Amide-Catalysed Isomerisation of 5,6-Dihydroisoquinolines: a Novel Synthesis of 1,2-Dihydroisoquinolines†

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Knoevenagel condensation of 2-acylcyclohexanones or 2-ethoxycarbonylcyclohexanone with either cyanoacetamide or malononitrile followed by silver salt alkylation gave the 5,6,7,8-tetrahydroisoquinolines (3a—i). Chromic acid oxidation of the 5,6,7,8-tetrahydroisoquinolines (3a—i) to the corresponding tetralones (4a—i) followed by sodium borohydride reduction and *p*-toluenesulphonic acid-catalysed dehydration of the resulting alcohols (5a—i) gave the 5,6-dihydroisoquinolines (6a—i). Reaction of 5,6-dihydroisoquinolines (6a—g) with potassium amide in liquid ammonia gave a mixture of the 1,3-dihydroisoquinolines (7a—g) and the isoquinolines (8a—g). The C-1 unsubstituted 1,2-dihydroisoquinoline (7c) was found to be very unstable. In the case of the 5,6-dihydroisoquinolines (6h and 6i), reaction of potassium amide in liquid ammonia resulted in a mixture of 1-aminoisoquinoline (9) and the isoquinolines (8h and 8i). All the above compounds have been characterised by spectral data. A probable pathway for the formation of the 1,2-dihydroisoquinolines (7a—g) and the isoquinolines (8a—i) is suggested.

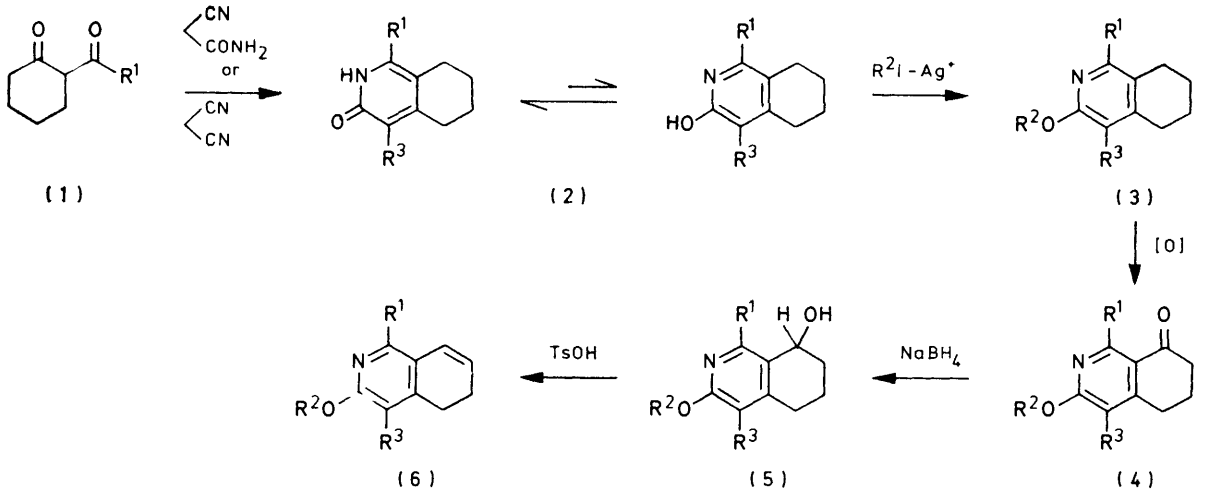
POTASSIUM amide in liquid ammonia is known to convert 1,3- and 1,4-cyclohexadienes quantitatively to benzene and cyclohexene.[1] Similarly, potassium t-butoxide in dimethyl sulphoxide converts 1,4-dihydronaphthalene to naphthalene and tetralin.[2] We report here an unusual reaction where potassium amide in liquid ammonia converts 5,6-dihydroisoquinolines to the corresponding 1,2-dihydroisoquinolines and the fully aromatic isoquinoline derivatives. This general method of synthesis of stable ‡ 1,2-dihydroquinolines is the first of its kind in the literature.

RESULTS AND DISCUSSION

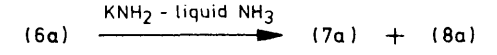
During the course of our study on the total synthesis of 2-azasteroid derivatives,[3] it became essential to synthesise 5,6-dihydroisoquinolines (6) as model compounds. These compounds were readily synthesised according to Scheme 1. Knoevenagel condensation of 2-acetylcyclohexanone and cyanoacetamide resulted[4] in the formation of the pyridone derivative (2a) which on ethylation by the silver salt method[5] yielded the compound (3a). Oxidation of (3a) with chromic acid gave the 8-oxo-derivative (4a), the structure of which was confirmed by its n.m.r. spectral data.[6] Compound (3b) was synthesised by a similar sequence of reactions starting from 2-propionylcyclohexanone, obtained by the condensation of 2-morpholinocyclohexanone[7] and propionyl chloride. Chromic acid oxidation of (3b) followed by column chromatography of the crude product yielded the pure keto-compound (4b), $\nu_{max.}$ (Nujol) 2 240 (C≡N) and 1 680 cm^{-1}. The downfield shift of the methylene quartet (δ 3.0 ⟶ 3.2) in the n.m.r. spectrum of the oxidation product compared to that in the tetralin (3b) (δ 2.4 ⟶ 3.0) was a clear indication that oxidation had taken place at the 8-position. A detailed study[6] of the oxidation of similar 5,6,7,8-tetrahydroisoquinoline derivatives has been carried out earlier and the oxidation product has been shown conclusively to be the 8-oxo- rather than the 5-oxo-derivative by chemical as well as n.m.r. spectral (lanthanide shift reagent) methods. Sodium borohydride reduction of (4a) proceeded smoothly and quantitatively to give the corresponding alcohol [(5a); $\nu_{max.}$ (Nujol) 3 540 cm^{-1} (OH)]. The alcohol, when refluxed with *p*-toluenesulphonic acid in benzene, underwent dehydration to give the olefin (6a). The olefinic protons in the n.m.r. spectrum of (6a) (δ 5.8—6.8, m, 2 H) clearly showed the presence of the double bond in the compound. The 5,6-dihydroisoquinoline (6b) was prepared by the same sequence of reactions from the ketone (4b) and characterised by its spectral data. Compounds (6a) and (6b) were used as model compounds to study the Birch reduction of the double bond in them. During the course of the study, it was found that (6b), on reaction with potassium in liquid ammonia in the presence of a trace amount of iron(III) chloride, gave rise to two new compounds (t.l.c.). These compounds were purified by preparative layer chromatography (p.l.c.) (silica gel) and further crystallisation. The more polar component was a pale yellow solid [$\lambda_{max.}$ 238 (ε 16 400), 256 (12 180) and 305 nm (10 170)] having a high degree of conjugation in the molecule. The n.m.r. spectrum ($CDCl_3$) of this solid showed signals at δ 1.0 (s, 3 H, Me), 1.5—2.1 (quintet, 2 H), 4.1 (s, 3 H, OMe), 4.4—4.8 (m, 1 H), 6.2 (br s, 1 H, D_2O exchangeable), and 6.8—7.4 (m, 4 H, Ar-H). The presence of aromatic signals in the n.m.r. spectrum indicated that dehydrogenation of the carbocyclic ring had taken place and this was further supported by the lack of methylene proton signals other than those due to the C-1 ethyl substituent in the high-field region. As the methoxy group was intact (n.m.r.) in the compound, the D_2O-exchangeable proton could arise from an NH proton. The quintet nature of the methylene signal indicated the presence of a $CH-CH_2-CH_3$ moiety. The multiplet at δ 4.4—4.8 could arise from the proton at C-1. From the above spectral data, the 1,2-dihydroisoquinoline structure (7b) could be assigned to this compound, which was further supported

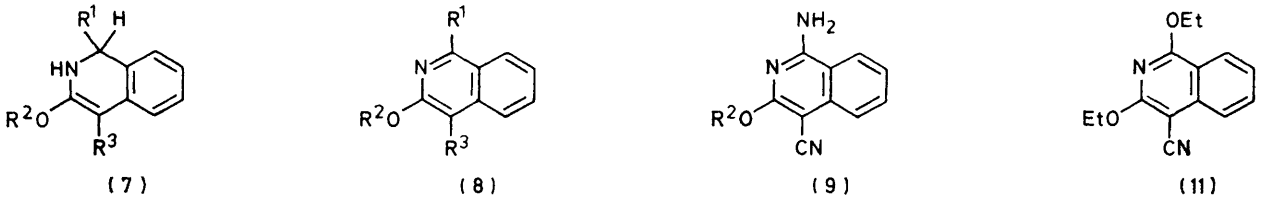
† Preliminary communication; T. R. Kasturi and Lalitha Krishnan, *Tetrahedron Lett.*, 1980, 865.

‡ 1,2-Dihydroisoquinolines unsubstituted at nitrogen are known to be unstable.



a ; R^1 = Me ; R^2 = Et ; R^3 = CN
b ; R^1 = Et ; R^2 = Me ; R^3 = CN
c ; R^1 = H ; R^2 = Me ; R^3 = CN
d ; R^1 = C_6H_4OMe-*p* ; R^2 = Me ; R^3 = CN
e ; R^1 = CH_2Ph ; R^2=Me; R^3 = CN
f ; R^1 = Ph ; R^2 = Me ; R^3 = CN
g ; R^1 = Et ; R^2 = Me ; R^3 = H
h ; R^1 = OMe ; R^2 = Me ; R^3 = CN
i ; R^1 = OEt ; R^2 = Me ; R^3 = CN





by spin-decoupling studies. Irradiation of the NH proton signal at δ 6.2 resulted in the collapse of the δ 4.4—4.8 multiplet to a triplet, as expected. Further, irradiation of the methylene signal between δ 1.5 and 2.1 resulted in the same multiplet becoming a doublet. A survey of the literature [8] indicated that the C-1 proton of stable 1,2-dihydroisoquinolines occurs in the δ 4.4—4.8 region which lends further support to the assigned structure (7b). The molecular ion at *m/e* 214 in the mass spectrum of (7b) confirmed that it is isomeric with the starting 5,6-dihydroisoquinoline.

The less polar component of the above-mentioned reaction product, which was also obtained as a solid, was shown to be the fully aromatised isoquinoline derivative (8b) by its n.m.r. spectrum.

The 5,6-dihydroisoquinoline (6a) obtained by sodium borohydride reduction followed by *p*-toluenesulphonic acid-catalysed dehydration of the ketone (4a) was treated with potassium in liquid ammonia with a trace of $FeCl_3$ as described above. The product consisted again of two components which could be separated by p.l.c. (silica gel). The less polar compound was found to be the fully aromatised derivative (8a) as inferred from its spectral data. The more polar component was shown to be the 1,2-dihydroisoquinoline derivative (7a); δ($CDCl_3$) 1.37—1.44 (superimposed d and t, 2Me, 6 H), 1.69 (br s, D_2O-exchangeable, NH, 1 H), 4.3—4.5 (m, 2 H, OCH_2Me), 4.6—4.7 (m, 1 H, NCH), and 6.9—7.3 (m, 4 H, Ar-H). D_2O Exchange of the NH proton resulted in the collapse of the δ 4.6—4.7 multiplet to a quartet. Irradiation of the methyl signals resulted in the collapse of the same multiplet to a broad singlet and the δ 4.3—4.5 multiplet to a quartet. The anomalous behaviour of the methylene protons of OCH_2Me giving rise to an AB quartet is surprising. The non-equivalence of the methylene protons is perhaps caused by anisotropic effects and also by the presence of a chiral centre at C-1.

From the nature of the products obtained, it was clear that the 5,6-dihydroisoquinoline derivatives (6a) and (6b) were not reduced by potassium amide in liquid

ammonia. They seemed to have undergone isomerisation to yield (2a) and (7b) and aromatisation to yield (8a) and (8b). The absence of any reduction product in the reaction could be due to the fact that no free metal was present in the system to supply electrons. It is well known [8] that amides can be formed readily when alkali metals react with ammonia, a trace amount of iron catalysing the reaction. Secondary reactions involving potassium amide are known to take place when potassium is used in Birch reductions.[1] Based on the above-mentioned observation, it was conjectured that potassium amide, formed *in situ*, was responsible for the conversion of the 5,6-dihydroisoquinoline derivatives to compounds (7) and (8). In order to verify this hypothesis, a solution of (6a) in tetrahydrofuran was treated with a freshly prepared solution of potassium amide in liquid ammonia. After the usual work up, t.l.c. of the crude product indicated formation of the same two products [(7a) and (8a)]. The experiment clearly confirmed the hypothesis.

The amide-catalysed formation of a 1,2-dihydroisoquinoline from (6a) is the first report of its kind, and prompted us to investigate the generality of this reaction.

As the first step, it was decided to study the effect of replacing the 1-alkyl group by an aryl (*p*-methoxyphenyl, phenyl) and a benzyl group. The corresponding 5,6-dihydroisoquinolines (6d—f) could be easily prepared by suitable choice of starting materials. Thus, Knoevenagel condensation of 2-anisoylcyclohexanone with cyanoacetamide followed by methylation gave the compound (3d), which was transformed to the 5,6-dihydroisoquinoline (6d) by the reaction sequence indicated. On treatment with potassium amide in liquid ammonia under the conditions described above, compound (6d) gave the 1,2-dihydroisoquinoline (7d) and the fully aromatised derivative (8d). The C-1 proton in (7d) appeared as a broad doublet at δ 4.6—4.7 in the n.m.r. spectrum and this signal collapsed to a singlet on D_2O exchange. The n.m.r. spectrum of (8d) showing the presence of two methoxy-groups (δ 3.9 and 4.2) and aromatic protons (δ 6.9—8.2, *m*) confirmed the structure.

The 1-phenyl and 1-benzyl derivatives of 4-cyano-3-methoxy-5,6-dihydroisoquinoline were prepared starting from 2-benzoylcyclohexanone and 2-phenacylcyclohexanone, respectively. The structures of all the compounds were confirmed by their spectral data. Treatment of the 5,6-dihydroisoquinolines (6e) and (6f) with potassium amide in liquid ammonia gave in each case the 1,2-dihydroisoquinoline (7e) and (7f) and the fully aromatised isoquinoline (8e) and (8f), respectively, characterised by their spectral data. The C-1 proton in (7e) appeared as a multiplet (δ 4.3—4.5) which collapsed to a clear triplet on removal of the NH coupling by D_2O exchange, whereas that of (7f) appeared as a doublet at δ 4.6 which collapsed to a singlet on D_2O exchange. The reaction was therefore not affected when the C-1 alkyl group was replaced by an aryl group.

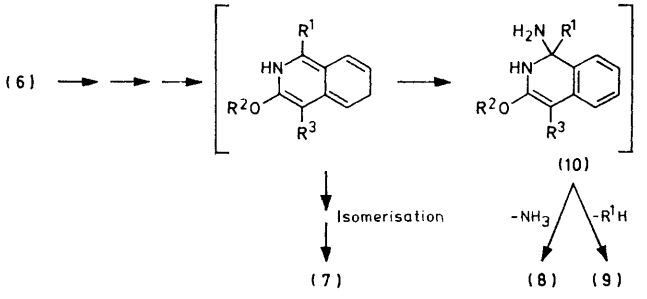
The next compound to be studied in the series was (6c), which lacked a C-1 substituent. This was prepared starting from 2-aminomethylenocyclohexanone and ethyl cyanoacetate. When (6c) was subjected to the above reaction with potassium amide in liquid ammonia, the crude product obtained showed the presence of two compounds. The less polar component was the expected 4-cyano-3-methoxyisoquinoline (8c), as evidenced from the n.m.r. spectrum. Analysis of the more polar component revealed it to be a mixture of the 1,2-dihydroisoquinoline [(7c), δ 4.4, 1 H, C-1 proton] and the aromatised isoquinoline (8c). It was very difficult to isolate (7c) in a pure state as it was very unstable, slowly aromatising to (8c).

In order to confirm whether the presence of the 4-cyano-group was essential for these reactions, the 5,6-dihydroisoquinoline (6g) was synthesised. Decyanation of (2b) by refluxing with 48% hydrobromic acid proceeded smoothly to give (2g) which was methylated to yield (3g). The tetralin (3g) was then converted to the 5,6-dihydroisoquinoline (6g) by the usual set of reactions. Potassium amide in liquid ammonia reacted with (6g) yielded two products (t.l.c.) which were purified and characterised from their spectral data as (7g) and (8g), thus proving that the isomerisation and aromatisation reactions could take place even in the absence of the 4-cyano-group.

The compound (6h), in which the C-1 substituent is a methoxy-group, was the next to be studied in this series. The tetrahydroisoquinoline (2h) was prepared by Knoevenagel condensation of 2-methoxycarbonylcyclohexanone and malononitrile. It was converted to the 5,6-dihydroisoquinoline (6h) which was subjected to reaction with potassium amide in liquid ammonia as before. The product thus obtained again consisted of two components, as shown by t.l.c. The less polar compound was shown to be the completely aromatised compound (8h). The more polar component showed n.m.r. signals at δ 4.4 (s, 3 H, OMe) and 7.0—8.4 (m, 4 H, Ar-H). The absence of any signal in the δ 4.4—4.8 region except the methoxy-signal indicated that this was not the 1,2-dihydroisoquinoline derivative. Secondly, the presence of only a three-proton singlet at δ 4.4 suggested that one of the methoxy-groups had been removed. Elemental analysis indicated that an additional nitrogen had been introduced into the molecule. The only logical explanation that could be offered was that one of the methoxy-groups was replaced by an amino-group during the reaction. Methylation of this compound using methyl iodide and potassium carbonate in acetone yielded the *NN*-dimethyl derivative, the structure of which was confirmed by the n.m.r. spectrum. In order to verify which of the methoxy-groups (C-1 or C-3) had been replaced by NH_2, the compound (6i) bearing an ethoxy-group at C-1 was prepared. Reaction of (6i) with potassium amide in liquid ammonia gave the fully aromatised isoquinoline (8i) as one of the products. The other product obtained from the reaction mixture showed the absence of the ethoxy-group (n.m.r.) and was identical with the compound obtained in the reaction of (6h). This showed that the ethoxy-group had been

substituted by an amino-group, and the compound was thus (9).

The reaction of (6) to give (7) could be visualised as an isomerisation reaction, wherein the heterocyclic ring is reduced at the expense of the carbocyclic ring. Scheme 2 illustrates the probable mechanism of formation of the



products (7), (8), and (9). In order to explain the formation of the amino-isoquinoline (9), a common intermediate (10) has been proposed.

The C-1 position of isoquinolines is known to be very reactive towards nucleophilic substitution.[9] Thus it is possible that the amino-derivative (9) could be formed either by an intermediate of the type (10) or by direct displacement of the alkoxy-group in the isoquinoline (8h) and (8i). However, the isolation of the starting material (11) without any change, on treatment with KNH_2, ruled out the latter possibility.

In conclusion, the amide-catalysed isomerisation reaction of 5,6-dihydroisoquinolines to 1,2-dihydroisoquinolines is a general reaction. Variation in the nature of the substituents (alkyl or aryl) at C-1 does not alter the course of the reaction. The cyano-group at C-4 was found not to be essential for the reaction. However, an alkoxy-group at C-1 is labile to nucleophilic displacement by the amide ion.

EXPERIMENTAL

General.—All m.p.s and b.p.s are uncorrected. U.v. spectra were recorded in 95% ethanol on a Unicam SP700A and i.r. spectra on a Perkin-Elmer 700. The ^1H n.m.r. spectra were recorded on Varian T-60 or HA-100 spectrometers. High-resolution n.m.r. spectra were recorded on a Brucker WH-270 instrument. Chemical shifts are quoted relative to $SiMe_4$ as internal standard. T.l.c. was carried out using silica gel supplied by B.D.H., Bombay, and column chromatography using either alumina or silica gel supplied by B.D.H., Bombay. All microanalyses were carried out by Mr. Ramaprasad and Mr. Thyagarajan of this Department.

2-*Acylcyclohexanones.*—All these were prepared by the acylation of the corresponding ketones according to the general procedure.[10]

Cope–Knoevenagel Condensations and Alkylations.—General procedure. (a) *Condensation.* (*i*) Condensation of the β-keto-ester and malononitrile was carried out according to the procedure of Van der Baan and Bickelhaupt [11] to give (2h) and (2i). (*ii*) Condensation of 2-acetylcyclohexanones and cyanoacetamide was carried out by the method of Freeman *et al.*[4] to give (2a). Compounds (2b), (2e), and (2f) were prepared according to the method of A. Rosowsky.[12] Compound (2c) was prepared according to Bentley *et al.*[13] Compound (2d) was synthesised by condensation of 2-(*p*-anisoyl)cyclohexanone with cyanoacetamide. The crude product thus obtained was used in the next stage without further characterisation.

(b) *Alkylation of the pyridinols.* The crude condensation product obtained by the Knoevenagel condensation in the previous step (1 mol), Ag_2O (0.5 mol) and methyl iodide (40% molar excess) were refluxed in benzene for 8 h. The reaction mixture was cooled, and silver iodide was filtered off and washed with additional benzene. The benzene solution was washed with an ice-cold solution of 10% sodium hydroxide solution and then water. The organic layer was dried and the solvent was removed *in vacuo* to give the crude methylated product, which was purified further.

Chromic Acid Oxidation of Tetralins.—General procedure. To a stirred solution of the tetralin (0.11 mol) in a mixture of acetic acid (245 ml) and concentrated sulphuric acid (18 ml) $Na_2Cr_2O_7 \cdot 2H_2O$ (50 g, 0.165 mol) was added in small portions over a period of *ca.* 2 h such that the temperature was maintained below 60 °C. Stirring was continued for another 10 h at room temperature. The reaction mixture was diluted with water (1.5 l) and extracted with benzene–ether (1 : 1) (4 × 250 ml). The combined organic extracts were washed successively with water (8 × 100 ml), saturated aqueous sodium hydrogencarbonate (8 × 60 ml), and water (4 × 100 ml), and dried. Removal of the solvent gave a dark brown residue which was purified by chromatography over neutral alumina.

Sodium Borohydride Reduction of the Ketones (4) *and Acid-catalysed Dehydration of the Alcohols* (5).*—General procedure.* To a stirred solution of the ketone (0.1 mol) in methanol, $NaBH_4$ (0.25 mol) was added portionwise such that the temperature was kept below 60 °C. Stirring was continued for 3 h at room temperature. The solvent was removed *in vacuo* and the residue was treated with water. The solid obtained was filtered, dried, and recrystallised to give the pure 8-hydroxy-compound.

The alcohol so obtained was refluxed with a trace of toluene-*p*-sulphonic acid in benzene for 3 h. The cooled reaction mixture was washed with saturated hydrogencarbonate solution to remove toluene-*p*-sulphonic acid. The organic extract was washed with water and dried. Solvent removal *in vacuo* gave the 5,6-dihydroisoquinoline.

Amide-catalysed Isomerisation and Aromatisation of 5,6-dihydroisoquinolines.—General procedure. To a stirred blue solution of freshly cut potassium (600 mg) in distilled ammonia (200 ml) a pinch of anhydrous iron(III) chloride was added and stirring was continued for 30 min. When the blue colour had disappeared the dihydroisoquinoline (6) (0.004 mol) in dry THF (10 ml) was added. Stirring was continued for another 30 min. At the end of this period solid ammonium chloride was added to quench the reaction, and the ammonia was allowed to evaporate. The residue was treated with water and extracted with ether. The ether extract was washed with brine and dried over anhydrous Na_2SO_4. Solvent removal *in vacuo* gave the crude product which was further purified by chromatography.

1-*Amino*-4-*cyano*-3-*methoxyisoquinoline* (9). The 5,6-dihydroisoquinoline (6b) (540 mg) on treatment with KNH_2 in liquid ammonia followed by the usual work-up gave a mixture of isoquinoline (8h) (320 mg, 60%) and the amino-isoquinoline (9) (200 mg, 35%), m.p. 173—175 °C;

TABLE 1

Physical data of 5,6,7,8-tetrahydroisoquinolines (3)

Compound	M.p. (°C) (solvent)	Yield (%)	δ (CCl_4)	Analysis [Found (Calculated)] C	H	N
(3a) [a]	114—116 (Benzene)	42				
(3b)	52—54 (Benzene)		1.2 (t, 3 H), 1.6—2.0 (m, 4 H), 2.4—3.0 (m, 6 H), 4.0 (s, 3 H)	72.6 (72.2)	7.8 (7.4)	13.4 (13.0)
(3c) [b]	83—85 (Hexane)	19	1.8—2.0 (m, 4 H), 2.6—3.0 (m, 4 H), 4.0 (s, 3 H), 7.9 (s, 1 H)			14.6 (14.9)
(3d)	110—112 (Benzene–hexane)	68	1.4—2.0 (m, 4 H), 2.5—3.0 (m, 4 H), 3.8 (s, 3 H) 3.9 (s, 3 H), 6.8—7.6 (4 H)	73.5 (73.47)	6.45 (6.12)	9.15 (9.53)
(3e)	66—68 (Hexane)	44.5	1.8 (m, 4 H), 2.4—3.0 (m, 4 H, 3.9 (s, 3 H), 4.1 (s, 2 H), 7.2 (s, 5 H)	77.3 (77.7)	6.5 (6.50)	10.3 (10.07)
(3f)	122—124 (Benzene–hexane)	76.5	1.6—2.0 (m, 4 H) 2.75 (t, 2 H), 3.1 (t, 2 H) 4.1 (s, 3 H), 7.3—7.7 (m, 5 H)			10.2 (10.60)
(3g) [c,d]		84	1.2 (t, 3 H), 1.5—1.9 (m, 4 H), 2.3—2.9 (m, 6 H), 3.8 (s, 3 H), 6.2 (br s, 1 H)	75.1 (75.41)	8.6 (8.9)	7.05 (7.33)
(3h) [d,e]	82—84 (Hexane)		1.6—2.0 (m, 4 H), 2.3—3.0 (m, 4 H), 4.0 (s, 6 H)	66.2 (66.04)	6.7 (6.43)	12.8 (12.85)
(3i) [c,e]			1.4 (t, 3 H), 1.6—1.9 (m, 4 H), 2.4—3.0 (m, 4 H) 4.0 (s, 3 H), 4.4 (q, 2 H)			11.9 (12.07)

[a] Lit.[6] 114—115 °C. [b] The precursor (2c) was prepared from 2-aminomethylenecyclohexanone. [c] The precursor (2g) was prepared by treatment of (2b) with refluxing 48% HBr for 8 h. The precursor 1-hydroxytetrahydroisoquinolines were prepared following the procedure of van Der Baan and Bickelhaupt.[10] [d] N.m.r. was recorded in $CDCl_3$. [e] The product was obtained as a viscous oil.

TABLE 2

Physical data of 8-keto-isoquinolines (4)

Compound	M.p. (°C) (Solvent)	Yield (%)	$\nu_{max.}$/cm^{-1}	δ ($CDCl_3$)	Analysis [Found (Calculated)] C	H	N
(4a) [a]	91—92 (Benzene–hexane)	78					
(4b)	70—72 (Benzene–hexane)	34	2 340, 1 680	1.3 (t, 3 H), 2.2 (m, 2 H), 2.6—2.8 (m, 2 H) 3.0—3.2 (m, 4 H), 4.1 (s, 3 H)	67.4 (67.81)	6.3 (6.09)	12.5 (12.17)
(4c) [b]	140—142 (Benzene–hexane)	39	2 250, 1 680	2.2 (q, 2 H), 2.7 (t, 2 H), 3.2 (t, 2 H), 4.2 (s, 3 H), 8.9 (br s, 1 H)			13.5 (13.90)
(4d)	155—157 (Benzene)	65	2 240, 1 680	2.2—3.4 (m, 6 H), 4.1 (s, 3 H), 4.4 (s, 3 H), 7.0—7.8 (m, 4 H)	70.4 (70.00)	6.2 (6.54)	9.35 (9.10)
(4e)	75—77 (Benzene–hexane)	51	2 210, 1 670	2.2 (quintet, 2 H). 2.7 (t 2 H), 3.1 (t, 2 H), 4.0 (s, 3 H), 4.6 (s, 2 H), 7.3 (s, 5 H)	74.0 (74.0)	5.1 (5.48)	9.3 (9.60)
(4f)	140—142 (Benzene–hexane)	50	2 240, 1 670	2.2 (q, 2 H), 2.6 (t, 2 H), 3.1 (t, 2 H), 4.0 (s, 3 H), 7.3 (s, 5 H)	72.9 (73.40)	4.6 (5.03)	9.6 (10.07)
(4g)		67	1 670	1.2 (t, 3 H), 1.9—3.4 (m, 6 H), 3.9 (s, 3 H), 6.3 (br s, 1 H)	70.0 (70.42)	7.0 (7.32)	6.35 (6.83)
(4h)	168—170 (Benzene–hexane)	65	2 240, 1 680	1.83—2.6 (m, 4 H), 2.8—3.1 (m, 2 H), 4.0, 4.07 (2 s, 6 H)	62.2 (62.07)	5.2 (5.17)	12.05 (12.07)
(4i)	120—122 (Benzene–hexane)	60	2 260, 1 670	1.4 (t, 2 H), 2.2—2.6 (m, 2 H), 2.6—3.0 (m, 2 H), 3.8 (s, 3 H), 4.2 (q, 2 H), 5.6—6.6 (m, 2 H)	63.2 (63.40)	5.9 (5.70)	11.05 (11.39)

[a] Reported m.p. 91—92 °C. [b] N.m.r. was recorded in CCl_4 solution. [c] The product was obtained as a viscous oil.

δ($CDCl_3$ + [$^2H_6$]DMSO) 4.4 (s, OMe, 3 H) and 7.0—8.4 (m, Ar-H, 4 H) (Found: N, 20.82. $C_{11}H_9N_3O$ requires N, 21.05%). The mixture was separated by preparative t.l.c.

4-Cyano-1-NN-dimethylamino-8-methoxyisoquinoline (13). Refluxing a solution of the aminoisoquinoline (9) (100 mg) in benzene containing methyl iodide and anhydrous potassium carbonate yielded the dimethyl derivative (13) (100 mg); δ 3.3 (s, NMe_2, 6 H), 4.0 (s, OMe, 3 H), and 7.2—7.4 (m, Ar-H, 4 H) (Found: C, 68.0; H, 5.5; N, 18.2. $C_{13}H_{13}N_3O$ requires C, 68.30; H, 5.70; N, 18.50%).

Treatment of 4-cyano-1-ethoxy-3-methoxy-5,6-dihydroisoquinoline (6i) *with* KNH_2. Treatment of the 5,6-dihydroisoquinoline (6i) (570 mg) with KNH_2 in liquid ammonia resulted in the formation of mixture of two compounds which was separated by preparative t.l.c. The less polar component was shown to be (8i) and the more polar component was identical with (9).

Treatment of 4-cyano-1,3-diethoxyisoquinoline (11) *with* KNH_2. To a solution of potassium (100 mg; 2.5 mmol) in ammonia (50 ml) a pinch of anhydrous $FeCl_3$ was added and stirred for 30 min. To the resulting KNH_2 solution, 85 mg (0.36 mmol) of isoquinoline [11] (11) in THF (5 ml) was added and stirred for 45 min. The reaction mixture was decomposed by adding solid NH_4Cl, and ammonia was allowed to evaporate. Water (25 ml) was added to the residue, then extracted with ether. The ether extract was washed several times with brine and dried over anhydrous Na_2SO_4. Removal of solvent gave a residue (70 mg) which was identical with the starting material (t.l.c. and m.p., 142—146 °C).

TABLE 3

(*a*) Physical data of 5,6-dihydroisoquinolines (6)

Compound	M.p.	Yield (%)	δ ($CDCl_3$)	Analysis [Found (Calculated)] C	H	N
(6a) [a]	106—108	83.5	1.4 (t, 3 H), 2.2—2.4 (m, 2 H), 2.5 (s, 3 H), 3.0 (m, 2 H), 4.5 (q, 2 H), 5.9—6.8 (m, 2 H)	72.85 (72.90)	6.8 (6.54)	13.4 (13.48)
(6b)	56—58	81.5	1.3 (t, 3 H), 2.1—3.2 (m, 6 H), 4.0 (s, 3 H), 5.8—6.8 (m, 2 H)	72.6 (72.90)	6.7 (6.54)	13.5 (13.08)
(6c) [a]	88—90		2.2—2.8 (m, 2 H), 3.0—3.4 (m, 2 H), 4.0 (s, 3 H), 5.8—6.6 (m, 2 H), 8.0 (br s, 1 H)			14.7 (15.05)
(6d) [a]	180—182	89	2.2—3.2 (m, 4 H), 3.8 (s, 3 H), 4.1 (s, 3 H), 6.0—7.8 (m, 6 H)	74.15 (73.97)	5.65 (5.48)	9.35 (9.60)
(6e)	62—64	91.5	2.0—2.6 (m, 2 H), 3.0 (m, 2 H), 4.0 (s, 3 H), 4.1 (s, 2 H), 5.8—6.7 (m, 2 H), 7.2 (s, 5 H)	77.9 (78.30)	5.6 (5.80)	9.9 (10.15)
(6f)	115—117		2.2—2.6 (m, 2 H), 3.1 (t, 2 H), 5.8—6.7 (m, 2 H), 7.2—7.7 (m, 5 H)	77.4 (77.85)	4.9 (5.34)	10.2 (10.70)
(6g) [a,b]		86.5	1.3 (t, 3 H), 2.0—3.0 (m, 6 H), 5.7—6.7 (m, 3 H)	75.9 (76.19)	7.5 (7.94)	7.2 (7.41)
(6h)	85—87	99	2.2—2.6 (m, 2 H), 2.8—3.1 (m, 2 H), 4.0 (s, 6 H), 5.8—6.8 (m, 2 H)	66.3 (66.70)	5.85 (5.55)	13.25 (12.96)
(6i)	87—89	96	1.4 (t, 3 H), 2.0—2.55 (m, 2 H), 2.6—3.0 (m, 2 H), 3.95 (s, 3 H), 4.2—4.55 (q, 2 H), 5.6—6.0 (m, 1 H), 6.3—6.6 (m, 1 H)	68.1 (67.82)	6.2 (6.09)	12.4 (12.17)
(*b*) Physical data of 1,2,dihydroisoquinolines (7)						
(7a)	132—135	56	1.4 (d and t, 6 H), 4.3—4.5 (m, 2 H), 4.6—4.7 (m, 1 H), 4.9 (br s, 1 H), 6.9—7.3 (m, 4 H)	72.85 (72.90)	6.75 (6.54)	13.4 (13.08)
(7b)	110—112	57	1.0 (t, 3 H), 1.5—2.1 (quintet, 2 H), 4.1 (s, 3 H), 4.4—4.8 (m, 1 H), 6.2 (br s, 1 H), 6.8—7.4 (m, 4 H)	72.5 (72.90)	6.8 (6.54)	13.4 (13.08)
(7d)	204—206	51	1.4 (br s, 1 H), 4.1 (s, 3 H), 4.2 (s, 3 H), 4.6—4.7 (br t, 1 H), 6.8—8.2 (m, 8 H)	73.6 (73.98)	5.2 (5.48)	9.4 (9.60)
(7e)	78—80	52	1.6 (br s, 1 H), 3.1 (d, 2 H), 3.9 (s, 3 H), 4.3—4.5 (m, 1 H), 7.2—8.4 (m, 9 H)	78.0 (78.30)	5.3 (5.80)	9.8 (10.15)
(7f)	195—197	50	1.6 (br s, 1 H), 4.1 (s, 3 H), 4.6 (br d, 1 H), 7.2—8.2 (m, 9 H)	77.3 (77.85)	5.1 (5.30)	10.4 (10.70)
(7g)	102—104	57.5	1.0 (t, 3 H), 1.5—2.1 (quintet, 2 H), 4.1 (s, 3 H), 4.4—4.8 (m, 1 H), 6.2 (br, 1 H), 6.8—7.4 (m, 5 H)	75.85 (76.19)	7.6 (7.94)	7.2 (7.41)
(*c*) Physical data of isoquinolines (8)						
(8a) [a]	125—127 [c]	27.5				
(8b) [a]	96—98	23.5	1.5 (t, 3 H), 3.3 (q, 2 H), 4.2 (s, 3 H), 7.2—8.1 (m, 4 H)	73.8 (73.60)	5.3 (5.66)	12.9 (13.20)
(8c) [a]	127—130	43	4.1 (s, 3 H), 7.2—8.0 (m, 4 H), 9.0 (br, s, 1 H)			14.8 (15.20)
(8d)	132—134	40	3.9 (s, 3 H), 4.2 (s, 3 H), 6.9—8.2 (m, 8 H)	74.1 (74.50)	4.35 (4.83)	9.2 (9.66)
(8e) [a]	70—72	46	4.0 (s, 3 H), 4.5 (s, 2 H), 7.8—8.2 (m, 9 H)			9.9 (10.20)
(8f) [a]	184—186	46.5	4.4 (s, 3 H), 7.2—8.2 (m, 9 H)	78.0 (78.40)	4.3 (4.76)	10.25 (10.76)
(8g) [a,d]		30	1.5 (t, 3 H), 3.3 (q, 2 H), 4.2 (s, 3 H), 7.2—8.0 (m, 5 H)	76.7 (77.10)	6.1 (6.40)	7.2 (7.50)
(8h) [a,d]		60	4.1 (s, 3 H), 4.2 (s, 3 H), 7.2—8.4 (m, 4 H)	67.0 (67.30)	4.3 (4.67)	12.7 (13.08)
(8i) [a]	140—142		1.4 (t, 3 H), 4.3 (s, 3 H), 4.4 (q, 2 H), 7.2—8.4 (m, 4 H)	68.6 (68.42)	5.25 (5.26)	12.0 (12.30)

[a] N.m.r. recorded in CCl_4 solution. [b] Obtained as a gum. [c] Lit.[6], m.p. 125—127 °C. [d] Obtained as a viscous oil.

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