

SYNTHESIS OF 1-SUBSTITUTED 3,4-DIARYLISOQUINOLINE DERIVATIVES

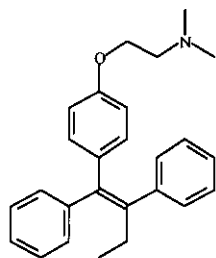
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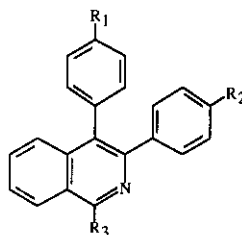
Abstract - 3,4-Diaryl-2*H*-isoquinolin-1-ones and corresponding 1-chloro derivatives were easily prepared in a way involving i) condensation of 2-arylylbenzyl chlorides with arylmethylamines; ii) treatment of the resulting 1-aryl-*N*-1-hydroxyarylmethylisoindol-3-ones with LDA leading to an opening reaction and subsequent ring closure; iii) dehydration in boiling formic acid which generally provided the expected isoquinolones in good yields.; iv) chlorination of the 2*H*-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-arylylbenzoyl 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

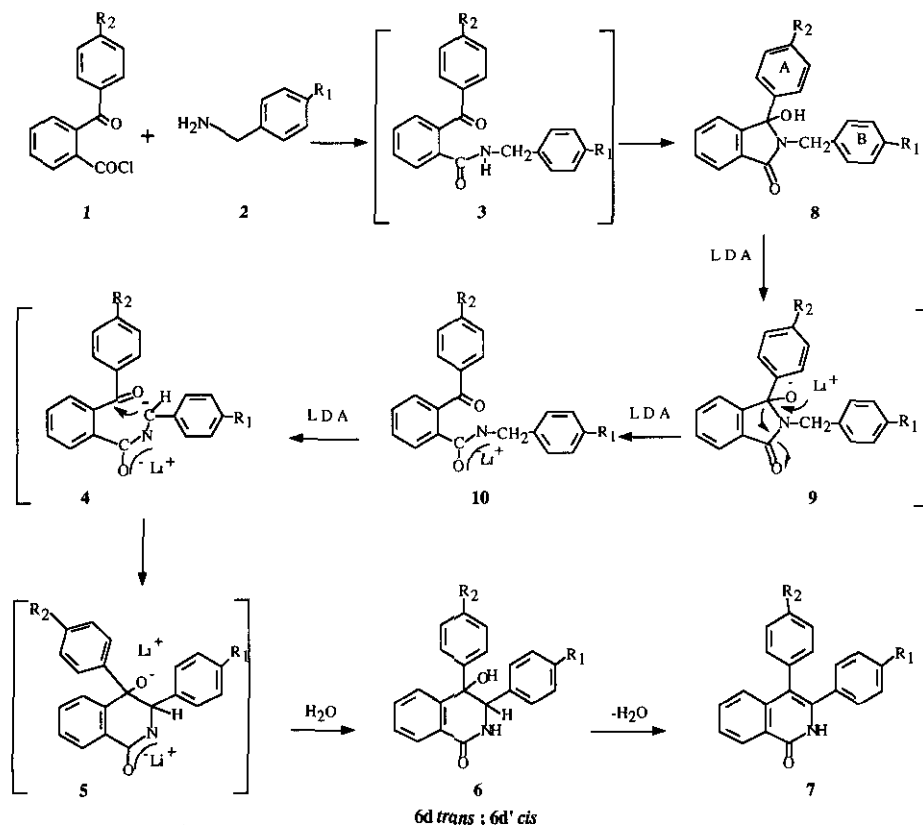
As a matter of fact, the reaction of 2-arylylbenzoyl chlorides (1)² with benzylamines (2) led to 1-aryl-*N*-arylmethyl-1-hydroxyisoindol-3-ones (8) whose structures were established on the basis of ¹H nmr spectra. Thus, ¹H nmr shows the lack of NH-CH₂ coupling, two nonequivalent protons at 4.04 and 4.72

ppm (CH_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- $\text{CH}_2\text{-CO-R}$ substituted phthalimide rearrangement, namely 3-acyl (or 3-alkyloxycarbonyl)-4-hydroxyquinolin-1-ones, this ring extension is obviously related to the Gabriel Colman ring enlargement.³

Scheme 1



a : R₁=R₂=H ; b : R₁=H ; R₂=OCH₃ ; c : R₁=OCH₃ ; R₂=H ; d : R₁=R₂=OCH₃

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 R_fs values on tlc. ¹H 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 ¹H and ¹³C nmr spectra of the major component (**6d**) were fully performed. These inspection was confirmed by the combined use of 2D ¹H-¹H and ¹³C 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-OH, 3-H and 2,6-H 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-OH and 3-H, 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.)

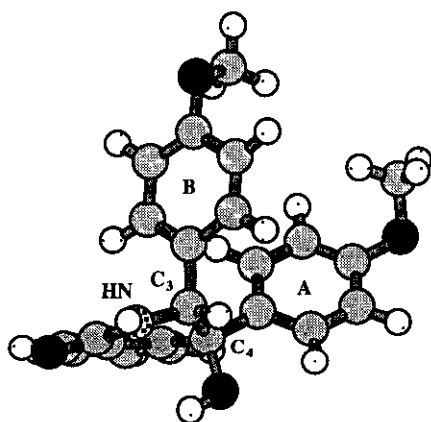
* Compound specific response.

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'**).

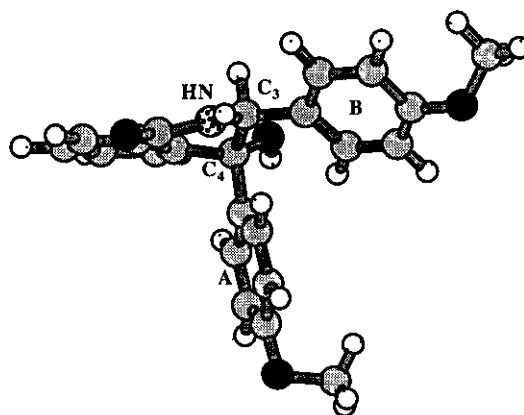
Furthermore, the absence of NOE between NH and 2,6-H of Ar-A in the two isomers should indicate a *trans* equatorial-equatorial configuration of the *p*-anisyl group for **6d** (*trans* 1) and a *cis* equatorial-axial

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).

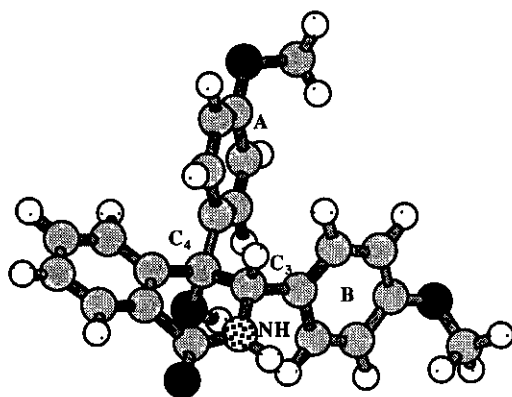
Figure 1



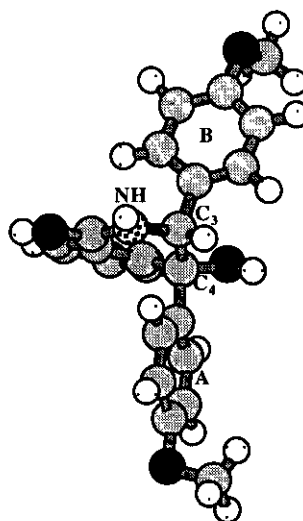
cis-1 (A axial, B equatorial)



cis-2 (A equatorial, B axial)



trans-1 (A and B equatorial)



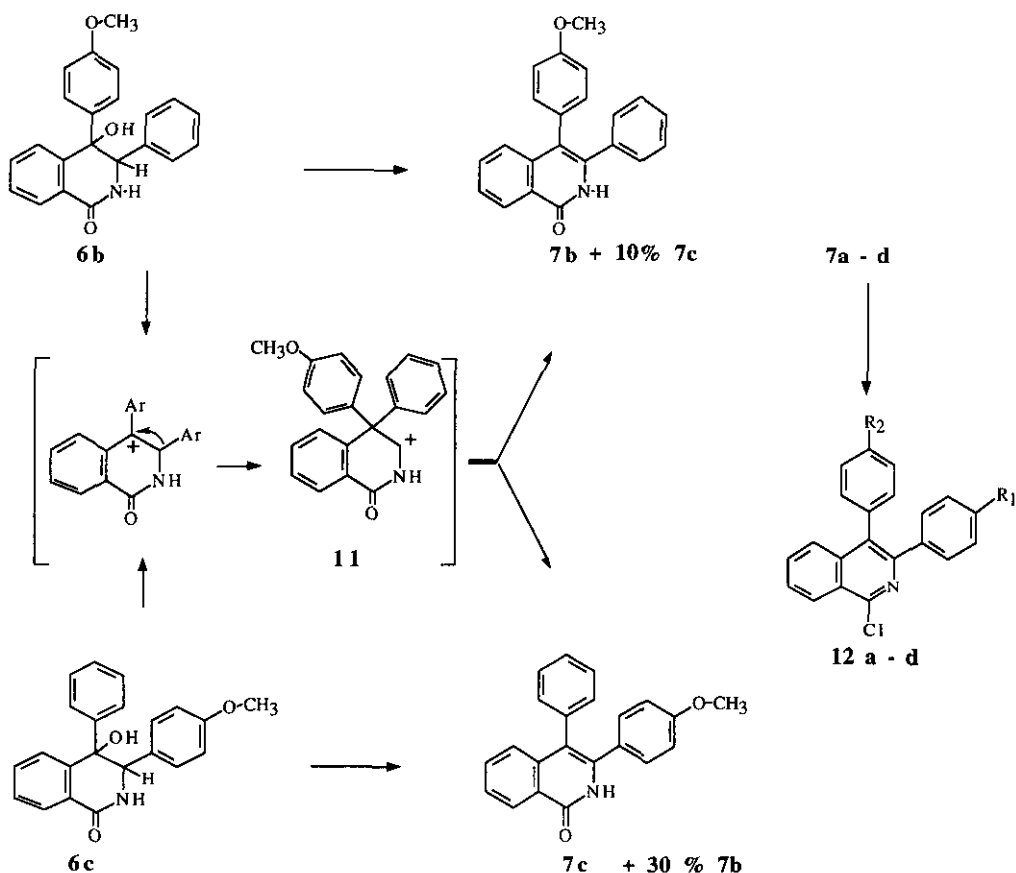
trans-2 (A and B axial)

These results are in agreement with ^1H nmr data recently reported for tetrahydro-3,4-diaryl-2-methyl-isoquinolin-4-ols ⁷ from which it appeared likely that ^1H 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-diarylisquinolin-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 ^1H 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 ^1H 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-tetrahydroisoquinolin-1-ones which gave the expected compound, double aryl migrations ($3 \rightarrow 4$ and $4 \rightarrow 3$) took place (Scheme 2).

Examples of $3 \rightarrow 4$ 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-triarylethylamines¹⁰ the markedly superior migration aptitude of *p*-anisyl versus phenyl in carbocation reactions¹¹ involving concomitant 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-2*H*-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. ¹H and ¹³C Nmr spectra were recorded in a Bruker 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 acids² with excess of SOCl₂ at room temperature for 12 h, followed by removal of excess SOCl₂ 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 NaHCO₃, H₂O, dried (MgSO₄) and evaporated under *vacuum*. 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**).

¹H Nmr (CDCl₃) δ : 3.17 (s, 1H, OH), 4.04, 4.72 (d, each 1H, J = 15 Hz, N-CH₂), 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). ¹³C-Nmr (CDCl₃) δ : 167.6 (C = O), 91.62 (C1-OH).

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

¹H Nmr (CDCl₃) δ : 3.28 (s, 1H, OH), 3.73 (s, 3H, OCH₃), 4.07, 4.72 (d, each 1H, J = 15 Hz, N-CH₂), 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 ($\text{C}=\text{OCH}_3$), 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-CH₃), 42.65 (CH₂).

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%	
			°C	%		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	OCH ₃	OCH ₃	140	88	C ₂₃ H ₂₁ NO ₄	73.58	73.95	5.64	5.98	3.73	3.66
<i>trans</i> 6d'	OCH ₃	OCH ₃	212	4	C ₂₃ H ₂₁ NO ₄	73.58	73.16	5.64	5.86	3.73	3.92
<i>cis</i>											
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 ₂ Cl	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).

^1H Nmr (DMSO d_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 (DMSO d_6) δ 167 (C = O), 90.8 (C1-OH).

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

^1H 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-2H-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 $_4$ Cl (100 ml) solution and extracted with CH $_2$ Cl $_2$ (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-2H-isoquinolin-1-one (6a).

^1H Nmr (DMSO d_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 (DMSO d_6) δ : 164 (C = O), 74.6 (C4-OH), 64 (C3-H).

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

^1H 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-2H-isoquinolin-1-one (6c).

^1H Nmr (DMSO d_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-2H-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 $_2$ Cl $_2$ -AcOEt (10 : 1) as eluent. Pure *cis* **6d'** was isolated in 4 % yield.

^1H 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 (CDCl₃) δ : 165.4 (C = O), 159-158 (2 $\underline{\text{C}}$ OCH₃) 143.17 (C4a), 134.2(C9), 133 (C6), 129.7 (CAA' Ar-B), 128.35 (C7), 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 OCH₃).

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

^1H Nmr (CDCl₃) δ : 2.67 (s, 1H, OH), 3.72 (s, 3H, OCH₃ Ar-A), 3.78 (s, 3H, OCH₃ 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 Dehydration 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 *vacuum* and H₂O (50 ml) was added to the residue. The resulting white crystals were filtered and recrystallized from C₂H₅OH (**7a**, **7b**) or toluene (**7c**, **7d**). Pure **7c** was not isolated. *Trans* (**6d**) and *cis* (**6d'**) gave the same product (**7d**).

3,4-Diphenyl-2H-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, $J = 1\text{H}$, H-8), 11.6 (s, 1H, NH).

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

^1H Nmr (CDCl₃) δ : 3.80 (s, 3H, OCH₃), 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)-2H-isoquinolin-1-one (7d).

^1H Nmr (CDCl₃) δ : 3.77 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 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 POCl₃ (50 ml) was refluxed for 2.5 h, after cooling POCl₃ was evaporated *in vacuo*, then the residue was poured into ice-water and a saturated aqueous K₂CO₃ solution was added. **12a-d** were extracted with CH₂Cl₂ (3 x 50 ml). The organic layer was washed with H₂O, dried (MgSO₄) and evaporated under vacuum. The chloro compounds (**12a-d**) were recrystallized from cyclohexane. Pure **12c** was obtained by chromatography on silica gel column, eluting with CH₂Cl₂.

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

^1H Nmr (CDCl₃) δ : 3.84 (s, 3H, OCH₃), 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 (CDCl₃) δ : 3.75 (s, 3H, OCH₃), 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).

¹H Nmr (CDCl₃) δ : 3.76 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 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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