Procedure for the Synthesis of 1-aryl-*N*-arylmethyl-1-hydroxyisoindol-3-ones (**8a-d**).

2-Aroylbenzoyl chlorides (**1a,b**) were prepared from 2-benzoyl- or 2-(4-methoxybenzoyl)benzoic acids[2] with excess of $SOCl_2$ at room temperature for 12 h, followed by removal of excess $SOCl_2$ at reduced pressure. The crude product was dissolved in toluene and the solvent removed under *vacuum*. The crude material was used without further purification.

In a typical reaction, 2-benzoylbenzoyl chloride (**2a**) (10 g, 0.04 mol) dissolved in dry toluene (100 ml) was added dropwise to a magnetically stirred mixture of benzylamine (**1b**) (4.2 g, 0.04 mol) and triethylamine (4 g, 0.04 mol) in dry toluene (100 ml). The resulting mixture was refluxed for 3 h. After cooling, the reaction was quenched by addition of water (100 ml) and the layers were separated. The organic layer was washed successively by saturated aqueous $NaHCO_3$, H_2O, dried ($MgSO_4$) and evaporated under *vaccum*. The white solid residue was purified by recrystallization from toluene. Acidification of the aqueous layer by 6N HCl provided the recovered starting acid (10 %).

N-Benzyl-1-hydroxy-1-phenylisoindol-3-one (**8a**).

^{1}H Nmr ($CDCl_3$) δ : 3.17 (s, 1H, OH), 4.04, 4.72 (d, each 1H, J = 15 Hz, N-C<u>H</u>2), 7.10-7.35 (m, 10H, Ar-A + Ar-B + H-7), 7.40-7.50 (m, 2H, H-5, H-6), 7.79 (m, 1H, H-4). ^{13}C-Nmr ($CDCl_3$) δ : 167.6 (C = O), 91.62 (C1-OH).

N-Benzyl-1-hydroxy-1-(4-methoxyphenyl)isoindol-3-one (**8b**).

^{1}H Nmr ($CDCl_3$) δ : 3.28 (s, 1H, OH), 3.73 (s, 3H, OCH_3), 4.07, 4.72 (d, each 1H, J = 15 Hz, N-C<u>H</u>2), 6.70 (d, 2H, J = 8.9 Hz, BB'Ar-A), 7.09 (br s, 5H, Ar-B), 7.17 (d, 2H, J = 8.9 Hz, AA'Ar-A),

7.22 (dd, J = 6.7 Hz and 1.8 Hz, 1H, H-7), 7.37 (m, 1H, H-5), 7.43 (m, 1H, H-6), 7.67 (m, 1H, H-4). ^{13}C-Nmr ($CDCl_3$) δ : 167.8 (C = O), 159 ($\underline{C}OCH_3$), 149 (C7a), 132.6 (C6), 130.13 (C8), 130 (C3a), 129.2 (C5), 127.54 (CAA'-Ar-A), 126.7-128 (CAr-B), 123.2 (C4), 122.6 (C7), 113.5 (CBB'-Ar-A), 91.35 (C1-OH), 55 (O-$\underline{C}H_3$), 42.65 ($\underline{C}H_2$).

Table 2. Melting points, yields and analytical data for compounds (**8, 6, 7, 12 a-d**).

	R_1	R_2	mp (lit)	Yield	Formula	Analyses C%		H%		N%	
			℃	%		Calcd	Found	Calcd	Found	Calcd	Found
8a	H	H	150	76	$C_{21}H_{17}NO_2$	79.98	79.75	5.43	5.53	4.44	4.33
8b	H	OCH_3	175	38	$C_{22}H_{19}NO_3$	76.50	76.29	5.54	5.67	4.06	4.09
8c	OCH_3	H	159	78	$C_{22}H_{19}NO_3$	76.50	76.42	5.54	5.76	4.06	4.08
8d	OCH_3	OCH_3	138	49	$C_{23}H_{21}NO_4$	73.58	73.38	5.64	5.83	3.73	3.86
6a	H	H	<280	74	$C_{21}H_{17}NO_2$	79.98	79.83	5.43	5.51	4.44	4.34
6b	H	OCH_3	195	74	$C_{22}H_{19}NO_3$	76.50	76.51	5.54	5.77	4.06	3.70
6c	OCH_3	H	196	87	$C_{22}H_{19}NO_3$	76.50	76.62	5.54	5.77	4.06	4.03
6d *trans*	OCH_3	OCH_3	140	88	$C_{23}H_{21}NO_4$	73.58	73.95	5.64	5.98	3.73	3.66
6d' *cis*	OCH_3	OCH_3	212	4	$C_{23}H_{21}NO_4$	73.58	73.16	5.64	5.86	3.73	3.92
7a	H	H	256[a]	97							
7b	H	OCH_3	260	93	$C_{22}H_{17}NO_2$	80.71	80.56	5.23	5.18	4.28	4.22
7c + 1/3 **7b**	OCH_3	H		95[b]							
7d	OCH_3	OCH_3	271	95	$C_{23}H_{19}NO_3$	77.29	76.11	5.36	5.51	3.92	3.85
12a	H	H	196[a]	91							
12b	H	OCH_3	183	80	$C_{22}H_{16}NOCl$	76.41	76.11	4.66	4.95	4.05	3.77
12c	OCH_3	H	133	78[c]	$C_{22}H_{16}NOCl$	76.41	76.71	4.66	4.59	4.05	3.85
12d	OCH_3	OCH_3	136	86	$C_{23}H_{18}NO_2Cl$	73.50	73.26	4.83	5.01	3.73	3.77

[a] see ref.12
[b] Overall yield from **6c**.
[c] Overall yield from **7c**.

1-Hydroxy-*N*-(4-methoxybenzyl)-1-phenylisoindol-3-one (**8c**).

^{1}H Nmr ($DMSOd_6$) δ : 3.72 (s, 3H, OCH_3), 4.20, 4.49 (d, each 1H, J = 15 Hz, N-CH_2), 6.78 (m, 2H, BB'Ar-B), 7.16 (m, 2H, AA'Ar-B), 7.23 (s, 1H, OH), 7.27-7.36 (m, 6H, Ar-A + H-7), 7.50-7.60 (m, 2H, H-6, H-5), 7.80 (m, 1H, H-4). ^{13}C Nmr ($DMSOd_6$) δ 167 (C = O), 90.8 (C1-OH).

1-Hydroxy-*N*-(4-methoxybenzyl)-1-(4-methoxyphenyl)isoindol-3-one (**8d**).

^{1}H Nmr ($CDCl_3$) δ : 3.52 (s, 1H, OH), 3.68 (s, 3H, OCH_3 Ar-B), 3.77 (s, 3H, OCH_3 Ar-A), 3.98, 4.6 (d, each 1H, J = 15 Hz, N-CH_2), 6.63 (d, 2H, J = 8.7 Hz ; BB'Ar-B), 6.77 (d, 2H, J = 8.8 Hz, BB'Ar-A), 7.1 (d, 2H, J = 8.7 Hz, AA'Ar-B), 7.22 (d, 2H, J = 8.8 Hz, AA'Ar-A), 7.24 (m, 1H, H-7), 7.35-7.49 (m, 2H, H-5, H-6), 7.72 (m, 1H, H-4).

General Procedure for the Synthesis of 3,4-Diaryl-1,2,3,4-tetrahydro-4-hydroxy-2*H*-isoquinolin-1-ones (**6a-d**).

In a typical reaction, a solution of lithium diisopropylamide mono(tetrahydrofuran) (complex from Aldrich 1.5 M in cyclohexane, 3 molar equivalents) was added dropwise to a stirred solution of isoindol-3-one (**8a**) (6.3 g, 0.02 mol) in dry THF (200 ml) at -78° under argon atmosphere. A highly blue colour appeared immediately. The mixture was allowed to reach room temperature and left overnight, then quenched with saturated NH_4Cl (100 ml) solution and extracted with CH_2Cl_2 (2 x 200 ml). The organic layer was washed with brine (200 ml) and dried ($MgSO_4$). The white crystals obtained after evaporation were recrystallized from toluene.

4-Hydroxy-3,4-diphenyl-1,2,3,4-tetrahydro-2*H*- isoquinolin-1-one (**6a**).

^{1}H Nmr ($DMSOd_6$) δ : 5.03 (d, 1H, J = 3 Hz, H-3), 6.21 (s, 1H, OH), 7.08-7.20 (m, 6H, Ar-A + H-5), 7.31 (s, 5H, Ar-B), 7.54 (m, 2H, H-6, H-7), 8.02 (dd, J = 6.9 Hz and 2 Hz, 1H, H-8), 8.29 (d, 1H, J = 3 Hz, NH). ^{13}C Nmr ($DMSOd_6$) δ : 164 (C = O), 74.6 (C4-OH), 64 (C3-H).

4-Hydroxy-4-(4-methoxyphenyl)-3-Phenyl-1,2,3,4-tetrahydro-2*H*-isoquinolin-1-one (**6b**).

^{1}H Nmr ($CDCl_3$) δ : 3.63 (s, 1H, OH), 3.76 (s, 3H, OCH_3), 5.00 (d, 1H, J = 2.9 Hz, H-3), 6.16 (br s, 1H, NH), 6.76 (m, 2H, BB'Ar-A), 7.05-7.25 (m, 8H, Ar-B + AA'Ar-A + H-5), 7.25-7.50 (m, 2H, H-6, H-7), 8.04 (dd, J = 7.8 Hz and 1.9 Hz, 1H, H-8).

4-Hydroxy-3-(4-methoxyphenyl)-4-phenyl-1,2,3,4-tetrahydro-2*H*-isoquinolin-1-one (**6c**).

^{1}H Nmr ($DMSOd_6$) δ : 3.71 (s, 3H, OCH_3), 5.00 (d, 1H, J = 2.9 Hz, H-3), 6.11 (s, 1H, OH), 6.75 (d, 2H, J = 8.5 Hz, BB'Ar-B), 7.03 (d, 2H, J = 8.5 Hz, AA'Ar-B), 7.18 (dd, 1H, J = 7.7 Hz and 1.7 Hz, H-5), 7.31 (br s, 5H, Ar-A), 7.50-7.57 (m, 2H, H-6, H-7), 8.04 (dd, 1H, J = 6.9 Hz and 1.5 Hz, H-8), 8.2 (d, 1H, J = 2.9 Hz NH). ^{13}C Nmr ($CDDl_3$) δ : 164 (C = O), 74.6 (C3-OH).

3,4-*trans*-4-hydroxy-3,4-di-(4-methoxyphenyl)-1,2,3,4-tetrahydro-2*H*-isoquinolin-1-one (**6d**).

6d (6.3 g, 84 %) was obtained from crystallization. The mother liquors contained isomer *cis* and *trans*. Pure compound was separated by chromatography on silica gel column with CH_2Cl_2-AcOEt (10 : 1) as eluent. Pure *cis* **6d'** was isolated in 4 % yield.

^{1}H Nmr ($CDCl_3$) δ : 3.12 (s, 1H, OH), 3.74 (s, 3H, OCH_3 Ar-B), 3.78 (s, 3H, OCH_3 Ar-A), 4.97 (d, 1H, J = 1.65 Hz, H-3), 6.05 (d, 1H, J = 1.65 Hz, NH), 6.71 (d, 2H, J = 8.7 Hz, BB'Ar-B), 6.78 (d, 2H, J = 8.9 Hz, BB'Ar-A), 6.98 (d, 2H, J = 8.7 Hz, AA'Ar-B), 7.15 (d, 2H, J = 8.9 Hz, AA'Ar-A),

7.09 (dd, 1H, J = 7.6 Hz and 2 Hz, H-5), 7.39-7.45 (m, 2H, H-6, H-7), 8.11 (m, 1H, H-8). ^{13}C Nmr ($CDCl_3$) δ : 165.4 (C = O), 159-158 (2 C OCH_3) 143.17 (C4a), 134.2(C9), 133 (C6), 129.7 (CAA' Ar-B), 128.35 (C_7), 128.17 (CAA' Ar-A), 127.6 (C8, C8a, C,5, C15), 113.3-112.9 (2 CBB'Ar-A, Ar-B), 75.31 (C4) 65.6 (C3), 55 (2 OCH_3).

3,4-*cis*-4-hydroxy-3.4-di-(4-methoxyphenyl)-1,2,3,4-tetrahydro-2*H*-isoquinolin-1-one (**6d'**).

^1H Nmr ($CDCl_3$) δ : 2.67 (s, 1H, OH), 3.72 (s, 3H, OCH_3 Ar-A), 3.78 (s, 3H, OCH_3 Ar-B), 5.02 (s, 1H, H-3), 5.73 (s, 1H, NH), 6.60 (s, 4H, Ar-A), 6.72 (m, 2H,BB'Ar-B), 6.8 (m, 2H,AA' Ar-B), 7.47 (m, 1H, H-5), 7.5-7.62 (m, 2H, H-5, H-6), 8.21 (m, 1H, H-8).

General Procedure for Dehydratation of Compounds (**7a-d**).

A mixture of compound (**6a-d**, 0.015 mol) was heated in refluxing HCOOH (100 ml) for 0.5 h. The cooled reaction mixture was evaporated under *vacum* and H_2O (50 ml) was added to the residue. The resulting white crystals were filtered and recrystallized from C_2H_5OH (**7a**, **7b**) or toluene (**7c**, **7d**). Pure **7c** was not isolated. *Trans* (**6d**) and *cis* (**6d'**) gave the same product (**7d**).

3,4-Diphenyl-2*H*- isoquinolin-1-one (**7a**).[12]

^1H Nmr (DMSO-d_6) δ : 7.17-7.35 (m, 11H, Ar-A + Ar-B + H-5), 7.55 (m, 1H, H-7), 7.68 (m, 1H, H-6), 8.35 (dd, J = 1H, H-8), 11.6 (s, 1H, NH).

4-(4-Methoxyphenyl)-3-phenyl-4-2*H*-isoquinolin-1-one (**7b**).

^1H Nmr ($CDCl_3$) δ : 3.80 (s, 3H, OCH_3), 6.83 (d, 2H, J = 8.6 Hz, BB'Ar-A), 7.07 (d, 2H, J = 8.6 Hz, AA' Ar-A), 7.26 (s, 5H, Ar-B), 7.37 (m, 1H, H-5), 7.45-7.59 (m, 2H, H-6, H-7), 8.45 (dd, 2H, J = 7.7 Hz and 1.5 Hz, H-8), 9.44 (s, 1H, NH).

3,4-Di-(4-methoxyphenyl)-2*H*- isoquinolin-1-one (**7d**).

^1H Nmr ($CDCl_3$) δ : 3.77 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 6.76 (d, 2H, J = 8.7 Hz, BB'Ar-B), 6.85 (d, 2H, J = 8.5 Hz, BB'Ar-A), 7.07 (d, 2H, J = 8.5 Hz, AA'Ar-B), 7.13 (d, J = 8.7 Hz, 2H, AA'Ar-A), 7.35 (m, 1H, H-5), 7.47 (m, 1H, H-7), 7.57 (m, 1H, H-6), 8.49 (dd, 1H, J = 7.6 Hz and 1.9 Hz, H-8), 8.72 (s, 1H, NH).

General Procedure for the Synthesis of 3,4-diaryl-1-chloro-isoquinolines (**12a-d**).

In a typical reaction, a mixture of **7a** (4 g, 13.5 mmol) in $POCl_3$ (50 ml) was refluxed for 2.5 h, after cooling $POCl_3$ was evaporated *in vacuo*, then the residue was poured into ice-water and a saturated aqueous K_2CO_3 solution was added. **12a-d** were extracted with CH_2Cl_2 (3 x 50 ml). The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated under vaccum. The chloro compounds (**12a-d**) were recrystallized from cyclohexane. Pure **12c** was obtained by chromatography on silica gel column, eluting with CH_2Cl_2.

1-Chloro-4-(4-methoxyphenyl)-3-phenylisoquinoline (**12b**).

^1H Nmr ($CDCl_3$) δ : 3.84 (s, 3H, OCH_3), 6.90 (d, 2H, J = 8.7 Hz, BB'Ar-A), 7.13 (d, 2H, J = 8.7 Hz, AA' Ar-A), 7.18-7.25 (m, 5H, Ar-B), 7.69-7.62 (m, 3H, H-5, H-6, H-7), 8.39 (m, 1H, H-8).

1-Chloro-3-(4-methoxyphenyl)-4-phenylisoquinoline (**12c**).

^1H Nmr ($CDCl_3$) δ: 3.75 (s, 3H, OCH_3), 6.72 (d, J = 8.8 Hz, 2H, BB'Ar-B), 7.31 (d, 2H, J = 8.9 Hz,

AA'Ar-B), 7.22-7.44 (m, 5H, Ar-A), 7.62 (m, 3H, H-5, H-6, H-7), 8.38 (m, 1H, H-8).

1-Chloro-3,4-di-(4-methoxyphenyl) isoquinoline (**12d**).

^{1}H Nmr ($CDCl_3$) δ : 3.76 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.74 (d, 2H, J = 8.7 Hz, BB'), 6.93 (d, 2H, J = 7.9 Hz, BB'Ar-A), 7.14 (d, 2H, J = 8.7 Hz, AA'Ar-B), 7.32 (d, 2H, J = 8.9 Hz, AA'Ar-A), 7.31-7.71 (m, 3H, H-5, H-6, H-7), 8.38 (m, 1H, H-8).

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