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

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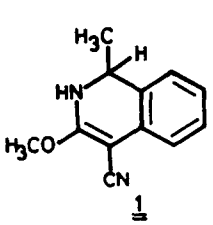
Abstract Potassamide induced *in situ* alkylation of 1-alkyl- 4-cyano-3-methoxy-5,6-dihydroisoquinolines (**2a** & **2b**) with alkyl iodides (CH_3I, CH_3CH_2I & cyclohexyl iodide) gave the 5-alkyl- and 5,9-dialkyl-5,6-dihydroisoquinolines (**4a-d** & **3a-e**), isoquinoline derivatives,(**5a-b**) and diastereomeric mixture of 4- alkyl-1,2,3,4-tetrahydroisoquinolin-3(2H)-ones (**6a-e** & **6'a-e**) Structures were assigned on the basis of spectral data [Mass, ^1H & ^{13}C NMR, 2D NOESY & HC-COLOC] Amide induced *in situ* alkylation of compounds **3a** and **4a** with CH_3I gave in almost quantitative yield the dimethylated compounds **3d** and **3a** respectively. While KNH_2/liq NH_3 methylation of 1,2- dihydroisoquinoline, **1** with CH_3I gave the mixture of compounds, **6a** & **6'a** and the isoquinoline derivative **5a**, NaH/benzene reaction of **1** with CH_3I gave exclusively **5a** N-methylation of the mixture of compounds **6a** & **6'a** with NaH/CH_3I gave the methylated derivatives, **7** & **8** A suitable mechanism has been proposed for the formation of products

1,2-Dihydroisoquinolines are interesting species due to their chemical reaction[1] and their potential as building blocks in the synthesis of alkaloids[2] and medicinal agents [3,4] We have recently reported [5] a novel and useful method for the synthesis of stable 1,2- dihydroisoquinoline derivatives We planned to synthesize N-sugar derivatives[6] of 1,2-dihydroisoquinoline compound, **1** by alkylation with appropriate halo sugars, as the presence of the ionic species, **9** is already visualised in the formation of 1,2-dihydroisoquinolines [5] As model studies, the *in situ* alkylation of 1,2-dihydroisoquinoline compounds formed in the KNH_2/liq NH_3 reaction with alkyl iodides was initially undertaken The results obtained in this study are discussed further

Reaction of 4-cyano-3-methoxy-1-methyl-5,6-dihydroisoquinoline (**2a**) with KNH_2/liq NH_3 in the presence of a trace amount of ferric chloride was carried out as described earlier [5] The reaction mixture was quenched by addition of CH_3I Addition of NH_4Cl and workup of the reaction gave mixture of products, which was purified by column chromatography followed by PTLC This resulted in the isolation of four compounds designated, **A-D** in the order of increasing polarity (TLC)

The least polar compound, **A** (30 %) analysing for $C_{14}H_{16}N_2O$ exhibited an IR absorption at 2220

cm^{-1} The signals at δ 1 18(d, J=7 2Hz, 3H), 1 26(t, J=7 5Hz, 3H), 2 24(dd, J=17 4 & 7 2Hz, 1H), 2 48-2 60(m, 1H), 2 79(q, J=7 5Hz, 2H), 3 3(qn, J=7 5Hz, 1H) were seen in its ^1H NMR spectrum in addition to the methoxy and olefinic signals as in the case of 5,6-dihydroisoquinoline, **2a** It is evident that the compound has been dimethylated Irradiation of the proton signals at δ 3 3(qn) and 2 79(q) resulted in the collapse of the methyl doublet at δ 1 18 and the methyl triplet at δ 1 26 to two singlets respectively. Hence, methylation has occured at C-5 & C-9 positions, and the structure **3a** was assigned to compound **A**.



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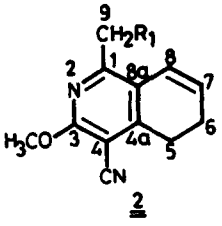
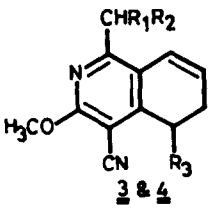


2

a, R_1= H
b, R_1= CH_3



3 & 4

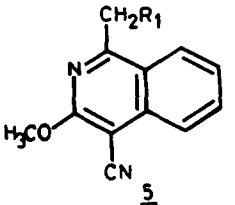
3 (a) R_1=CH_3, R_2=H, R_3=CH_3, (b) R_1= Et, R_2= H, R_3=Et; (c) R_1= , R_2= H, R_3= ,
(d) R_1= R_2= R_3= CH_3, (e) R_1= Et, R_2= CH_3, R_3= Et

4 (a) R_1= H, R_2= H, R_3= CH_3, (b) R_1= H, R_2= H, R_3= Et, (c) R_1= H, R_2= H, R_3= ,
(d) R_1= H, R_2= CH_3, R_3= Et

Compound,**B** (25 %) analysing for $C_{13}H_{14}N_2O$ and showing spectral characteristics (IR & ^1H NMR) similar to those of 5,6-dihydroisoquinoline **2a**, also exhibited ^1H NMR signals at δ 1 16 (d, J=7 2Hz, 3H) and 3 29 (qn, J=7 3Hz, 1H) On the basis of double irradiation experiments, (irradiation of the signal at δ 3 29(qn) resulted in the collapse of methyl doublet at δ 1 16 to a singlet) compound **B** was assigned structure **4a**

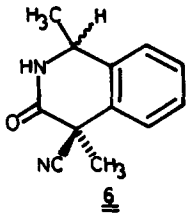
The medium polar Compound, **C** (8 %) was shown to be the already reported[5] isoquinoline derivative **5a**

The most polar Compound, **D** (20 %) analysing for $C_{12}H_{12}N_2O$ exhibited IR absorption frequencies at 3250(-NH or -OH), 2260 (-CN) & 1680 cm^{-1} (-CONH) ^1H NMR spectrum of this compound showed two sets of signals for each type of proton in the ratio of 3 1 viz , doublets at δ 1 59 (J=6 7Hz) & 1 68 (J=6 7Hz) (3H), singlets at δ 1 99 & 1 9 (3H), a quartet at δ 4 75 (J=6 7Hz) & a doublet of quartet at δ 4 84 (J=6 6Hz & 3Hz) collapsing to a quartet on D_2O exchange (1H), sets of aromatic protons at δ 7 22-7 63 (4H) and broad singlets at δ 8 36 & 8 43 (1H) It is evident that demethylation as well as alkylation has occurred (^{13}C NMR spectrum also indicated 23 well resolved signals) The mixture of compounds [7] could be the diastereomeric forms of structure **6**



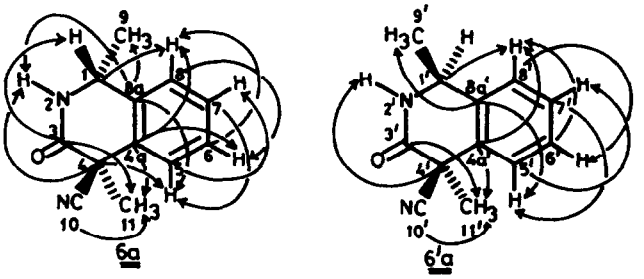
5

a R_1= H ; b R_1= CH_3



6

2D HC-COLOC[8,9] & NOESY[10] experiments were undertaken in order to assign the correct structure as well as the relative configuration. A COrrelation LOngrange Coupling spectrum (^{1}H-^{13}C, COLOC) of compound **D** revealed long range coupling (^{3}J) of the C-4 quaternary carbon with the N_2-H proton for both the compounds. Of the two downfield carbons(-C=O, δ 167 62 & 167 83), only one (δ , 167 62) showed long range coupling (^{3}J) to the methine C_1-H. Further, the long range coupling (^{3}J) of C-10 carbon(-CN, δ 119 98) with the C_{11}-3H protons for both the compounds is also observed [Tables-1 & 2] The mixture of compounds could thus be assigned the diastereomeric structures **6a** & **6'a**



HC-COLOC Correlations of 6a & 6'a

NOESY spectrum revealed correlation between C_9-3H (δ 1 59) & C_{11}-3H (δ 1 99) protons for the major diastereomer However, there is no NOESY correlation between the same for the minor diastereomer [Tables-1 & 2] On this basis, the major diastereomer was assigned structure **6a** with C_1-Me & C_4-Me in *syn* configuration, while the minor diastereomer structure **6'a** with C_1-Me & C_4-Me in *anti* configuration This was further substantiated by N-methylation studies

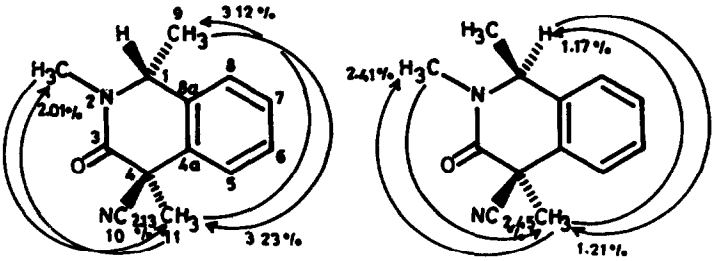
Table 1 High Resolution ^{1}H and ^{13}C NMR Assignment of 6a in $CDCl_3$ Solution (δ)

Position	13C	1H	HC-COLOC	NOESY
1	51 15	4 84	C1 → H9,H8,H2	H1 → H9,H8,H2
2	—	8 43	—	H2 → H11,H9,H1
3	167 62	—	C3 → H11,H1	—
4	43.81	—	C4 → H11,H5 ,H2	—
4a	131 95	—	C4a → H11,H8,H6	—
5	126 77	7 57	C5 → H7,H5	H5 → H11,H6
6	128 49	7 43	C6 → H8,H6	H6 → H7,H5
7	128 79	7 39	C7 → H7,H5	H7 → H8,H6
8	126 13	7 22	C8 → H8,H6	H8 → H9,H7,H1
8a	134 18	—	C8a → H9,H5,H2,H1	—
9	25 38	1 59	C9 → H1	H9 → H11,H8,H2,H1
10	119 98	—	C10 → H11	—
11	29 56	1 99	—	H11 → H9,H5,H2

Table 2 High Resolution ^{1}H and ^{13}C NMR Assignment of 6'a in $CDCl_3$ Solution (δ)

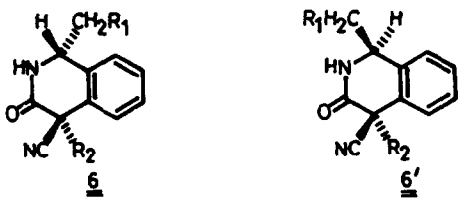
Position	13C	1H	HC-COLOC	NOESY
1'	49 58	4 75	C1' → H9',H8'	H1' → H11',H9',H8',H2'
2'	—	8 36	—	H2' → H9',H1'
3'	167 83	—	C3' → H11'	—
4'	44 79	—	C4' → H11',H2'	—
4a'	132 48	—	C4a' → H11',H8'	—
5'	126 35	7 63	C5' → H7',H5'	H5' → H11',H6'
6'	128 58	7 48	C6' → H8',H6'	H6' → H7',H5'
7'	128 86	7 42	C7' → H5',H7'	H7' → H8',H6'
8'	125 22	7 25	C8' → H6',H8'	H8' → H9',H7',H1'
8a'	134 38	—	C8a' → H9',H5'	—
9'	21 74	1 68	—	H9' → H8',H2',H1'
10'	119 98	—	C10' → H11'	—
11'	26 65	1 90	—	H11' → H5',H1'

Methylation [NaH/CH_3I] of the diastereomeric mixture (**6a** & **6'a**) gave two separable [PTLC, 8 1, hexane EtOAc] N-methylated compounds, **7** (major) & **8** (minor), corresponding to the major and minor isomers of **6** NOE experiments of the methylated compounds further confirmed the assigned structures



7 8

In order to explore the generality of this reaction, we repeated the reaction of alkyl iodides with different 5,6-dihydroisoquinolines, (**2a** & **2b**) which could be prepared by the reaction of the corresponding β-diketones with cyanoacetamide by the general method [5] Reaction of 1-alkyl-4-cyano-3-methoxy-5,6-dihydroisoquinolines (**2a** & **2b**) in KNH_2/liq NH_3 followed by quenching with different alkyl iodides (CH_3I, CH_3CH_2I & cyclohexyl iodide) gave the expected sets of compounds, **3a-e**, **4a-d**, **5a-b**, **6b-e** & **6'b-e** characterised by spectral data



6 6'

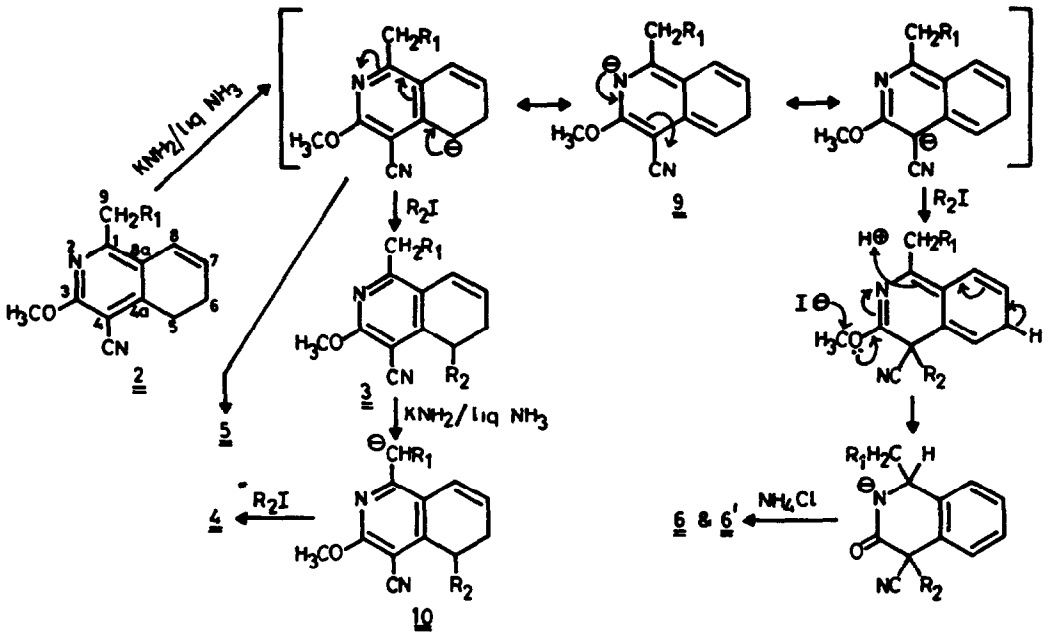
(b) $R_1 = H$, $R_2 = Et$, (c) $R_1 = H$, $R_2 =$

(d) $R_1 = R_2 = CH_3$, (e) $R_1 = CH_3$, $R_2 = Et$

MECHANISM OF FORMATION OF PRODUCTS

The formation of products in the above alkylation can be visualised as in Scheme - 1 The initially formed C-5 benzylic anion can lead to 5-alkyl-5,6- dihydroisoquinoline, **4a-e** and isoquinoline, **5a-b** derivatives The 5,9-dialkyl derivative, **3a-e** is formed from **10** by the generation of C-1Me anion followed by alkylation This is confirmed by the methylation of **3a** & **4a** leading to the formation of dialkyl compounds **3d** & **3a** respectively Alkylation at C-4 position of the isomeric C-4 anion followed by demethylation gives diastereomeric compounds, **6a-e** & **6'a-e**

In order to get the N-alkyl products, alkylation of 1,2- dihydroisoquinoline derivative, **1** in KNH_2/liq NH_3 followed by quenching with CH_3I was attempted This also lead to the formation of **6a** & **6'a** along with the isoquinoline derivative, **5a** When the alkylation of 1,2-dihydroisoquinoline, **1** was attempted with NaH/CH_3I, only **5a** was obtained. It is strange that the N-alkylation does not take place under these reaction conditions



Scheme-1

EXPERIMENTAL

All melting points are uncorrected UV (nm) and IR (cm^{-1}) spectra were recorded on HITACHI Model 557 Double wave length/Double beam and HITACHI 270-50 Infrared spectrophotometers respectively NMR spectra were recorded on Jeol FX-90Q, 22 49MHz (^{13}C), Bruker ACF200, Bruker WH-270 and Bruker AMX400, 100 61MHz (^{13}C) spectrometers with Me_4Si as internal standard(δ = 0 ppm) Mass spectra (70eV) were recorded on a Jeol MS-DX 303 spectrometer fitted with a built-in direct inlet system Analytical and preparative TLC were carried out using silica gel Column chromatography was carried out using silica gel All organic exctracts were dried over anhydrous Na_2SO_4

Potassamide reaction followed by *in situ* alkylation of 5,6-dihydroisoquinolines (2a-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 alkyl iodide (8 mmol) was added Solid NH_4Cl was added after 5 minutes to quench the reaction The 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 were separated by column chromatography followed by PTLC [hexane EtOAc, (8 1)]

Reaction of 4-cyano-3-methoxy-1-methyl-5,6-dihydroisoquinoline (2a):

(a) Quenching with CH_3I: Treatment of the 5,6-dihydroisoquinoline (2a) (800mg) with KNH_2/liq NH_3 and quenching with CH_3I gave (i) 4-cyano-1-ethyl-3-methoxy-5-methyl-5,6- dihydroisoquinoline, 3a (least polar, 270mg, 30 %) viscous liquid , UV λ_{max} 324 (4040), 270 (12995), 242 (9333), IR (neat) 2220, 1625 cm^{-1} ; ^1H NMR (270MHz, $CDCl_3$) δ 1 18 (d, J=7 2Hz, 3H), 1.26 (t, J=7 5Hz, 3H), 2 24 (dd, J=17 4 & 7.2Hz, 1H, C_6-H), 2 48-2.60 (m, 1H, C_6-H), 2 79 (q, J=7.5Hz, 2H), 3 3 (qn, J=7 5Hz, 1H, C_5-H), 4 02 (s, 3H, -OMe), 5.9-6 0 (m, 1H, C_7-H) and 6.55 (dd, J=10 & 3Hz, C_8-H), ^{13}C NMR (22 49MHz, $CDCl_3$) δ 12 62(q), 19 50(q), 27 84(t), 28.92(t), 30.87(d), 54 01(q), 92 58(s), 114 47(s), 119 72(s), 120 80(d), 126 06(d), 156 94(s), 160 03(s), 162 19(s), MS m/e (relative intensity) 228 (M^+,

100 %), 227 (46), 213 (76), 199 (31), 185 (13), 170 (10), HRMS calcd for $C_{14}H_{16}N_2O$ 228.1263 Found, 228 1250, (ii) 4-cyano-3- methoxy-1,5-dimethyl-5,6-dihydroisoquinoline, **4a** (medium polar, 210mg, 25 %) m p 92-93°C, UV λ_{max} 324 (4193), 270 (11872), 244 (8866), IR (Nujol) 2220, 1625 cm^{-1}, ^1H NMR (270Mz, $CDCl_3$) δ 1 16 (d, J=7 2Hz, 3H), 2 24 (dd, J=17 8 & 6 5Hz, 1H, C_6-H), 2 47 (s, 3H, ArMe), 2 47-2 60 (m, 1H, C_6-H), 3.29 (qn, J=7 3Hz, 1H, C_5-H), 4 0(s, 3H, -OMe), 5 7-6 06 (m, 1H, C_7-H) and 6 48 (dd, J=10 & 2Hz, C_8-H), ^{13}C NMR (22 49MHz, $CDCl_3$) δ 19 19(q), 21 57(q), 28 62(t), 30 46(d), 53 87(q), 92 46(s), 114 14(s), 120 10(s), 120 87(d), 125 85(d), 155 22(s), 156 42(s), 161 73(s), MS m/e (relative intensity) 214 (M^+, 100 %), 213 (42), 199 (81), 185 (22), 184 (20), 169 (10), Analysis calcd for $C_{13}H_{14}N_2O$, C, 72 90, H, 6 54, N, 13 08, Found, C, 72 97, H, 6 52, N, 13 09, (iii) 4-cyano-3-methoxy-1-methyl-5,6-dihydroisoquinoline, **5a** (60mg, 8 %, reported [5] m p 89-90° C), (iv) (1R*, 4R*)-4-cyano-1,4-dimethyl-1,2,3,4-tetrahydroisoquinolin- 3(2H)-one, **6a** & (1S*, 4R*)-4-cyano-1,4-dimethyl-1,2,3,4- tetrahydroisoquinolin-3(2H)-one, **6'a** (most polar, 155mg, 20 %) m p 148-150°C, UV λ_{max} 260 (247), 257 (240) , IR (nujol) 3290, 2260, 1680 cm^{-1} , ^1H NMR (200MHz, $CDCl_3$) δ 1 59 (d, J=7Hz, C_1-Me), 1 68 (d, J=7Hz, $C_{1'}$-Me), 1 90 (s, $C_{4'}$-Me), 1 99 (s, C_4-Me), 4 75 (q, J=7 5Hz, $C_{1'}$-H), 4 84 (dq, J=7 5 & 3Hz, C_1-H), 7 22-7 63 (m, ArH) 8 36 (bs, $N_{2'}$-H, D_2O exchangeable), 8 43 (bs, N_2-H, D_2O exchangeable), ^{13}C NMR (100 61MHz, $CDCl_3$) δ 21 74(q), 25 38(q), 26 65(q), 29 56(q), 43 81(s), 44 79(s), 49 58(d), 51 15(d), 119.98 (2 x s), 125 22(d), 126 13(d), 126 35(d), 126 77(d), 128 49(d), 128 58(d), 128 79(d), 128 86(d), 131 95(s), 132 48(s), 134 18(s), 134 38(s), 167 62(s), 167 83(s), MS m/e (relative intensity) 200 (M^+,7 %), 185 (25), 157 (100), 142 (10), 130 (15), 115 (13), 82 (73), HRMS calcd for $C_{14}H_{16}N_2O$ 200 1233 Found, 200 1230

(b) Quenching with CH_3CH_2I: Treatment of the 5,6- dihydroisoquinoline (800mg) with KNH_2/ liq NH_3 and quenching with CH_3CH_2I gave (i) 4-cyano-5-ethyl-3-methoxy-1-propyl-5,6-dihydroisoquinoline, **3b** (least polar, 250mg, 25 %) viscous liquid, UV λ_{max} 321 (2676), 297 (9018), 283 (10124), 245 (11287), IR (neat) 2220, 1625 cm^{-1}, ^1H NMR (270MHZ, $CDCl_3$) δ 0 92-1 01 (m, 6H), 1 5-1 75 (m, 4H), 2 4-2 47 (m, 2H, C6-CH_2), 2 73 (t, J=6Hz, 2H, C_1-CH_2), 2 98-3 07 (m, 1H, C_5-H), 4 01 (s, 3H, -OMe), 5 88-5 95 (m, 1H, C_7-H) and 6 54 (dd, J=9 & 2Hz, 1H, C_8-H), Analysis calcd for $C_{16}H_{20}N_2O$, C, 75 00, H, 7 81; N, 10 94 Found, C, 75 08, H, 7 78, N, 10 91, (ii) 4-cyano-5-ethyl-1-methyl-3-methoxy-5,6-dihydroisoquinoline, **4b** (medium polar, 200mg, 22 %) viscous liquid, UV λ_{max} 322 (4013), 299 (5107), 272 (13133), 244 (11066), IR (neat) 2220, 1625 cm^{-1} , ^1H NMR (270MHz, $CDCl_3$) δ 0 95 (t, J=7Hz, 3H), 1 55 (q, J=7Hz, 2H) 2 3-2 5 (m, 2H, C_6-CH_2), 2 47 (s, 3H, C_1-Me), 2 8-3 2 (m, 1H, C_5- H), 4 0 (s, 3H, -OMe), 5 9-5 96 (m, 1H, C_7-H) and 6 51 (dd, J=10 & 1Hz, C_8-H), MS m/e (relative intensity) 228 (M^+,63 %), 215 (12), 213 (15), 200 (20), 119 (100), 185 (13), 184 (34), 169 (15), HRMS calcd for $C_{14}H_{16}N_2O$, 228 1263 Found, 228 1251, (iii) 4- cyano-3-methoxy-1-methyl-5,6-dihydroisoquinoline, **5a** (60mg, 7 %, reported [5] m p 89-90°C), (iv) (1R*, 4R*)-4-cyano-4-ethyl-1-methyl-1,2,3,4-tetrahydroisoquinolin-3(2H)-one, **6b** & (1S*, 4R*)-4-cyano-4-ethyl-1-methyl-1,2,3,4-tetrahydroisoquinolin-3(2H)-one, **6'b** (most polar, 130mg, 15 %) m p 114-115°C, IR(nujol) 3320, 2240, 1670 cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) δ 1 07 (t, J=7.5Hz), 1 15 (t, J=7 5Hz), 1 56 (d, J=7Hz), 1 64 (d, J=7Hz), 2 05-2 38 (m), 4.69-4.86 (m, C_1-H), 7 16-7 60 (m, ArH), Analysis calcd for $C_{13}H_{14}N_2O$ C, 72 90, H, 6 54, N, 13 08 Found C, 72 87, H, 6 51, N, 13 05

(c) Quenching with cyclohexyl iodide Treatment of 5,6-dihydroisoquinoline (800mg) with KNH_2/liq NH_3 and quenching with cyclohexyl iodide gave (i) 4-cyano-5,9-bis(cyclohexyl)-3-methoxy-5,6- dihydroisoquinoline, **3c** (least polar, 280mg, 20 %) viscous liquid, IR (nujol) 2220, 1630 cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) δ 0 92-1 42 (m, 11H), 1 45-1 91 (m, 11H), 2 31-2 96 (m, 5H), 4 0 (s, 3H, - OMe), 5 76-6 42 (m, 1H), 6 49 (dd, J=10 & 3Hz, 1H), MS m/e (relative intensity) 364 (M^+, 15 %), 351 (10), 298 (10), 282 (100), 255 (25), 225 (15), 199 (40), 83 (45), 55 (50), HRMS calcd for $C_{24}H_{32}N_2O$ 364 2514 Found, 364.2496; (ii) 4-cyano-5-cyclohexyl-3-methoxy-1-methyl-5,6-dihydroisoquinoline, **4c** (medium polar, 180mg, 16 %) m p 96-97°C, IR (nujol) 2220, 1630 cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) δ 1 04-1 86 (m, 11H), 2 36-2 44 (m, 2H), 2 49 (s, 3H), 2 76-2 98 (m, 1H), 4 02 (s, 3H, -OMe), 5 82-6 06 (m, 1H), 6 49 (dd, J=10 & 3Hz, 1H); MS m/e (relative intensity) 282 (M^+, 45 %), 267 (10), 253 (10), 225 (10), 199 (100), 184 (15), 169 (10), 81 (20), 55 (35), HRMS calcd for $C_{18}H_{22}N_2O$, 282 1732 Found, 282 1721, (iii)

4-cyano-3-methoxy-1-methyl-5,6-dihydroisoquinoline, **5a** (85mg, 10%, reported [5] m p. 89-90°C), (iv) (1R*, 4R*)-4-cyano-4-cyclohexyl-1-methyl-1,2,3,4-tetrahydroisoquinolin-3(2H)-one, **6c** & (1S*, 4R*)-4-cyano-4-cyclohexyl-1-methyl-1,2,3,4-tetrahydroisoquinolin-3(2H)-one, **6'c** (highly polar, 140mg, 13 %) m p. 112-113°C; IR (nujol) 3280, 2240, 1660 cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) δ 1 36 (d, J=7 2Hz), 1 46-1 96 (m), 2 22-2.43 (m), 4.64-4 86 (m, C_1-H), 7 18-8 22 (m, ArH), Analysis calcd for $C_{17}H_{20}N_2O$ C, 76 12, H, 7 46; N, 10.45. Found· C, 76 09; H, 7 44, N, 10 41.

Reaction of 4-cyano-1-ethyl-3-methoxy-5,6-dihydroisoquinoline (2b):

(a) Quenching with CH_3I: Treatment of the 5,6- dihydroisoquinoline (856mg) with KNH_2/liq NH_3 and quenching with CH_3I gave (i) 4-cyano-1-isopropyl-3-methoxy-5-methyl-5,6-dihydroisoquinoline, **3d** (least polar, 150mg, 16 %) viscous liquid, IR (nujol) 2220, 1625 cm^{-1}, ^1H NMR (200MHz, $CDCl_3$) δ 1 18 (d, J=6 7Hz, 3H), 1 23 (d, J=6 7Hz, 3H), 1 35 (d, J=7 2Hz, 3H), 2 43- 2 83 (m, 2H, C_6-H), 3 11-3 29 (m, 2H) 4 02 (s, 3H, -OMe), 5 89-5 99 (m, 1H, C_7-H), 6 56 (dd, J=10 & 3Hz, C_8-H), MS m/e (relative intensity) 242 (M^+, 60 %), 227 (100), 213 (65), 199 (60), 185 (39), 169 (15), 115 (20), 77 (20), HRMS calcd for $C_{15}H_{18}N_2O$ 242 1623 Found, 242 1541, (ii) 4-cyano-1-ethyl-3-methoxy-5-methyl-5,6-dihydroisoquinoline, **3a** (medium polar, 150mg, 16 %) (iii) 4-cyano-1- ethyl-3-methoxy isoquinoline, **5b** (70mg, 8 %, reported [5] m p 96- 98°C), (iv) (1R*, 4R*)-4-cyano-1-ethyl-4-methyl-1,2,3,4- tetrahydroisoquinolin-3(2H)-one, **6d** & (1S*, 4R*)-4-cyano- 1-ethyl-4-methyl-1,2,3,4-tetrahydroisoquinolin-3(2H)-one, **6'd** (highly polar, 100mg, 12 %) m p 172-176°C, IR (nujol) 3250, 2240, 1670 cm^{-1}, ^1H NMR (60MHz, $CDCl_3$) δ 1 0 (t, J=7Hz), 1 97 (s), 2 02 (s), 1 57-1 9 (m), 4 4-4 75 (m, C_1-H), 7 1-7 67 (m, ArH) and 8 0 (bs, -CONH, D_2O exchangeable), Analysis calcd for $C_{13}H_{14}N_2O$ C, 72 90, H, 6 54, N, 13 08 Found C, 72 83, H, 6 51, N, 13 01

(b) Quenching with CH_3CH_2I : Treatment of 5,6-dihydroisoquinoline(856mg) with KNH_2/liq NH_3 and quenching with CH_3CH_2I gave (i) 1-(2'-butyl)-4-cyano-5-ethyl-3-methoxy-5,6-dihydroisoquinoline, **3e** (least polar, 200mg, 19 %) viscous liquid, UV λ_{max} 325 (5815), 269 (16061), 244 (12254), IR (neat) 2230, 1630 cm^{-1}, ^1H NMR (270MHz, $CDCl_3$) δ 0 77-1 25 (m, 9H), 1 49-1 87 (m, 4H,) 2 40-2 43 (m, 2H, C_6-H), 2 98-3 11 (m, 2H, C_5-H & C_1-H), 4 01 (s, 3H, -OMe), 5 88-5 95 (m, 1H, C_7-H), 6 61 (dd, J=10 & 2 5Hz, C_8-H), MS m/e (relative intensity) 270 (M^+, 75 %), 271 (40), 269 (20), 255 (50), 242 (100), 228 (20), 213 (30), 185(30), HRMS calcd for $C_{17}H_{22}N_2O$ 270 1732 Found, 270 1776, (ii) 4-cyano-1,5-diethyl-3-methoxy-5,6- dihydroisoquinoline, **4d** (medium polar, 450mg, 47 %) viscous liquid, UV λ_{max} 324 (4974), 270 (13550), 244 (10037), IR (neat) 2230, 1630, 1570 cm^{-1}, ^1H NMR (60MHz, $CDCl_3$) δ 0 95 (t, 7 5Hz, 3H), 1 25 (t, J=7Hz, 3H), 1 46-1 61 (m, 2H), 2 40-2 41 (m, 2H, C_6-2H), 2 79 (q, J=7Hz, 2H), 2 99-3 07 (m, 1H, C_5-H), 4 03 (s, 3H, -OMe), 5 89-5 96 (m, 1H, C_7-H), 6 55 (d, J=10Hz, C_8-H), ^{13}C NMR (22 49MHz, $CDCl_3$) δ 11 51, 12 16, 25 38, 25 60, 27 33, 37 31, 53 57, 92 80, 114 37, 119 69, 120 77, 125 86, 155 78, 159 47, 161 74, MS m/e, (relative intensity) 242 (M^+, 80 %), 243 (20), 241 (18), 227 (20), 213 (100), 198 (20), 185(30), 170(15), 145(15), HRMS calcd for $C_{15}H_{18}N_2O$ 242 1419 Found, 242 1427, (iii) 4-cyano-1-ethyl-3-methoxyisoquinoline, **5b** (65mg, 8 %, reported [5], m p 96- 98°C), (iv) (1R*, 4R*)-4-cyano-1,4-diethyl-1,2,3,4- tetrahydroisoquinolin-3(2H)-one, **6e** & (1S*, 4R*)-4-cyano-1,4-diethyl-1,2,3,4-tetrahydroisoquinolin-3(2H)-one, **6'e** (highly polar, 100mg, 12 %) m p 161-162°C, UV λ_{max} 261 (249), IR (nujol) 3300, 2260, 1680 cm^{-1}, ^1H NMR (270MHz, $CDCl_3$) δ 1 09 (t, J=7Hz), 1 11 (t, J=7Hz), 1 67-1 79 (m), 1 87-1 97 (m), 2 08-2 34 (m), 4 46-4 52 (m, C_1-H), 6 73 (bs, -CONH, D_2O exchangeable) 7 2-7 57 (m, ArH), MS m/e (relative intensity) 228 (M^+,5 %), 226(5), 200(14), 199(100), 172(11), 171(87), 143(11), 142(11), Analysis calcd for $C_{14}H_{16}N_2O$ C, 73 68, H, 7 02, N, 12 28, Found C, 73 64, H, 7 06, N, 12 25

Methylation of mixture of compounds, 6a & 6'a with NaH/CH_3I:
NaH (15 mg, 0 5 mmol), mixture of compound, **6a** & **6'a** (40 mg, 0 2 mmol) and CH_3I (40 % molar excess) were taken in dry benzene (20 ml) and refluxed for 6 hrs The reaction mixture was acidified with AcOH and the benzene layer was separated The aqueous layer was extracted with two 5 ml portions of benzene and the combined benzene extract was washed with water, dried and the solvent evaporated Separation of the crude mixture by PTLC (silica gel) gave (i) (1R*, 4R*)-4- cyano-1,2,4-trimethyl-1,2,3,4-

tetrahydroisoquinolin-3-one, **7** (24 mg, 60 %, semisolid), IR (nujol) 3330, 2240, 1675 cm^{-1}; ^1H NMR (90MHz, $CDCl_3$) δ 1.64 (d, J=7Hz, 3H), 2.07 (s, 3H), 3 17 (s, 3H), 4.54 (q, J=7Hz, 1H), 7 12-7 53 (m, 4H), MS m/e (relative intensity) 214 (M^+, 10 %), 199 (100), 184 (55), 171 (25), 157 (94), 130 (85), 115 (50); HRMS calcd. for $C_{13}H_{14}N_2O$ 214.1106. Found 214 1139; (ii) (1S*, 4R*)-4-cyano-1,2,4-trimethyl-1,2,3,4- tetrahydroisoquinolin-3-one, **8** (8 mg, 30 %, semisolid); IR (nujol) 3330, 2240, 1675 cm^{-1}; ^1H NMR (90MHz, $CDCl_3$) δ 1.53 (d, J=7Hz, 3H), 1 90 (s, 3H), 3 16 (s, 3H), 4 57 (q, J=7Hz, 1H), 7 1-7 66 (m, 4H); MS m/e (relative intensity) 214 (M^+, 10 %), 199 (100), 184 (55), 171 (25), 157 (94), 130 (85), 115 (50); HRMS calcd for $C_{13}H_{14}N_2O$ 214.1106, Found 214 1129.

Methylation of 4-cyano-3-methoxy-1-methyl-1,2-dihydroisoquinoline (1):

[a] with KNH_2/liq.NH_3 : Treatment of 1,2- dihydroisoquinoline (400mg, 2 mmol) with KNH_2/liq - NH_3 followed by quenching with CH_3I gave the isoquinoline derivative, **5a** (100mg, 25 %) and the diastereomeric mixture of compounds, **6a** & **6'a** (200mg, 45 %).

[b] with NaH/benzene: A mixture of 1,2-dihydroisoquinoline (50 mg, 0 25 mmol), NaH (10 mg, 0 35 mmol) and CH_3I (40 % molar excess) in dry benzene (10 ml) was refluxed for 6 hrs. The reaction mixture was acidified with AcOH and the benzene layer was separated, washed with water, dried and the solvent removed. The crude product obtained was purified by column chromatography (silica gel) to give exclusively compound, **5a**.

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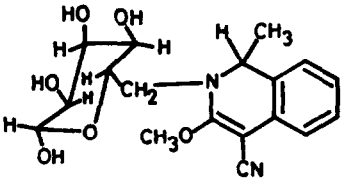
6 This was undertaken as part of a Department of Science and Technology, New Delhi , project, Synthesis of **11** was envisaged



11

7 The highly polar compound **D** could not be separated by TLC However, methylation resulted in the separation of the two compounds

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