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Potassamide Induced *In Situ* Benzylation of 5,6-Dihydroisoquinolines: Structure of Novel Products

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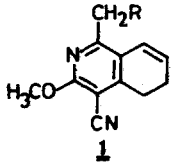
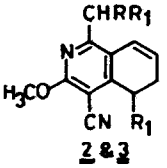
Abstract

Potassamide induced *in situ* benzylation of 1-alkyl-4-cyano-3-methoxy-5,6-dihydroisoquinolines (**1a-b**) with benzyl iodide gave the 5-benzyl-, 5,9-dibenzyl- and 4,4-dibenzyl-5,6-dihydroisoquinolines (**9a-b**, **8a-b** & **10a-b**), isoquinoline derivatives (**4a-b**) and diastereomeric mixture of 4-benzyl-1,2,3,4-tetrahydroisoquinolin-3(2*H*)-ones (**11a-b** & **11'a-b**). Structures were assigned on the basis of spectral data [Mass, ^{1}H & ^{13}C NMR, 2D NOESY]. A few reactions carried out to transform the diastereomeric mixture of compounds **11a** & **11'a** to the spirobenzylisoquinoline system **7a** isomeric with naturally occurring ochotensane system **6a** are discussed.

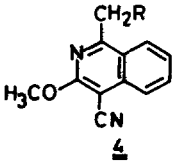
We have recently reported[1] the *in situ* alkylation of 5,6-dihydroisoquinolines **1a-b** in presence of KNH_2/liq.NH_3 leading to a variety of products (**2-5** & **5'**) characterised using modern spectroscopic techniques. In view of the biological importance of benzylisoquinoline alkaloids,[2] we intended to use similar reaction sequence with benzyl iodide to obtain the various benzylisoquinoline derivatives. Further, we were interested to synthesise spirobenzylisoquinoline systems **7a** & **7b** from one of the expected product viz., 4-benzyl-1,2,3,4-tetrahydroisoquinolin-3(2*H*)-ones **11a/11'a** by suitable transformations



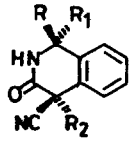
1
a: R = H
b: R = CH_3



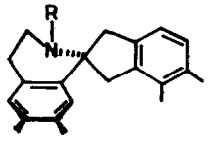
2 & 3
R = R_1 = alkyl



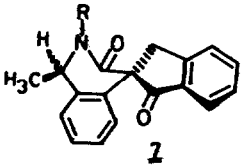
4
a: R = H
b: R = CH_3



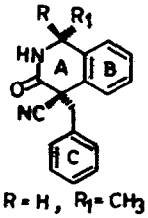
5, R = H, R_1 = R_2 = alkyl
5', R_1 = H, R = R_2 = alkyl



6a, R = CH_3, Ochotensane
6b, R = H, Norochotensane

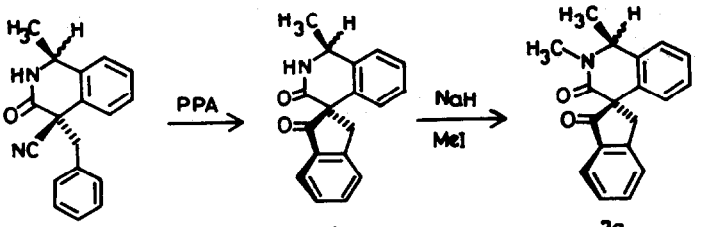


7
a: R = CH_3
b: R = H



11a, R = H, R_1 = CH_3
11'a, R = CH_3, R_1 = H

(Scheme 1). The spirobenzylisoquinoline systems **7a** & **7b**, thus formed, would be isomeric with the naturally occurring ochotensane and norochotensane skeletal systems **6a** & **6b** of alkaloids.[3-5] The results obtained in this study are discussed further.



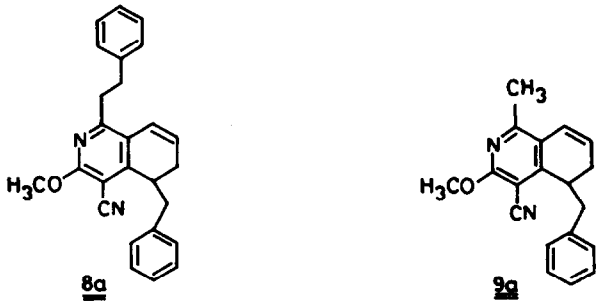
11a/ 11'a 7b 7a

Scheme 1

Reaction of 4-cyano-3-methoxy-1-methyl-5,6-dihydroisoquinoline (**1a**) with KNH_2/liq.NH_3 in the presence of trace amount of ferric chloride was carried out as described earlier.[1] The reaction mixture was quenched by addition of benzyl iodide. Addition of NH_4Cl and workup of the reaction gave mixture of products, which was purified by column chromatography followed by preparative TLC . This resulted in the isolation of five compounds, **A-E** in the order of increasing polarity (TLC).

The least polar compound **A** (34%), analysing for $C_{26}H_{24}N_2O$ [HRMS calcd. for 380.6342 Found: 380.6412] exhibited IR absorption at 2220 cm^{-1} corresponding to an aromatic nitrile. The ^1H NMR spectrum showed signals at δ 1.92-2.13 (m, 2H), 2.42-2.56 (m, 2H), 2.84-3.38 (m, 4H), 3.24 (q, J=7.6 Hz, 1H) and 6.98-7.43 (m, 10H, ArH) along with the methoxy and olefinic signals as in the substrate **1a**. Based on these observations, compound **A** was inferred to be 5,9-dibenzylated and the structure **8a** was assigned for it.

The compound **B** (24%), analysing for $C_{19}H_{18}N_2O$ [HRMS calcd. for 290.4532 Found: 290.4610] exhibited IR absorption at 2220 cm^{-1}. ^1H NMR spectrum showed signals at δ 2.52 (s, 3H), 2.67-2.73 (m, 2H), 3.04-3.12 (m, 2H), 3.22-3.42 (m, 1H) and 7.23-7.56 (m, 5H, ArH) along with the methoxy and olefinic proton signals as in the substrate **1a**. The above observations indicated that the compound **B** is monobenzylated at C-5 position and structure **9a** was assigned.



8a 9a

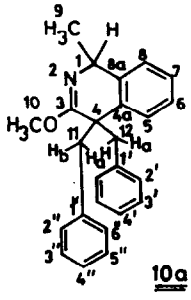
The compound **C** (8%), a white solid, analysing for $C_{25}H_{25}NO$ [HRMS calcd. 355.5435 Found: 355.5452] exhibited IR absorption at 1625 cm^{-1}. The nitrile stretching vibration was absent. ^1H NMR spectrum showed upfield signals at δ 0.45 (d, J=7.0 Hz, 3H), 3.21 (d, J=13.2 Hz, 1H), 3.22 (d, J=13.2

Hz, 1H), 3.54 (d, J=13.2 Hz, 1H), 3.55 (d, J=13.2 Hz, 1H), 3.75 (s, 3H) and 4.06 (q, J=7.0 Hz, 1H). In the down field region, signals integrating for ten protons [δ 6.64-6.71 & 6.95-7.03] as multiplets and signals corresponding to the aromatic ABCD type protons at δ 6.82 (d, J=7.7 Hz, 1H), 7.14 (t, J=7.1 Hz, 1H), 7.35 (t, J=7.7 Hz, 1H) and 7.63 (d, J=7.9 Hz, 1H) were seen.

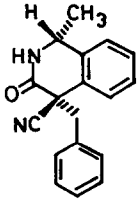
It is evident from the IR spectrum that the compound is decyanated. The upfield signals at δ 0.45 & 4.06 and at δ 3.75 (s, 3H) in the ^{1}H NMR spectrum confirmed the presence of the CH_3-CH< and -OCH_3 units in the compound. Also, the ^{1}H NMR spectrum showed four doublets integrating for four protons between δ 3-4 with the same coupling constant of J=13.2 Hz indicating that these protons in the molecule are chemically as well as magnetically nonequivalent and geminally coupled. The downfield signals of the ^{1}H NMR spectrum integrating for fourteen protons confirmed the presence of two benzyl and B-ring aromatised system in the molecule. Based on the spectral data, it was concluded that the substrate **1a** should have been decyanated and dibenzylated at C-4 carbon and the structure **10a** was tentatively assigned for compound C. ^{13}C NMR spectrum of the compound showing signals at δ 24.52, 45.35, 45.55, 47.82, 50.19, 52.46, 124.03, 124.72, 124.80, 124.87, 124.93, 126.17, 126.26, 126.76, 128.19, 128.59, 133.11, 136.17, 136.34, 138.20 and 158.41 further supported the assigned structure **10a**.

To confirm the assigned structure **10a**, 2D NOESY[6] experiment was carried out. The NOESY spectrum showed the correlation between the C-11 & C-12 benzylic protons. The correlation between the aromatic C-5 proton with C-11 as well as C-12 H_a protons are also observed. It was concluded from these observations that both the benzylic units in the molecule are in close proximity. Also, the correlations of aromatic C-8 proton with C-1 methine as well as C-9 methyl protons are seen. Thus, the NOESY spectral observation further substantiated the assigned structure **10a** for compound C.

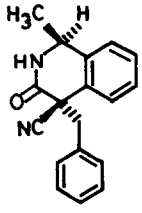
Compound D was identified as the known isoquinoline derivative **4a**.



10a



11a

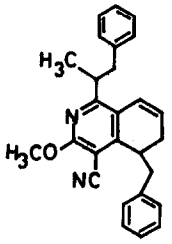


11'a

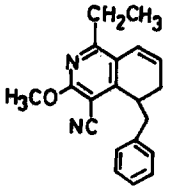
The highly polar compound **E** (20%) analysing for $C_{18}H_{16}N_2O$ [HRMS calcd. for 276.2342 Found: 276.2430] exhibited IR absorptions at 3220, 3100, 2260 & 1670 cm^{-1} corresponding to an amide carbonyl and a saturated nitrile group in the molecule. In the ^{1}H NMR spectrum, two sets of signals viz., δ 0.74 (d, J=7.6 Hz), 1.47 (d, J=7.6 Hz), 3.48 (q, J_{AB}=13.2 Hz, $\Delta\nu_{AB}$=31.2 Hz), 3.62 (q, J_{AB}=13.2 Hz, $\Delta\nu_{AB}$=31.2 Hz), 4.52 (q, J=7.6 Hz), 4.60 (dq, J=7.6 & 3.4 Hz, collapsing to a quartet on D_2O exchange), 6.62-6.92 (m, 2H, D_2O exchangeable) and 7.02-7.64 (m, ArH) in the ratio of 1:1 for each type of protons were seen. Also, ^{13}C NMR spectrum showed thirtysix well resolved signals indicating that compound **E** should be the diastereomeric mixture[1] of compounds **11a** & **11'a**.

The potassamide induced *in situ* benzylation of 4-cyano-1-ethyl-3-methoxy-5,6-dihydroisoquinoline (**1b**) was also studied. The potassamide reaction of **1b** followed by quenching with benzyl iodide resulted

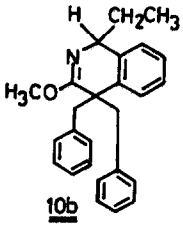
in the formation of five pure compounds. The isolated compounds were identified as the benzyl derivatives **8b, 9b & 10b,** fully aromatised isoquinoline derivative **4b** and the diastereomeric mixture of compounds **11b & 11'b** based on their spectral data (*Vide* experimental).



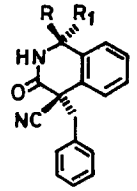
8b



9b



10b



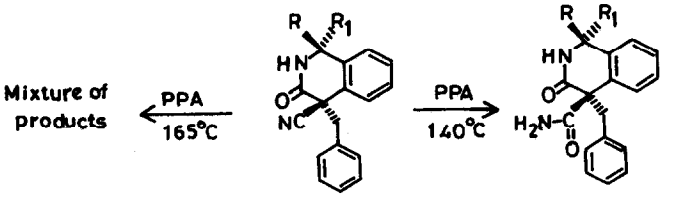
11b, R=H, R_1=Et

11'b, R=Et, R_1=H

Synthetic Approach Towards the Isomeric Ochotensane System

As already mentioned, our aim was the synthesis of skeleton **7a & 7b** isomeric to ochotensane & norochotensane systems **6a & 6b** (Scheme 1) from **11a/11'a**. It was initially decided to cyclise nitrile group (**11a/11'a**) on to the C-ring by an acid catalysed intramolecular electrophilic substitution reaction[7] (Hõesch reaction) in an one step process leading to the formation of spiro center in the C-4 position, isomeric to the spirobenzylisoquinoline alkaloids having the spiro center in the C-1 position.

At first, the intramolecular electrophilic substitution reaction of diastereomeric mixture of compounds **11a & 11'a** was carried out in presence of PPA at 140°C. From the reaction mixture, we have isolated a highly polar compound which did not show the nitrile absorption in its IR spectrum. Instead, absorptions at 3330, 3300, 1680 and 1650 cm^{-1} were seen. The ^1H NMR spectrum showed the same pattern of signals as in the substrate **11a & 11'a**, except the two broad signals at δ 6.05 & 6.53. The mass spectrum of the compound exhibited a molecular ion at m/e 294 (M^+, 100%). Based on these spectral data, it was concluded that the nitrile group in the C-4 position was hydrolysed to the diastereomeric amides **12 & 12'**. Since the reaction resulted in in the formation of amides **12 & 12'** under PPA reaction condition at 140°C, the reaction was carried out under higher temperature (165°C), perhaps to force the nitrile group towards cyclisation. The product, isolated after the workup, showed IR absorption (broad) between 1640-1720 cm^{-1}. However, the crude reaction mixture showed the presence of a number of compounds which were difficult to separate. Perhaps, hydrolysis of the secondary amide group present in the molecule has occurred and this has led to a number of side products.



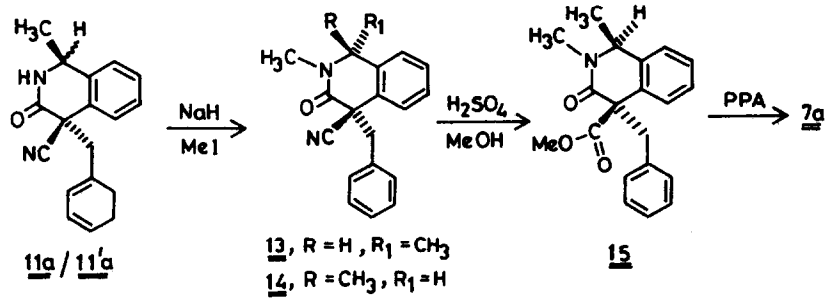
11a, R=H, R_1=CH_3

11'a, R=CH_3, R_1=H

12, R=H, R_1=CH_3

12', R_1=CH_3, R=H

It is known that the intramolecular electrophilic substitution reaction under PPA condition could better be carried out with carboxylic acid and its derivatives.[7,8] In view of this, the following alternative scheme 2 was visualised towards the synthesis of spirobenzylisoquinoline system **7a**.



Initially, the diastereomeric mixture of compounds **11a/11'a** was methylated with NaH/CH_3I and the two methylated compounds were separated by rigorous preparative TLC. The least polar compound (M^+, m/e 290) showed the IR absorptions at 2260, 1670 cm^{-1}. The ^1H NMR spectrum showed a signal at δ 3.43 as singlet along with the other expected signals. The upfield C-1 methyl signal at δ 0.44 suggested that the C-1 methyl protons are shielded by aromatic ring current and hence the compound was assigned structure **13** with C-1 methyl and C-4 benzyl groups in the *syn* configuration. The highly polar compound (M^+, m/e 290) also showed ^1H NMR signals similar to those of compound **13**, with small variations in the chemical shift. Hence, structure **14** with C-1 methyl and C-4 benzyl groups in the *anti* configuration was assigned to the highly polar compound.

In order to transform the nitrile selectively to the ester **15** without affecting tertiary amide group present in the ring system, (Scheme 2) acid catalysed reaction[8] of **14** in methanol was undertaken. The reaction resulted in the formation of the expected carbomethoxy derivative **15**, as seen from its ^1H NMR spectrum which showed the methyl singlet at 3.96 along with the other signals as in the starting compound **14**. The methyl ester, thus formed, was subjected to the PPA cyclisation reaction at 90°C. However, the starting compound was recovered back quantitatively. Minor alteration of reaction conditions also did not bring about cyclisation.

EXPERIMENTAL

All melting points are uncorrected. IR (cm^{-1}) spectra were recorded on HITACHI 270-50 Infrared spectrometer. NMR spectra were recorded on Jeol FX-90Q and Bruker AMX400, 100.61 MHz (^{13}C) spectrometers with Me_4Si as internal standard (δ = 0 ppm). Mass spectra were recorded on a Jeol MS-DX 303 spectrometer fitted with built-in direct inlet system. Column chromatography, analytical and preparative TLC were carried out using silica gel. All organic extracts were dried over anhydrous Na_2SO_4.

Potassamide reaction followed by *in situ* benzylation of 5,6-dihydroisoquinolines (1a-b): General Procedure

Freshly cut potassium (600 mg) was added to distilled ammonia (200 ml) and a pinch of ferric chloride was added and the solution stirred vigorously for about 45 minutes, after which a solution of the 5,6-dihydroisoquinoline (4 mmol) in dry THF (5 ml) was added in one lot. Stirring was continued for another hour after which benzyl iodide (8 mmol) was added. Solid NH_4Cl was added after 5 minutes to quench the reaction. Ammonia was allowed to evaporate and the residue after dissolving in water was

extracted with $CHCl_3$. The organic layer was washed with water, dried and solvent removed. The mixture of products was separated by column chromatography followed by preparative TLC [hexane:EtOAc, (8:1)].

Potassamide reaction of 4-cyano-3-methoxy-1-methyl-5,6-dihydroisoquinoline (1a):

Quenching with benzyl iodide

Potassamide reaction of 5,6-dihydroisoquinoline (**1a**, 800mg) followed by quenching with benzyl iodide gave (i) 4-cyano-5-benzyl-3-methoxy-1-(2-phenylethyl)-5,6-dihydroisoquinoline, **9a** (least polar, 320mg, 30%) viscous liquid, IR (nujol) 2218, 1620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.92-2.13 (m, 2H), 2.42-2.56 (m, 2H), 2.84-3.38 (m, 4H), 3.24 (q, J=7.6Hz, 1H, C_5-H), 4.12 (s, 3H, -OCH_3), 5.48-5.76 (m, 1H, C_7-H), 6.22 (dd, J=11.2 & 2.4 Hz, 1H, C_8-H), 6.82-7.42 (m, 10H, Ar-H); MS m/e (relative intensity) 380 (M^+, 70%), 288 (30), 197 (20), 91 (100); Analysis calcd. for $C_{26}H_{24}N_2O$: C, 82.11; H, 6.32: N, 7.37. Found: C, 82.10; H, 6.30: N, 7.38%; (ii) 5-benzyl-4-cyano-1-methyl-3-methoxy-5,6-dihydroisoquinoline, **8a** (medium polar, 290mg, 28%) viscous liquid, IR (nujol) 2220, 1625 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 2.52 (s, 3H, C_1-Me), 2.67-2.73 (m, 2H), 3.04-3.12 (m, 2H), 3.22-3.42 (m, 1H, C_5-H), 4.03 (s, 3H, -OCH_3), 5.88-6.02 (m, 1H, C_7-H), 6.58 (dd, J=11.2 & 2.4 Hz, 1H, C_8-H) and 7.16-7.34 (m, 5H, Ar-H); MS m/e (relative intensity) 290 (M^+, 20%), 275 (85), 199 (15), 184 (15), 115 (25), 91 (100); Analysis calcd. for $C_{19}H_{18}N_2O$: C, 78.62; H, 6.21; N, 9.66. Found: C, 78.60; H, 6.23; N, 9.64%; (iii) 4,4-dibenzyl-1-methyl-3-methoxy-1,4-dihydroisoquinoline, **10a** (medium polar, 70mg, 8%) m.p. 112°C, IR (nujol) 1640, 1620 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 0.45 (d, J=7.0 Hz, 3H, C_1-Me), 3.21 (d, J=13.2 Hz, 1H, -CH_2Ph), 3.22 (d, J=13.2 Hz, 1H, -CH_2Ph), 3.54 (d, J=13.2 Hz, 1H, - CH_2Ph), 3.55 (d, J=13.2 Hz, 1H, -CH_2Ph), 3.75 (s, 3H, - OCH_3), 4.06 (q, J=7.0 Hz, 1H, C_1-H), 6.64-6.71 (m, 5H, Ar-H), 6.82 (d, J=7.7 Hz, 1H), 6.95-7.03 (m, 5H, Ar-H), 7.14 (t, J=7.1 Hz, 1H), 7.35 (t, J=7.7 Hz, 1H), 7.63 (d, J=7.9 Hz, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 25.74 (q), 46.59 (t), 46.79 (t), 49.06 (s), 51.44 (d), 53.69 (q), 125.26, 126.03, 127.40, 127.49, 129.42, 129.82, 134.34, 137.40, 137.56, 139.42, 140.83, 157.46, 159.67; Ms m/e (relative intensity) 355 (M^+, 10%), 340 (10), 290 (20), 275 (10), 264 (100), 249 (10), 198 (15), 186 (20), 91 (95); Analysis calcd. for $C_{25}H_{25}NO$: C, 84.51; H, 7.04; N, 3.94. Found: C, 84.50; H, 7.06; N, 3.92%; (iv) 4-cyano-1-methyl-3-methoxyisoquinoline, **4a** (85mg, 10% , m.p. 136-37°C, reported[1]); (v) (1R*, 4R*)-4-benzyl-4-cyano-1-methyl-1,2,3,4-tetrahydroisoquinolin-3(2*H*)-one, **11a** & (1S*, 4R*)-4-benzyl-4-cyano-1-methyl-1,2,3,4-tetrahydroisoquinolin-3(2*H*)-one, **11'a** (highly polar, 200mg, 22%) m.p. 138°C, IR (nujol) 3220, 3100, 2260, 1680 cm-1; ^1H NMR (400 MHz, $CDCl_3$): δ 0.74 (d, J=7.6 Hz, C_1-Me), 1.47 (d, J= 7.6 Hz, $C_{1'}$-Me), 3.48 (q, J_{AB}=13.2 Hz, $\Delta\nu_{AB}$=31.2 Hz, C_4-CH_2Ph), 3.62 (q, J_{AB}=13.2 Hz, $\Delta\nu_{AB}$=31.2 Hz, $C_{4'}$- CH_2Ph), 4.52 (q, J=7.6 Hz, $C_{1'}$-H), 4.60 (dq, J=7.6 & 3.4 Hz, C_1-H), 6.62-6.92 (m, 2H, -NH), 7.02-7.64 (m, Ar-H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 21,39 (q), 25.09 (q), 46.67 (t), 48.21 (t), 49.01 (d), 49.16 (s), 51.16 (s), 51.39 (d), 119.18 (s), 119.87 (s), 124.58, 127.50, 127.66, 127.88, 127.99, 128.17, 128.27, 128.32, 128.63, 128.79, 128.90, 129.36, 129.96, 130.41, 130.69, 132.80, 133.20, 134.42, 135.28, 165.76, 166.58; MS m/e (relative intensity) 276 (M^+, 90%), 261 (10), 196 (10), 181 (60), 115 (20), 106 (20), 91 (100), 65 (75); Analysis calcd. for $C_{18}H_{16}N_2O$: C, 78.26; H, 5.80; N, 10.14. Found: C, 78.28; H, 5.78; N, 10.13%.

Potassamide reaction of 4-cyano-1-ethyl-3-methoxy-5,6-dihydroisoquinoline (1b):

Quenching with benzyl iodide

Potassamide reaction of 5,6-dihydroisoquinoline (**1b**, 856mg) followed by quenching with benzyl iodide gave (i) 4-cyano-5-benzyl-1-(1-methyl-2-phenylethyl)-3-methoxy-5,6-dihydroisoquinoline, **9b** (least polar, 320mg, 30%) viscous liquid, IR (nujol) 2220, 1625 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 1.24 (d, J=7.2Hz, 3H), 2.52-3.61 (m, 8H), 4.08 (s, 3H, -OCH_3), 5.81-5.88 (m, 1H, C_7-H), 6.46 (dd, J=10.6 & 2.4 Hz, 1H, C_8-H), 6.94-7.46 (m, 10H, Ar-H); MS m/e (relative intensity) 394 (M^+, 70%), 379 (20), 303 (100), 287 (20), 264 (10), 212 (45), 91 (90), 65 (15); Analysis calcd. for $C_{27}H_{26}N_2O$: C, 82.23; H, 6.60: N, 7.11. Found: C, 82.20; H, 6.62: N, 7.13%; (ii) 4-cyano-5-benzyl-1-ethyl-3-methoxy-5,6-dihydroisoquinoline, **8b** (medium polar, 290mg, 28%) viscous liquid, IR (nujol) 2220, 1620 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 1.02 (t, J=7.2 Hz, 3H, -CH_2CH_3), 2.62-3.36 (m, 4H), 3.52 (q, J=7.6 Hz, 1H, C_5-H), 4.07 (s, 3H, -OCH_3), 5.76-5.82 (m, 1H, C_7-H), 6.42 (dd, J=11 & 2.4 Hz, 1H, C_8-H) and 6.96-7.32 (m, 5H, Ar-H); Analysis calcd. for $C_{20}H_{20}N_2O$: C, 78.95; H, 6.58; N, 9.21. Found: C, 78.92; H, 6.56; N, 9.23%; (iii) 4,4-dibenzyl-1-ethyl-3-methoxy-1,4-dihydroisoquinoline, **10b** (medium polar, 70mg, 8%) m.p. 112°C, IR (nujol) 1645, 1625 cm^{-1} ^1H NMR (90 MHz, $CDCl_3$): δ 0.72 (t, J=7.2 Hz, 3H, C_1-CH_2CH_3), 1.42 (m, 2H, C_1-CH_2CH_3), 3.18 (d, J=13.2 Hz, 1H, -CH_2Ph), 3.21 (d, J=13.2 Hz, 1H, -CH_2Ph), 3.52 (d, J=13.2

Hz, 1H, -CH_2Ph), 3.55 (d, J=13.2 Hz, 1H, -CH_2Ph), 3.88 (s, 3H, -OCH_3), 4.21 (t, J=7.0 Hz, 1H, C_1-H), 6.48-6.64 (m, 4H, Ar-H), 6.80 (d, J=7.7 Hz, 1H), 6.93-7.06 (m, 6H, Ar-H), 7.12 (t, J=7.2 Hz, 1H), 7.32 (t, J=7.5 Hz, 1H), 7.61 (d, J=7.7 Hz, 1H); Analysis calcd. for $C_{26}H_{27}NO$: C, 84.55; H, 7.32; N, 3.79. Found: C, 84.53; H, 7.34; N, 3.78%; (iv) 4-cyano-1-ethyl-3-methoxyisoquinoline, **4b** (polar, 70 mg, 8% m.p. 96-98°C reported[1]); (v) (1R*, 4R*)-4-cyano-4-benzyl-1-ethyl-1,2,3,4-tetrahydroisoquinolin-3(2*H*)-one, **11b** & (1S*, 4R*)-4-cyano-4-benzyl-1-ethyl-1,2,3,4-tetrahydroisoquinolin-3(2*H*)-one, **11'b** (highly polar, 250mg, 24%) m.p. 141°C, IR (nujol) 3250, 2260, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.81 (t, J=7.6 Hz, 3H), 0.88 (t, J=7.6 Hz, 3H), 1.24-2.02 (m, 4H), 3.48 (q, J_{AB}=13.2 Hz, $\Delta\nu_{AB}$=31.2 Hz), 3.52 (q, J_{AB}=13.2 Hz, $\Delta\nu_{AB}$=31.2 Hz), 4.24-4.45 (m, 2H, C_1-H & $C_{1'}$-H), 6.62-6.93 (m, 2H, -NH), 6.98-7.58 (m, Ar-H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 7.42 (q), 10.55 (q), 27.76 (t), 32.59 (t), 47.64 (t), 47.93 (t), 49.47 (s), 50.05 (s), 54.03 (d), 57.26 (d), 119.38, 119.67, 124.78, 126.28, 127.88, 127.97, 128.09, 128.27, 128.32, 128.48, 128.62, 128.86, 128.97, 130.40, 130.54, 130.73, 132.75, 132.87, 133.23, 133.50, 165.96, 166.29; MS m/e (relative intensity) 290 (M^+, 55%), 261(100), 199(35), 170(20), 142(20), 115(20), 91(90), 69(30), 65(60); Analysis calcd. for $C_{19}H_{18}N_2O$: C, 78.62; H, 6.21; N, 9.66. Found: C, 78.62; H, 6.20; N, 9.64%.

Polyphosphoric acid reaction of 11a/11'a at 140°C

The substrate (**11a/11'a**, 100 mg, 0.3 mmol) and polyphosphoric acid (PPA, excess) were refluxed at 140°C for 12 hr. To the reaction mixture 5 ml of 20% HCl was added and refluxed further for another 5 hr. Then it was brought to pH 10 and the resulting crude product was extracted with $CHCl_3$, washed with water, dried over anhydrous sodium sulphate and the solvent was evaporated. The crude product thus obtained was passed through silica column (eluent: $CHCl_3$/EtOAc, 9:1) to give the mixture of compounds, **12** & **12'** (80mg, 80%) m.p. 220°C, IR (nujol) 3360-3180, 1680, 1640 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 0.48 (d, J=7.6 Hz, C_1-Me), 1.36 (d, J=7.6 Hz, $C_{1'}$-Me), 3.62 (q, J_{AB}=13.2 Hz, $\Delta\nu_{AB}$=31.2 Hz), 3.66 (q, J_{AB}=13.2 Hz, $\Delta\nu_{AB}$=31.2 Hz), 4.52 (dq, J=7.6 & 3.6 Hz, C_1-H), 4.56 (q, J=7.6 Hz, $C_{1'}$-H), 5.58 (bs, 4H, $CONH_2$), 6.12 (bs, 1H, -CONH), 6.28 (bs, 1H, -CONH), 6.6-7.62 (m, Ar-H); MS m/e (relative intensity) 294 (M^+, 10%), 279(10), 250(30), 236(50), 203(20), 186(20), 172(25), 158(25), 130(25), 91(100), 69(30), 57(35); Analysis calcd. for $C_{18}H_{18}N_2O_2$ C, 73.47; H, 6.12; N, 9.52. Found: C, 73.45; H, 6.10; N, 9.51%.

Polyphosphoric acid reaction of 11a/11'a at 165°C

The substrate **11a/11'a** (100 mg, 0.3 mmol) and polyphosphoric acid (PPA, excess) were refluxed at 165°C for 12 hr. To this reaction mixture 5 ml of 20% HCl was added and refluxed further for another 5 hr. Then it was brought to pH 10 and the resulting crude product was extracted with $CHCl_3$, washed with water and dried over anhydrous sodium sulphate and the solvent was evaporated. The crude reaction mixture showed (TLC) the presence of a large number of compounds, which could not be separated.

Methylation of mixture of compounds 11a/11'a with NaH/CH_3I

A mixture of compounds **11a/11'a** (100mg, 0.3 mmol), sodium hydride (30 mg, 0.2 mmol) and 40% excess of methyl iodide were taken in 20ml of benzene and refluxed for 4 hr. The cooled reaction mixture was acidified with con. HCl and the organic layer was separated. The aqueaous layer was extracted with benzene and the combined organic extract was washed with water, dried over anhydrous Na_2SO_4 and the solvent evaporated. The crude reaction product obtained was separated by preparative TLC (eluent, hexane/EtOAc, 8:2) to yield (1R*, 4R*)4-cyano-1,2-dimethyl-4-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one, **13** (least polar) (40mg, 40%) viscus liquid, IR (nujol) 1680, 1615 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 0.76 (d, J=7.6 Hz, C_1-Me), 3.08 (s, 3H, -CONMe), 3.47 (d, J=12.6 Hz, 1H, H_a-CH_2Ph), 3.69 (d, J=12.6 Hz, 1H, H_b-CH_2Ph), 4.42 (q, J=7.6 Hz, C_1-H), 6.68-6.84 (m, 2H, Ar-H), 6.96-7.48 (m, 7H, Ar-H); Analysis calcd. for $C_{19}H_{18}N_2O_2$: C, 78.62; H, 6.21; N, 9.66. Found: C, 78.64; H, 6.20; N, 9.62%; (ii) (1S*, 4R*)-4-cyano-1,2-dimethyl-4-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one, **14** (more polar) (44mg, 45%) m.p. 218°C, IR (nujol) 1680, 1620 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 1.44 (d, J=7.2 Hz, C_1-Me), 2.94 (s, 3H, -CONMe), 3.39 (d, J=12.6 Hz, 1H, H_a-CH_2Ph), 3.78 (q, J=7.2 Hz, C_1-H), 3.97 (d, J=12.6 Hz, 1H, H_b-CH_2Ph), 6.54-6.76 (m, 2H, Ar-H), 6.94-7.72 (m, 7H, Ar-H); Analysis calcd. for $C_{19}H_{18}N_2O_2$: C, 78.62; H, 6.21; N, 9.66. Found: C, 78.67; H, 6.19; N, 9.60%.

Reaction of 14 with H_2SO_4/MeOH

Con. H_2SO_4 (1 ml) was added, with stirring, to the nitrile, **14** (50mg, 0.2 mmol) in 30 ml of abso-

lute methanol and the reaction mixture was refluxed at 130°C for 14-16 hr. After cooling, the reaction mixture was poured into cracked ice and the methanol was removed under vacuum. The resulting aqueous solution was neutralised with sodium bicarbonate and extracted with several portions of chloroform. The chloroform solution was washed with water and dried over anhydrous sodium sulphate, the chloroform was distilled, and the residue was purified by preparative TLC to yield (1S*, 4R*)-4-benzyl-4-methoxycarbonyl-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-one, **15**, (35mg, 70%) viscous liquid, IR (nujol) 1740, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (d, J=6.7 Hz, 3H, C_1-Me), 2,86 (s, 3H, -CONMe), 3.18 (d, J=6.7 Hz, 1H, - CH_2Ph), 3.98 (s, 3H, -OCH_3), 4.09 (d, J=6.7 Hz, 1H, -CH_2Ph), 7.20 (t, J=7.8 Hz, 1H, Ar-H), 7.47-7.61 (m, 5H, Ar-H), 7.71- 7.79 (m, 1H, Ar-H), 7.81 (d, J=7.1 Hz, 1H, Ar-H), 7.94 (d, J=8.3 Hz, 1H, Ar-H); Analysis calcd. for $C_{20}H_{20}N_2O_3$: C, 71.43; H, 5.95; N, 8.33. Found: C, 71.47; H, 6.02; N, 8.32%.

Polyphosphoric acid reaction of 15 at 90°C

The substrate **15** (50mg, 1 mmol) and polyphosphoric acid (PPA, excess) were refluxed at 90°C for 10 hr and the reaction mixture was diluted with water. The crude product was extracted with $CHCl_3$, washed with water and dried over sodium sulphate and solvent was evaporated. Removal of solvent gave back the entire starting compound **15**.

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