A New Route to Diarylisoquinolones

David J. Dodsworth,* Maria Pia-Calcagno, E. Ursula Ehrmann, Andres M. Quesada, and Oswaldo Nuñez S.
Departamento de Quimica, Universidad Simon Bolivar, Caracas, Apartado Postal 80659, Venezuela
Peter G. Sammes *
Department of Organic Chemistry, The University, Leeds LS2 9JT

The lithium salts derived from position 3 of phthalides react with Schiff's bases to form a mixture of *cis*- and *trans*-2,3-disubstituted 4-hydroxy-3,4-dihydro-1(2*H*)-isoquinolones, the former isomer predominating. Acid-catalysed dehydration of the alcohols gives 2,4-disubstituted 1(2*H*)-isoquinolones, as a result of aryl group migration, whilst the *cis*-isomers, with methanesulphonyl chloride–pyridine as dehydrating agent, produce the 2,3-disubstituted 1(2*H*)-isoquinolones.

The use of reactive species derived from phthalides continues to stimulate new synthetic applications in the preparation of polycyclic systems.[1] In this paper we report full details of a new method for the preparation of isoquinolone derivatives.[2] The method is based on the known reactivity of imines towards organometallic species.[3] It was originally considered that the reaction of lithium salts of phthalides with Schiff's bases would provide a simple route to the phthalide-isoquinoline alkaloids. Robinson has described some experiments along these lines using stabilised carbanions.[4] Our route, employing relatively unstabilised phthalide carbanions, would only be effective provided the intermediate amide anion (4) was insufficiently nucleophilic to attack the lactone function of the phthalide (Scheme 1, path ii). Alternatively, if such attack were to occur, a route (path i) to isoquinolone derivatives would be opened. In the event the latter course of events occurs with the simpler phthalides studied so far.

The highly coloured phthalide salt (2) was generated by the reaction of phthalide (1) with lithium di-isopropylamide in tetrahydrofuran. Reaction of the salt (2) with a Schiff's base (3) proceeded at temperatures up to room temperature, probably *via* the intermediate (4), directly followed by intramolecular attack of the nitrogen anion on the lactone carbonyl group leading to the cyclic amides (6) and (7). No evidence for the intermediacy of the free amino-phthalide (5) was obtained in this reaction. It is known that 3-aminomethylphthalide cyclises under the influence of base to generate 4-hydroxy-3,4-dihydro-1(2*H*)-isoquinolone.[5] The results of a series of reactions involving the phthalide (1a) and 5,6-dimethoxyphthalide (1b) and the anils (3a)—(3g) are tabulated (Table).

Formation of the cyclic amides (Scheme 1) generates two chiral centres at positions 3 and 4 and thus the reaction product is obtained as a mixture of the enantiomeric pairs (6) and (7), which are readily separable by either preparative layer or column chromatography on silica gel. The less polar components showed the expected AB system (after chemical exchange with deuterium oxide), J_{AB} 6—6.6 Hz, while the more polar isomers showed an AB system with J_{AB} 2—2.2 Hz (again after exchange with deuterium oxide). Dreiding models indicate that, for the enantiomers with a *trans*-configuration of the C-3 and C-4 hydrogens, the most favourable conformation is the one in which the C-3 phenyl is pseudoaxial. In this conformation the dihedral angle between the AB hydrogens approaches 90° and thus a small coupling constant could be expected.[6] Similarly, for the isomers with a *cis*-configuration of the C(3) and C(4) hydrogens, (7), molecular models indicate a dihedral angle of *ca.* 55° for each of the two possible conformations in which a larger coupling constant would be expected. A similar interpretation has been invoked for the *cis*- and *trans*-isomers of 3-aryl-4-carboxy-2-methyl-3,4-dihydro-1(2*H*)-isoquinolones and our observed coupling constants are in agreement with the reported values, assuming similar conformational effects.[7]

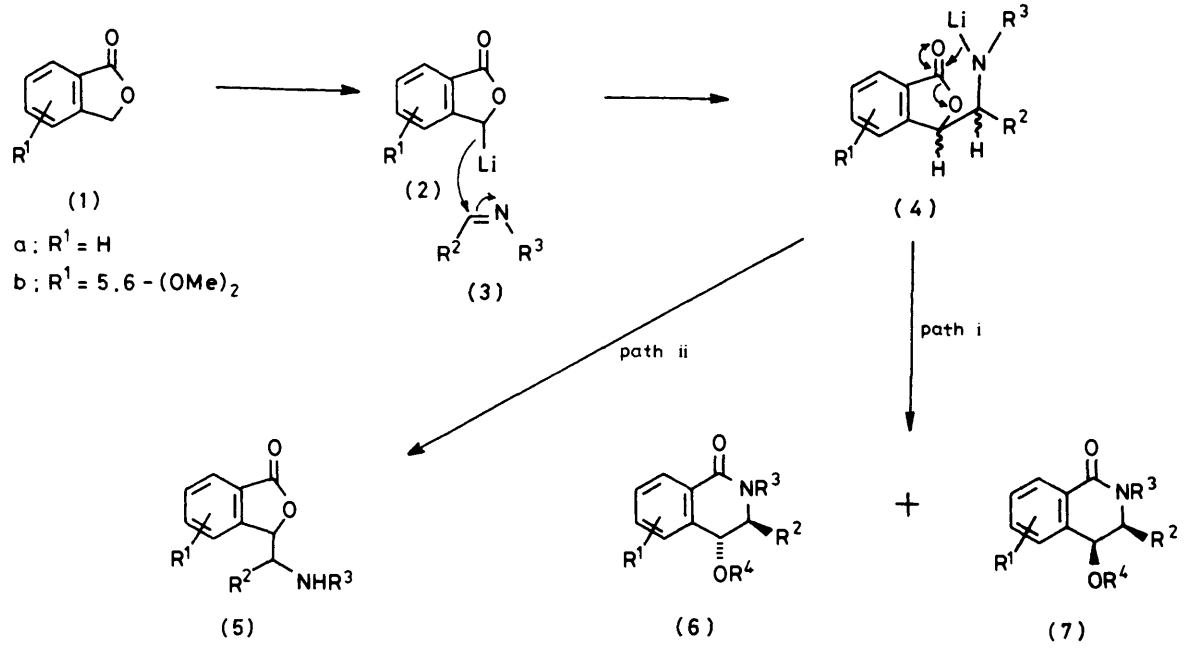
The *trans*-structure (6) is therefore assigned to the more polar components of the reaction mixtures, and the *cis*-structure (7) to the less polar isomers. The alcohols (Table) could be converted into the corresponding acetate ester by treatment with acetic anhydride in pyridine.

Although yields have not been optimised, the relative proportions of the *cis*- and *trans*-hydroxy isomers, (6) and (7), isolated in the above reactions were consistently in the range 2 : 1, respectively, and the preference for the *cis*-isomer requires explanation. The reaction system is formally analo-

Table. [a]

		3,4-Dihydro-1(2*H*)-isoquinolone					
		trans-Isomer			*cis*-Isomer		
Phthalide	Schiff's base	Product (%)	M.p. (°C) (R^4 = H)	Acetate M.p. (°C) (R^4 = Ac)	Product (%)	M.p. (°C) (R^4 = H)	Acetate M.p. (°C) (R^4 = Ac)
(1a)	(3a)	(6a) 22	281—283	162—164	(7a) 51	200—202	166—167
(1a)	(3b)	(6b) 18	251—283		(7b) 33	240—242	156—158
(1a)	(3c)	(6c) 15	189		(7c) 26	164—165	143—145
(1a)	(3d)	(6d) 16	111—118 [b]	192—195	(7d) 31	110—113	78—80
(1a)	(3e)	(6e) 20	216—218	197—198	(7e) 39	154	149—151
(1a)	(3f)	(6f) 7	216—218		(7f) 39	222—224	
(1a)	(3g)	*c*			(7g) 43	142—145	99—100
(1a)	(3c)	(6h) 23	*b*		(7h) 34	235—236	

[a] See Scheme 1 for formulae. [b] Amorphous solid. [c] Not isolated.



(3)

a ; $R^2 = R^3 = Ph$
b ; $R^2 = 4\text{-}MeC_6H_4$, $R^3 = Ph$
c ; $R^2 = 4\text{-}MeOC_6H_4$, $R^3 = Ph$
d ; $R^2 = R^3 = 4\text{-}MeOC_6H_4$
e ; $R^2 = Ph$, $R^3 = 4\text{-}MeOC_6H_4$
f ; $R^2 = 4\text{-}ClC_6H_4$, $R^3 = Ph$
g ; $R^2 = Ph$, $R^3 = CH_2Ph$

R^4 = H or Ac

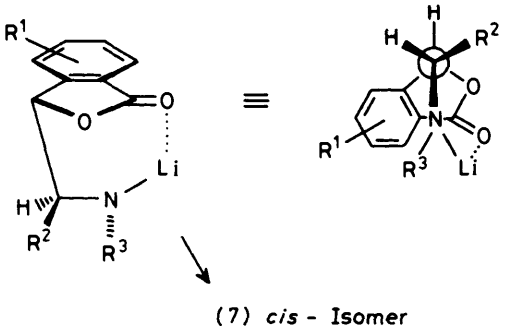
a ; $R^1 = H$, $R^2 = R^3 = Ph$
b ; $R^1 = H$, $R^2 = 4\text{-}MeC_6H_4$, $R^3 = Ph$
c ; $R^1 = H$, $R^2 = 4\text{-}MeOC_6H_4$, $R^3 = Ph$
d ; $R^1 = H$, $R^2 = R^3 = 4\text{-}MeOC_6H_4$
e ; $R^1 = H$, $R^2 = Ph$, $R^3 = 4\text{-}MeOC_6H_4$
f ; $R^1 = H$, $R^2 = 4\text{-}ClC_6H_4$, $R^3 = Ph$
g ; $R^1 = H$, $R^2 = Ph$, $R^3 = CH_2Ph$
h ; $R^1 = 6,7\text{-}(OMe)_2$, $R^2 = 4\text{-}MeOC_6H_4$, $R^3 = Ph$

Scheme 1.

gous to the condensation of enolates with carbonyl compounds in which the prevalent distribution is determined by internal asymmetric induction.[8] Thus the *cis*-isomer may be formed from a transition state in which the gauche interaction between the C-3 aryl group and the aromatic residue of the phthalide species is minimised (Scheme 2). Repetition of the reactions on a small scale, followed by ^1H n.m.r. examination of the crude product mixtures, showed the expected constant ratio of *ca.* 1 : 1.8 for the *cis*- and *trans*-isomers respectively.

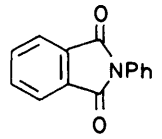
An attempt was made to extend the reaction to imines derived from aliphatic amines but these were not efficient since competing formation of the lithium derivative of the Schiff's base is possible under the conditions employed.[9] Thus, treatment of *N*-(benzylidene)benzylamine (3g) with lithium di-isopropylamide forms the anion (9). This anion can be alkylated, for example with methyl iodide, to give, after acid hydrolysis, α-phenylethylamine. For this imine (3g), however, proton exchange between the phthalide anion (2) and the imine is relatively slow and a moderate yield (43%) of the *cis*-alcohol (7g) could be isolated.

The chemistry of the alcohols (6) and (7) has been briefly explored. Oxidation of the *cis*-2,3-diphenyl alcohol (7a) with manganese dioxide in carbon tetrachloride resulted in its



Scheme 2.

conversion into *N*-phenylphthalimide (8) (48% yield). The products of dehydration of the alcohols (6) and (7) depend on the reaction conditions as well as the stereochemistry of the starting alcohol. Thus, treatment of either isomer with trifluoroacetic acid at room temperature effects dehydration. The products are not the corresponding 2,3-disubstituted isoquinolones (12) but, instead, the rearranged 2,4-disubstituted isomers (11) (Scheme 3). Formation of the carbonium



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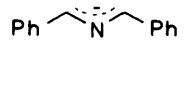

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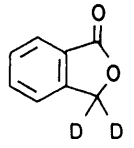

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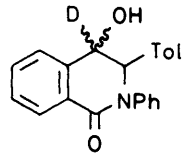
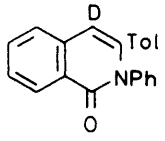


(14) *trans* - Isomer

(15) *cis* - Isomer



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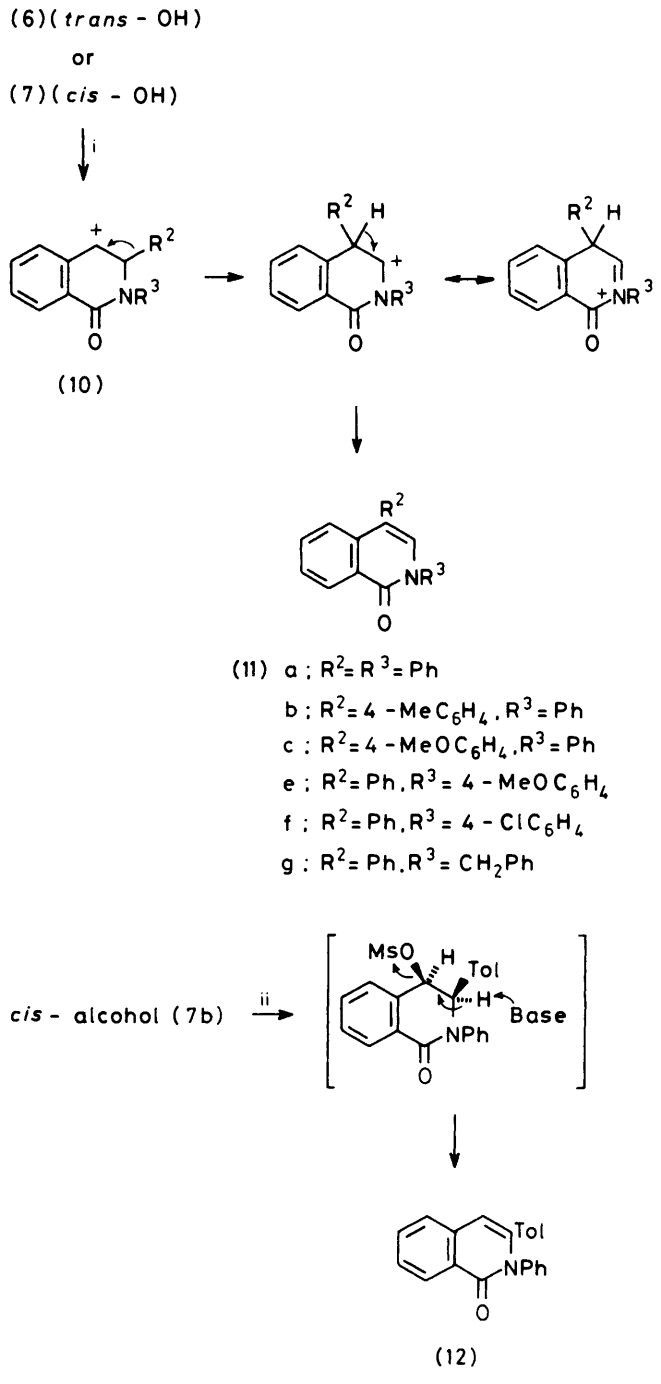

Scheme 3. *Reagents:* i, CF_3CO_2H; ii, $MeSO_2Cl$, pyridine

ion (10) must precede the aryl group shift and aromatisation of the ion (10) follows by loss of the C(4) proton to produce the isoquinolone (11). Dehydration under basic conditions depends on the stereochemistry of the starting alcohol. Thus the *cis*-alcohols (7), on reaction with methanesulphonyl chloride (mesyl chloride) in pyridine, undergo direct elimination (Scheme 3) to produce the 2,3-disubstituted isoquinolone; for example, (7b) affords (12). The *trans*-alcohols (6), in contrast, give a mixture of products with mesyl chloride in pyridine; for example, (6b) gives some of the rearranged isoquinolone (11b) as well as the unrearranged isomer (12). The 2,3-disubstituted isoquinolone (12) is readily distinguished from the corresponding 2,4-disubstituted isomer (11b) by the ^1H n.m.r. spectra. The former shows the C(4)-proton at δ 6.4 whilst in the latter the C(3)-proton occurs at above δ 7.0.

In order to check these mechanistic pathways for dehydration a sample of the deuteriated phthalide (13) was prepared by zinc–alkali reduction of phthalimide in deuterium oxide.[10] Condensation with *N*-(4-methylbenzylidene)aniline (3b), in the manner described above, produced the corresponding deuteriated alcohols (14) and (15) [*cf.* (6b) and (7b), respectively]. Whereas treatment of the *trans*-alcohol (14) with trifluoroacetic acid gave the 2,4-disubstituted isoquinolone (11b), with loss of the deuterium atom, treatment of the *cis*-isomer (15) with mesyl chloride in pyridine afforded the 2,3-disubstituted derivative (16), with retention of deuterium. These observations are in accordance with the mechanism depicted in Scheme 3.

Experimental

M.p.s were recorded with a Kofler block and are uncorrected. U.v. spectra were measured with a Beckmann DB-G spectrophotometer and i.r. spectra with a Perkin-Elmer 567 grating spectrophotometer. ^1H N.m.r. spectra were measured at either 60 or 100 MHz using tetramethylsilane as internal reference. Merck 60PF silica gel was used for thin layer chromatography (t.l.c.) and preparative layer chromatography (p.l.c.) and the separate fractions are reported in order of decreasing polarity. Solvents were dried and distilled under argon prior to use. Light petroleum refers to the fraction of boiling range 40—60 °C.

General Procedure for the Synthesis of 2,3-*Disubstituted* 4-*Hydroxy*-3,4-*dihydro*-1(2H)-*isoquinolones.*—A solution of phthalide in dry tetrahydrofuran (THF) (*ca.* 2 ml per mmol) was added dropwise to a solution of lithium di-isopropylamide (1.1 equiv.) at −70 to −60 °C, the latter being prepared by the addition of 1.5M-n-butyl-lithium in n-hexane to an equivalent amount of di-isopropylamine in THF (5 ml per mmol). The solution of the thus prepared 3-lithiophthalide was then

treated with a solution of the Schiff's base in THF (2 ml per mmol) at −50 to −40 °C. The mixture was warmed to 20 °C with stirring and then left for a further 8 h before being poured over ice–dilute hydrochloric acid. The quenched reaction mixture was extracted with chloroform, washed with water, dried ($MgSO_4$), filtered, and the solvent evaporated off under reduced pressure. The product isoquinolones were separated by p.l.c. or column chromatography through silica gel.

General Procedure for the Preparation of Acetates.—The 4-hydroxy-isoquinolones (0.3 mmol) were treated with acetic anhydride (0.9 ml) and pyridine (5 ml) at room temperature for 7 days before the mixture was quenched with ice and hydrochloric acid and extracted with chloroform. It was then washed with water, dried ($MgSO_4$), and filtered, and the solvent evaporated under reduced pressure to afford the acetate.

cis- *and* trans-4-*Hydroxy*-2,3-*diphenyl*-3,4-*dihydro*-1(2H)-*isoquinolone* (7a) *and* (6a).—Phthalide (1a) (0.67 g, 5 mmol) in THF (10 ml) was treated with lithium di-isopropylamide (5.5 mmol) and *N*-(benzylidene)aniline (0.91 g, 5 mmol). After work-up a viscous liquid was isolated; trituration with chloroform gave a cream solid, which was filtered off. Recrystallisation of the solid (MeOH) afforded fine prisms of the trans-*alcohol* (6a) (0.353 g, 22%), m.p. 281—283 °C; $\nu_{max.}$ 3 280 and 1 660 cm^{-1}; δ[$(CD_3)_2SO$] 4.83 (1 H, dd, *J* 2.2, 5.0 Hz), 5.33 (1 H, d, *J* 2.2 Hz), 6.18 (1 H, d, *J* 5.0 Hz), 7.1—7.7 (13 H, m), and 7.9—8.3 (1 H, m) (Found: M^+ 315.12606. $C_{21}H_{17}NO_2$ requires *M* 315.125 92).

Acetylation of the alcohol (6a) afforded trans-4-*acetoxy*-2,3-*diphenyl*-3,4-*dihydro*-1(2H)-*isoquinolone* (90%) as a viscous oil which slowly crystallised. Recrystallisation (acetone–n-hexane) gave small prisms, m.p. 162.5—164.5 °C, $\nu_{max.}$ 1 730 and 1 660 cm^{-1}; δ($CDCl_3$) 2.15 (3 H, s), 5.35 (1 H, d, *J* 2.0 Hz), 6.07 (1 H, d, *J* 2.0 Hz), 7.2—7.8 (13 H, m), and 8.2—8.5 (1 H, m) (Found: C, 77.4; H, 5.4; N, 3.9. $C_{23}H_{19}NO_3$ requires C, 77.3; H, 5.4; N, 3.9%).

Separation of the chloroform-soluble product by p.l.c. (2 : 1 chloroform–ethyl acetate) gave a white solid. Recrystallisation (chloroform–light petroleum) gave the cis-*alcohol* (7a) (0.804 g, 51%), 200—202 °C, $\nu_{max.}$ 3 380 and 1 640 cm^{-1}; δ($CDCl_3$) 1.93 (1 H, d, *J* 11.2 Hz, exchangeable with D_2O), 5.12 (1 H, d, *J* 6.4 Hz), 5.70 (1 H, dd, *J* 6.4, 11.2 Hz), 7.1—7.7 (13 H, m), and 8.1—8.4 (1 H, m). This was characterised as its acetate, cis-4-*acetoxy*-2,3-*diphenyl*-3,4-*dihydro*-1(2H)-*isoquinolone*, m.p. (acetone–light petroleum) 166—167 °C; $\nu_{max.}$ 1 750 and 1 660 cm^{-1}; δ($CDCl_3$) 2.20 (3 H, s), 5,42 (1 H, d, *J* 6.4 Hz), 6.75 (1 H, d, *J* 6.4 Hz), 6.9—7.8 (13 H, m), and 8.2—8.5 (1 H, m) (Found: C, 77.2; H, 5.35; N, 3.9. $C_{23}H_{19}NO_3$ requires C, 77.3; H, 5.4; N, 3.9%).

2,4-*Diphenyl*-1(2H)-*isoquinolone*.—A mixture of *cis*- and *trans*-4-hydroxy-2,3-diphenyl-3,4-dihydro-1(2*H*)-isoquinolone (0.183 g, 0.6 mmol) was heated in refluxing trifluoroacetic acid (2 ml) for 8 h. The cooled reaction mixture was poured into cold aqueous sodium carbonate solution and then extracted into chloroform, washed with water, dried ($MgSO_4$), and the solvent removed under reduced pressure. The residual oil was purified by p.l.c. (chloroform) to give the title compound (0.131 g, 73%), m.p. (n-hexane) 132—133 °C (lit.,[11] m.p. 134—136 °C), $\nu_{max.}$ 1 655 and 1 625 cm^{-1}; $\lambda_{max.}$ (EtOH) 215 (log ε 4.46), 234 (4.38), 296 (3.94), and 333 nm (3.65); δ($CDCl_3$) 7.1—7.8 (14 H, m) and 8.4—8.8 (1 H, m).

N-*Phenylphthalimide* (8).—*cis*-4-Hydroxy-2,3-diphenyl-3,4-dihydro-1(2*H*)-isoquinolone (7a) (0.75 g, 2.4 mmol) was heated with activated manganese dioxide (15 g) in refluxing carbon tetrachloride (100 ml) for 26 h. The reaction mixture was filtered, the solids washed with dichloromethane and the filtrates evaporated to afford a solid, which was recrystallised (ethyl acetate) to give needles of the title compound (0.36 g, 68%), m.p. 201—202 °C (lit.,[12] 207 °C) (Found: C, 75.4; H, 3.8; N, 6.3. Calc. for $C_{14}H_9NO_2$: C, 75.5; H, 4.05; N, 6.3%).

cis- *and* trans-4-*Hydroxy*-3-(4-*methylphenyl*)-2-*phenyl*-3,4-*dihydro*-1(2H)-*isoquinolone* (7b) *and* (6b).—Phthalide (1.34 g, 10 mmol) was treated with lithium di-isopropylamide (11 mmol) and *N*-(4-methylbenzylidene)aniline (3b) (2.00 g, 10 mmol) in the normal manner to produce a viscous yellow oil. P.l.c. (chloroform; 2 elutions) gave two main fractions. The most polar fraction, after crystallisation from ethyl acetate, gave the trans-*alcohol* (6b) (0.59 g, 18%), m.p. 251—253 °C, $\nu_{max.}$ 3 420 and 1 630 cm^{-1}; δ[$CDCl_3$–$(CD_3)_2SO$] 2.18 (3 H, s), 4.75 (1 H, dd, *J* 2.8, 6.0 Hz), 5.23 (1 H, d, *J* 2.8 Hz), 5.98 (1 H, d, *J* 6.0 Hz, exchangeable with D_2O), 6.95—7.7 (12 H, m), and 8.2—8.3 (1 H, m) (Found: C, 79.8; H, 5.6; N, 4.3. $C_{22}H_{19}NO_2$ requires C, 80.2; H, 5.8; N, 4.25%).

The less polar fraction was recrystallised (chloroform–light petroleum) to give fine needles of the cis-*alcohol* (7b); (1.10 g, 33%), m.p. 240—242 °C, $\nu_{max.}$ 3 400 and 1 630 cm^{-1}; δ($CDCl_3$) 1.87 (1 H, d, *J* 11.2 Hz, exchangeable with D_2O), 2.23 (3 H, s), 5.07 (1 H, d, *J* 6.8 Hz), 5.67 (1 H, dd, *J* 6.8, 11.2 Hz), 6.9—7.7 (12 H, m), and 8.1—8.4 (1 H, m) (Found: C, 79.8; H, 5.6; N, 4.3. $C_{22}H_{19}NO_2$ requires C, 80.2; H, 5.8; N, 4.25%). The acetate of the latter compound, cis-4-*acetoxy*-3-(4-*methylphenyl*)-2-*phenyl*-3,4-*dihydro*-1(2H)-*isoquinolone*, had m.p. 156—158 °C, $\nu_{max.}$ 1 755 and 1 660 cm^{-1}; δ($CDCl_3$) 2.13 (3 H, s), 2.23 (3 H, s), 5.30 (1 H, d, *J* 6.4 Hz), 6.65 (1 H, d, *J* 6.4 Hz), 6.9—7.7 (12 H, m), and 8.0—8.4 (1 H, m) (Found: C, 77.7; H, 5.75; N, 3.7. $C_{24}H_{21}NO_3$ requires C, 77.6; H, 5.7; N, 3.8%).

4-(4-*Methylphenyl*)-2-*phenyl*-1(2H)-*isoquinolone* (11b).—*trans*-4-Hydroxy-3-(4-methylphenyl)-2-phenyl-3,4-dihydro-1(2*H*)-isoquinolone (6b) (0.24 g, 0.4 mmol) was treated in the usual manner with trifluoroacetic acid. Recrystallisation of the product from n-hexane afforded the *title material* (0.14 g, 61%), m.p. 114—115 °C, $\nu_{max.}$ 1 655 and 1 630 cm^{-1}; δ($CDCl_3$) 2.43 (3 H, s), 6.9—7.75 (13 H, m), and 8.4—8.7 (1 H, m) (Found: C, 85.05; H, 5.5; N, 4.75. $C_{22}H_{17}NO$ requires C, 84.9; H, 5.5; N, 4.5%).

cis- *and* trans-4-*Hydroxy*-3-(4-*methoxyphenyl*)-2-*phenyl*-3,4-*dihydro*-1(2H)-*isoquinolone* (7c) *and* (6c).—In the usual way phthalide (0.67 g, 5 mmol) was treated with lithium di-isopropylamide (5.5 mmol) and *N*-(4-methoxybenzylidene)-aniline (3c) (1.05 g, 5.0 mmol), to afford a viscous yellow oil which was separated by p.l.c. (chloroform) into two fractions. The more polar fraction was resubjected to p.l.c. (10 : 1 benzene–light petroleum; 3 elutions) and yielded needles of the trans-*alcohol* (6c) (0.27 g, 15%), m.p. 189 °C, $\nu_{max.}$ 3 400 and 1 640 cm^{-1}; δ($CDCl_3$) 3.66 (3 H, s), 3.81 (1 H, d, *J* 8.0 Hz, exchangeable with D_2O), 4.72 (1 H, dd, *J* 2.4 8.0 Hz), 5.82 (1 H, d, *J* 2.4 Hz), 6.6—7.5 (12 H, m), and 7.9—8.1 (1 H, m) (Found: C, 76.3; H, 5.5; N, 4.1. $C_{22}H_{19}NO_3$ requires C, 76.5; H, 5.5; N, 4.1%).

The less polar fraction was recrystallised (chloroform–light petroleum) to give the cis-*alcohol* (7c) (0.44 g, 26%), m.p. 164—165 °C, $\nu_{max.}$ 3 400 and 1 640 cm^{-1}; δ($CDCl_3$) 2.03 (1 H, d, *J* 10.8 Hz, exchangeable with D_2O), 3.68 (3 H, s), 5.01 (1 H, d, *J* 6.5 Hz), 5.58 (1 H, dd, *J* 6.5, 10.8 Hz), 6.6—7.8 (12 H, m), and 8.1—8.3 (1 H, m). This material was characterised as the corresponding *acetate*, m.p. (acetone–n-hexane) 143—145 °C, $\nu_{max.}$ 1 745 and 1 655 cm^{-1}; δ($CDCl_3$)

2.15 (3 H, s), 3.73 (3 H, s), 5.30 (1 H, d, *J* 6.4 Hz), 6.65 (1 H, d, *J* 6.4 Hz), 6.7—7.7 (12 H, m), and 8.1—8.4 (1 H, m) (Found: C, 74.1; H, 5.5; N, 3.6. $C_{24}H_{21}NO_4$ requires C, 74.4; H, 5.5; N, 3.6%).

4-(4-*Methoxyphenyl*)-2-*phenyl*-1(2H)-*isoquinolone* (11c).—Dehydration of the *trans*-alcohol (6c) (0.14 g) with trifluoroacetic acid in the usual manner afforded the *title isoquinolone* (0.12 g, 90%), m.p. (n-hexane) 119—121 °C, $\lambda_{max.}$ (EtOH) 212 (log ε 4.47), 231sh (4.41), 294 (3.9), and 335 nm (3.63); $\nu_{max.}$ 1 655 and 1 625 cm^{-1}; δ($CDCl_3$) 3.90 (3 H, s), 6.9—7.7 (13 H, m), and 8.4—8.7 (1 H, m) (Found: C, 80.5; H, 5.3; N, 4.25. $C_{22}H_{17}NO_2$ requires C, 80.7; H, 5.2; N, 4.25%).

cis- *and* trans-4-*Hydroxy*-2,3-*bis*(4-*methoxyphenyl*)-3,4-*dihydro*-1(2H)-*isoquinolone* (7d) *and* (6d).—In the normal manner phthalide (0.68 g, 5 mmol) was treated with lithium di-isopropylamide (5.5 mmol) and *N*-(4-methoxybenzylidene)-4-methoxyaniline (1.12 g, 4.7 mmol). Isolation of the products by p.l.c. afforded two fractions. The most polar material was the trans-*alcohol* (6d) (0.28 g, 16%), isolated as an amorphous solid, $\nu_{max.}$ 3 400 and 1 640 cm^{-1}; δ($CDCl_3$) 3.43—3.67 (1 H, m, exchangeable with D_2O), 3.72 (3 H, s), 3.80 (3 H, s), 4.77 (1 H, m), 5.17 (1 H, m), 6.5—7.6 (11 H, m), and 7.9—8.2 (1 H, m). Acetylation of the latter material gave the corresponding trans-*acetate*, m.p. (ethanol) 192—195 °C, $\nu_{max.}$ 1 725 and 1 655 cm^{-1}; δ($CDCl_3$) 2.13 (3 H, s), 3.73 (3 H, s), 3.80 (3 H, s), 5.17 (1 H, d, *J* 2.4 Hz), 5.93 (1 H, d, *J* 2.4 Hz), 6.6—7.7 (11 H, m), and 8.1—8.4 (1 H, m) (Found: C, 71.4; H, 5.7; N, 3.25. $C_{25}H_{23}NO_5$ requires C, 71.9; H, 5.55; N, 3.4%).

The less polar fraction was the cis-*alcohol* (7d) (0.54 g, 31%), m.p. (chloroform–light petroleum) 110—113 °C; $\nu_{max.}$ 3 360 and 1 630 cm^{-1}; δ($CDCl_3$) 1.93 (1 H, d, *J* 11 Hz, exchangeable with D_2O), 3.73 (3 H, s), 3.80 (3 H, s), 5.02 (1 H, d, *J* 6.8 Hz), 5.67 (1 H, dd, *J* 6.8, 11 Hz), 6.6—7.7 (11 H, m), and 8.0—8.4 (1 H, m) (Found: C, 73.55; H, 5.7; N, 3.65. $C_{23}H_{21}NO_4$ requires C, 73.6; H, 5.6; N, 3.7%). Acetylation of the latter material afforded the corresponding *acetate*, m.p. (n-hexane) 78—80 °C, $\nu_{max.}$ 1 745 and 1 660 cm^{-1}; δ($CDCl_3$) 2.13 (3 H, s), 3.73 (3 H, s), 3.77 (3 H, s), 5.25 (1 H, d, *J* 6.1 Hz), 6.65 (1 H, d, *J* 6.8 Hz), 6.7—7.0 (11 H, m), and 8.0—8.3 (1 H, m) (Found: C, 71.8; H, 5.6; N, 3.65. $C_{25}H_{23}NO_5$ requires C, 71.9; H, 5.55; N, 3.4%).

cis- *and* trans-4-*Hydroxy*-2-(4-*methoxyphenyl*)-3-*phenyl*-3,4-*dihydro*-1(2H)-*isoquinolones* (7e) *and* (6e).—Phthalide (0.67 g, 5.0 mmol) was treated with lithium di-isopropylamide (5.5 mmol) and *N*-benzylidene-4-methoxyaniline (1.06 g, 5.0 mmol). P.l.c. separation of the products afforded two major fractions. The more polar fraction was the trans-*alcohol* (6e) (0.35 g, 20%), m.p. (chloroform–light petroleum) 216—218 °C; $\nu_{max.}$ 3 400 and 1 630 cm^{-1}; δ($CDCl_3$) 3.80 (3 H, s), 4.00 (1 H, m, exchangeable with D_2O), 4.78 (1 H, m), 5.25 (1 H, d, *J* 2.4 Hz), 6.7—7.6 (12 H, m), and 7.75—8.25 (1 H, m). The compound was characterised as its *acetate*, m.p. (ethanol) 197—198 °C; $\nu_{max.}$ 1 720 and 1 655 cm^{-1}, δ($CDCl_3$) 2.12 (3 H, s), 3.87 (3 H, s), 5.22 (1 H, d, *J* 2.4 Hz), 5.97 (1 H, d, *J* 2.4 Hz), 6.6—7.7 (12 H, m), and 8.0—8.4 (1 H, m) (Found: C, 74.2; H, 5.65; N, 3.75. $C_{24}H_{21}NO_4$ requires C, 74.4; H, 5.5; N, 3.6%).

The less polar fraction gave the cis-*alcohol* (7e) (0.675 g, 39%), m.p. (chloroform–light petroleum) 154 °C; $\nu_{max.}$ 3 400 and 1 630 cm^{-1}; δ($CDCl_3$) 2.58 (1 H, d, *J* 9.6 Hz, exchangeable with D_2O), 3.74 (3 H, s), 5.03 (1 H, d, *J* 6.6 Hz), 5.62 (1 H, dd, *J* 6.6, 9.6 Hz), 6.7—7.7 (12 H, m), and 8.0—8.35 (1 H, m) (Found: C, 75.8; H, 5.5; N, 4.1. $C_{12}H_{19}NO_3$ requires C, 76.5; H, 5.5; N, 4.1%). Its *acetate* had m.p. (acetone–n-hexane) 149—151 °C, $\nu_{max.}$ 1 725 and 1 650 cm^{-1}; δ($CDCl_3$) 2.16 (3 H, s), 3.73 (3 H, s), 5.28 (1 H, d, *J* 6.6 Hz), 6.65 (1 H, d, *J* 6.6 Hz), 6.7—7.7 (12 H, m), and 8.1—8.4 (1 H, m) (Found: C, 73.95; H. 5.5; N, 3.6. $C_{24}H_{21}NO_4$ requires C, 74.4; H, 5.5; N, 3.6%).

2-(4-*Methoxyphenyl*)-4-*phenyl*-1(2H)-*isoquinolone* (11e).—A mixture of *cis*- and *trans*-alcohols (7e) and (6e) (0.14 g) was treated in the usual manner with trifluoroacetic acid to give, after p.l.c. and crystallisation from n-hexane, colourless needles of the *title isoquinolone* (0.13 g, 97%), m.p. 151—153 °C, $\lambda_{max.}$ (EtOH) 215 (log ε 4.15), 293 (4.04), and 334 nm (3.76); $\nu_{max.}$ 1 660, 1 630, and 1 600 cm^{-1}; δ($CDCl_3$) 3.82 (3 H, s), 6.9—7.8 (12 H, m), and 8.4—8.7 (1 H, m) (Found: *m/z* 327.125 53. $C_{22}H_{17}NO_2$ requires *M*, 327.125 92).

cis- *and* trans-4-*Hydroxy*-3-(4-*methoxyphenyl*)-6,7-*dimethoxy*-2-*phenyl*-3,4-*dihydro*-1(2H)-*isoquinolone* (7h) *and* (6h).—In the usual manner 5,6-dimethoxyphthalide (0.48 g, 2.5 mmol) was treated with lithium di-isopropylamide (2.8 mmol) and *N*-(4-methoxybenzylidene)aniline (0.52 g, 2.5 mmol). After purification by p.l.c. (3 : 1 dichloromethane–ethyl acetate) two fractions were obtained. The more polar fraction was the trans-*alcohol* (7h), obtained as an amorphous solid (0.235 g, 23%), δ($CDCl_3$) 3.73 (3 H, s), 3.90 (3 H, s), 3.95 (3 H, s), 4.67 (1 H, d, *J* 2.0 Hz), 5.10 (1 H, d, *J* 2.0 Hz), 6.6—7.5 (9 H, m), and 7.60 (1 H, s). This material was characterised as its *acetate*, m.p. (ethanol) 179—181 °C, $\nu_{max.}$ 1 730 and 1 655 cm^{-1}; δ($CDCl_3$) 2.17 (3 H, s), 3.80 (3 H, s), 3.92 (3 H, s), 4.30 (3 H, s), 5.23 (1 H, d, *J* 2.0 Hz), 5.95 (1 H, d, *J* 2.0 Hz), 6.7—7.6 (9 H, m), and 7.83 (1 H, s) (Found: C, 69.7; H, 5.85; N, 3.1. $C_{26}H_{25}NO_6$ requires C, 69.8; H, 5.6; N, 3.1%).

The less polar material afforded the cis-*alcohol* (7h) (0.34 g, 44%), m.p. (acetone–n-hexane) 235—236 °C, $\nu_{max.}$ 3 340 and 1 640 cm^{-1}; δ($CDCl_3$) 1.81 (1 H, d, *J* 11.0 Hz, exchangeable with D_2O), 3.71 (3 H, s), 3.86 (3 H, s), 3.94 (3 H, s), 4.98 (1 H, d, *J* 6.0 Hz), 5.57 (1 H, dd, *J* 6.0, 11.0 Hz), 6.65—7.55 (9 H, m), and 7.67 (1 H, s) (Found: C, 71.0; H, 5.7; N, 3.5. $C_{24}H_{23}NO_3$ requires C, 71.1; H, 5.7; N, 3.45%).

cis- *and* trans-3-(4-*Chlorophenyl*)-4-*hydroxy*-2-*phenyl*-3,4-*dihydro*-1(2H)-*isoquinolones* (7f) *and* (6f).—Phthalide (0.94 g, 7 mmol) was treated with lithium di-isopropylamide (7.7 mmol) and *N*-(4-chlorobenzylidene)aniline (1.60 g, 7 mmol). The products were separated by column chromatography through silica gel. Elution with dichloromethane gave the cis-*alcohol* (7f) (0.96 g, 39%), m.p. (chloroform) 222—224 °C; $\nu_{max.}$ 3 300, 1 605, and 1 475 cm^{-1}; δ[$(CD_3)_2SO$] 4.98 (1 H, d, *J* 6.7 Hz), 5.56 (1 H, m), 6.02 (1 H, d, *J* 6.7 Hz), 6.8—7.5 (12 H, m), and 7.7—7.9 (1 H, m) (Found: C, 72.1; H, 4.5; N, 3.8. $C_{21}H_{16}ClNO_2$ requires C, 72.1; H, 4.6; N, 4.0%).

Further elution of the column (1 : 4 acetone–dichloromethane) gave the trans-*alcohol* (6f) (0.19 g, 7%), m.p. (chloroform–light petroleum) 216—218 °C; $\nu_{max.}$ 3 325 and 1 670 cm^{-1}; δ[$(CD_3)_2SO$] 4.80 (1 H, d, *J* 2.5 Hz), 5.32 (1 H, d, 2.5 Hz), 7.0—7.6 (12 H, m), and 8.4—8.6 (1 H, m) (Found: C, 71.8; H, 4.5; N, 3.9. $C_{12}H_{16}ClNO_2$ requires C, 72.1; H, 4.6; N, 4.0%).

Dehydration of a mixture of the alcohols (6f) and (7f) with trifluoroacetic acid afforded the *isoquinolone* (11f) (73%), m.p. 148—149 °C (Found: C, 75.85; H, 4.05; N, 4.3. $C_{21}H_{24}ClNO$ requires C, 76.0; H, 4.25; N, 4.2%).

Reaction of Phthalide with N-(*Benzylidene*)*benzylamine*.—Phthalide (0.67 g, 5 mmol) was treated with lithium di-isopropylamide (5.5 mmol) and the Schiff's base (0.97 g, 5 mmol). Separation of the products by p.l.c. gave a less polar, major component, characterised as cis-2-*benzyl*-4-*hydroxy*-

3-*phenyl*-3,4-*dihydro*-1(2H)-*isoquinolone* (7g) (0.71 g, 43%), m.p. (acetone–n-hexane) 142—145 °C; $\nu_{max.}$ 3 340, and 1 625 cm^{-1}; δ($CDCl_3$) 1.90 (1 H, d, *J* 10.0 Hz, exchangeable with D_2O), 3.57 (1 H, d, *J* 15 Hz), 4.67 (1 H, d, *J* 7.0 Hz), 5.32 (1 H, dd, *J* 7.0, 10.0 Hz), 5.68 (1 H, d, *J* 15 Hz), 6.8—7.6 (13 H, ml), and 7.9—8.3 (1 H, m) (Found: C, 80.2; H, 5.8; N, 4.3. $C_{22}H_{19}NO_2$ requires C, 80.2; H, 5.8; N, 4.3%).

The *acetate* of the latter material showed m.p. (n-hexane) 99—100 °C; $\nu_{max.}$ 1 750 and 1 640 cm^{-1}; δ($CDCl_3$) 2.07 (3 H, s), 3.72 (1 H, d, *J* 14.8 Hz), 4.92 (1 H, d, *J* 7.0 Hz), 5.62 (1 H, d, *J* 14.8 H z), 6.35 (1 H, d, *J* 7.0 Hz), 6.7—7.6 (13 H, m), and 8.1—8.4 (1 H, m) (Found: C, 77.7; H, 5.75; N, 3.7. $C_{24}H_{21}NO_3$ requires C, 77.6; H, 5.7; N, 3.8%).

No *trans*-alcohol was isolated from the remaining fractions from this reaction mixture.

2-*Benzyl*-4-*phenyl*-1(2H)-*isoquinolone* (11g).—Treatment of the *cis*-alcohol (7g) (0.31 g) with trifluoroacetic acid in the normal manner gave, after work-up, the *title compound* (0.15 g, 54%), m.p. 145—146 °C, $\lambda_{max.}$ (EtOH) 232 (log ε 436), 255 (3.95), 297 (3.96), and 355 nm (3.72); $\nu_{max.}$ 1 650 and 1 625, cm^{-1}; δ($CDCl_3$) 5.32 (2 H, s), 7.2—7.7 (14 H, m), and 8.5—8.8 (1 H, m) (Found: C, 84.75; H, 5.5; N, 4.5. $C_{22}H_{17}NO$ requires C, 84.9; H, 5.5; N, 4.5%).

Alkylation of N-(*Benzylidene*)*benzylamine*.—The Schiff's base (1.59 g, 10 mmol) in THF (15 ml) was added dropwise to a stirred solution of freshly prepared lithium di-isopropylamide (11 mmol) in THF (15 ml) at −10 to 0 °C. The intensely red solution was cooled to −40 °C and methyl iodide (2.13 g, 15 mmol) was added. The reaction mixture was allowed to warm to 20 °C before being quenched with 4M-hydrochloric acid. After extraction with chloroform the aqueous phase was basified with solid sodium carbonate and extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and evaporated to give α-phenylethylamine (1.10 g, 91%), identical in its i.r. and n.m.r. properties with an authentic specimen.

3,3-*Dideuteriophthalide* (13).[10]—Zinc dust (9.0 g) was treated with a solution of anhydrous copper sulphate (0.5 g) in deuterium oxide (2 ml, 99.9%) and a solution of sodium deuteroxide (4 g, 0.1 mol) in deuterium oxide (20 ml), the stirred mixture rapidly cooled to 5 °C and phthalimide (7.35 g, 5.5 mmol) added in portions, keeping the temperature of the mixture below 8 °C. After addition was complete, the reaction mixture was stirred at 8 °C for a further 30 min before being heated to 80 °C, to eliminate ammonia, and then filtered. The filtrate was acidified and the resulting solid recrystallised (water) to give needles of the deuteriated phthalide (3.1 g). A further quantity (1.7 g) of phthalide could be extracted from the aqueous mother-liquors with chloroform. The phthalide, m.p. 69—72 °C showed 76 ± 3% deuterium incorporation at position 3 (^1H n.m.r. analysis).

Reaction with the Deuteriated Phthalide (13).—In the usual manner the phthalide (13) (0.68 g, 5 mmol) was treated with lithium di-isopropylamide (5.5 mmol) and *N*-(4-methylbenzylidene)aniline (3b) (0.98 g, 5.1 mmol). The product alcohols were separated by p.l.c. The more polar product was *trans*-4-deuterio-4-hydroxy-3-(4-methylphenyl)-2-phenyl-3,4-dihydro-1(2*H*)-isoquinolone (14) (0.22 g, 13.5%), m.p. 243—245 °C, δ[$CDCl_3$–$(CD_3)_2SO$] 2.26 (3 H, s), 5.22 (1 H, s), 5.62 (1 H, s, exchangeable with D_2O), 6.8—7.5 (12 H, m), and 8.1—8.3 (1 H, m).

The less polar compound was the corresponding *cis*-isomer (15) (0.41 g, 24.5%), m.p. 224—229 °C, δ($CDCl_3$–D_2O) 2.28 (3 H, s), 5.02 (1 H, s), 6.9—7.5 (12 H, m), and 8.1—8.3 (1 H, m).

Dehydration of the trans-*Alcohol* (14).—(*a*) *With trifluoroacetic acid*. Reaction of the alcohol (85 mg) with trifluoroacetic acid in the usual manner afforded, after purification by p.l.c. and recrystallisation from ethyl acetate, the isoquinolone (11b) (57 mg, 71%), m.p. and mixed m.p. 113—115 °C, with i.r. and ^1H n.m.r. spectra identical with that obtained from an authentic specimen.

(*b*) *With mesyl chloride*. The alcohol (44 mg) in dry pyridine (2 ml) was treated with mesyl chloride (0.13 g) at −5 °C and then at room temperature for 2 days. After normal work-up, chloroform extraction afforded a 2 : 1 ratio of the 4- to 3-substituted isoquinolones. No proton signal was present at δ 6.4, indicating retention of deuterium in the 3-substituted isomer, *viz*. (16).

Dehydration of cis-*Alcohol* (15).—(*a*) *With trifluoroacetic acid*. Treatment of the alcohol with trifluoroacetic acid in the usual manner gave, after p.l.c. and recrystallisation of the product, the isoquinolone (11b) (83%), m.p. and mixed m.p. 110—112 °C, with a ^1H n.m.r. spectrum identical with that produced from the undeuteriated alcohol (7b).

(*b*) *With mesyl chloride*. The alcohol (0.15 g) in dry pyridine (2 ml) was treated with mesyl chloride (0.15 g) at −5 °C and the reaction mixture was stirred at room temperature for 2 days, quenched in ice–water, extracted with chloroform and the oily product was purified by p.l.c. (chloroform) to give a solid (0.138 g, 98%), m.p. 190—195 °C, which was not purified further. The material was identical in its chromatographic properties with an authentic sample of 3-(4-methylphenyl)-2-phenyl-1(2*H*)-isoquinolone (12), prepared from the mesyl chloride initiated dehydration of the undeuteriated *cis*-alcohol (7b). The undeuteriated isoquinolone (12) showed m.p. 197—198 °C (lit.,[13] m.p. 208 °C); δ($CDCl_3$) 2.33 (3 H, s), 6.44 (1 H, s), 7.0—7.7 (12 H, m), 8.3—8.5 (1 H, m), whereas the material isolated from the deuteriated alcohol (15) did not exhibit the signal at δ 6.44, and was therefore assigned as 3-(4-methylphenyl)-2-phenyl-[4-^2H]-1(2*H*)-isoquinolone (16).

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