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Anomalous ^{1}H NMR spectra of 3,4-dihydroisoquinolines and related compounds

S NARAYANASWAMI[a], S RAJESWARI, B R PAI, K NAGARAJAN[b], W J RICHTER[c] and S J SHENOY[b]

Department of Chemistry, Presidency College, Madras 600005, India

Research and Development Laboratories, Amrutanjan Limited, Madras 600004, India
[a]Present address: Pfizer Corporation, Sandwich, England
[b]Hindustan CIBA-GEIGY Research Centre, Bombay 400063, India
[c]CIBA-GEIGY Limited, Basel, Switzerland

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Abstract. Solutions of 3,4-dihydro-6,7-methylenedioxyisoquinoline (1) and analogues 2–5 and 9 as well as isoquinolines 7 and 8 in certain samples of $CDCl_3$, CCl_4, DMSO-d_6 or acetone-d_6 gave rise to anomalous ^{1}H NMR spectra with extreme line broadening, signals due to protons at C-1 and C-3 most often not being seen. The spectra of 1 and 3 were most striking in this respect. ^{1}H NMR spectra of the quaternary salt 10 and the model schiff base 11 were normal. Several hypotheses for the observed line broadening have been considered and rejected, a slow equilibrium 1 ⇄ 13 being one of them. $NaBH_4$ reduction of 1 and 2 followed by mass spectrometric analysis of the crude tetrahydroisoquinolines 16 and 17 ruled out a slow equilibrium 1 ⇄ 14 and 2 ⇄ 15 as contributory cause for line broadening. The crude reduction products unexpectedly contained N-ethyl species 22 and 25. Their formation is rationalised.

Keywords. 3,4-dihydroisoquinolines; isoquinolines; anomalous NMR spectra; $NaBH_4$ reduction.

1. Introduction

In the course of our many exercises in aporphine (Suguna and Pai 1977) and protoberberine (Pai *et al* 1982) chemistry, we had occasion to run routinely the ^{1}H NMR

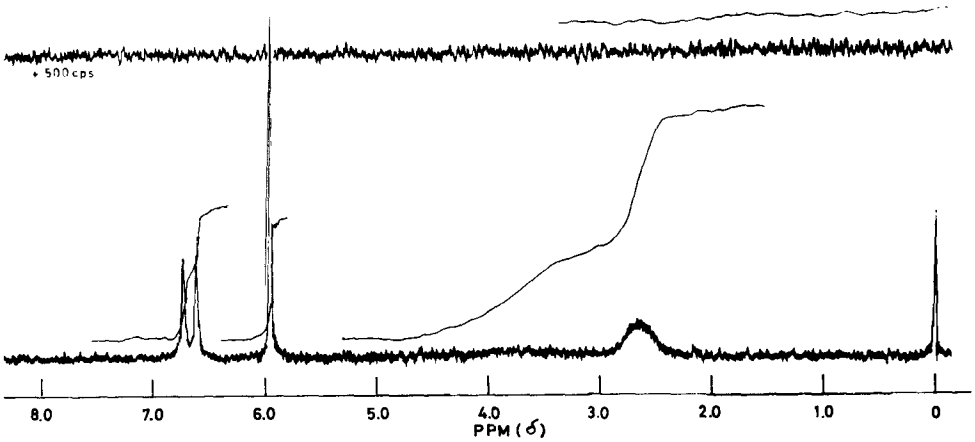


Figure 1. NMR spectrum of 1 in $CDCl_3$.

Table 1. ^{1}H NMR spectral data for 3,4-dihydroisoquinolines and related compounds.

Compound	Solvent(s)	δ (ppm) and shape of signals of protons at					
		C-1	C-5	C-8	C-3	C-4	Other C
	$CDCl_3$[a,a+d]	—	6·60 (s)	6·73 (s)	—	2·20–3·00 (vbh)	5·95 (s, CH_2O_2)
	$CDCl_3$[a] (−40°)	8·14 (bs)	6·61 (s)	6·72 (s)	3·67 (bt, J 8Hz)	2·62 (t, J 8Hz)	5·98 (s, CH_2O_2)
	$CDCl_3$[a] + D_2O	—	6·60 (s)	6·73 (s)	—	2·20–3·00 (vbh)	5·95 (s, CH_2O_2)
	$CDCl_3$[a] + HCl	8·35 (bs)	6·65 (s)	6·80 (s)	3·75 (bt, J 8Hz)	2·70 (at, J 8Hz)	5·95 (s, CH_2O_2)
	$CDCl_3$[a] + D_2O + CF_3COOH	—	6·65 (s)	6·85 (bs)	—	2·40–3·30 (vbh)	6·00 (s, CH_2O_2)
	$CDCl_3$[a] + D_2O + CF_3COOH	8·55 (bs)	6·85 (s)	7·20 (s)	3·95 (tf, J 8Hz)	3·10 (at, J 8Hz)	6·15 (s, CH_2O_2)
	$CDCl_3$[b,c,d,e]	8·10 (bt)	6·60 (s)	6·70 (s)	3·70 (tf, J 8Hz)	2·60 (at, J 8Hz)	5·93 (s, CH_2O_2)
	$CDCl_3$[e] + NiAcetate (25°)	—	6·46 (s)	6·66 (s)	—	2·62 (bh)	5·82 (s, CH_2O_2)
	$CDCl_3$[e] + NiAcetate (−60°)	8·11 (bs)	6·60 (s)	6·72 (s)	3·63 (at, J 8Hz)	2·62 (t, J 8Hz)	6·06 (s, CH_2O_2)
	CCl_4[f]	8·03 (bs)	6·55 (s)	6·67 (s)	3·65 (tf, J 8Hz)	2·55 (at, J 8Hz)	5·92 (s, CH_2O_2)
	CCl_4[g]	—	6·55 (s)	6·65 (s)	3·20–4·10 (vbh)	2·58 (at, J 8Hz)	5·92 (s, CH_2O_2)
	DMSO-d_6[a]	—	6·75 (s)	6·92 (s)	3·20–4·10 (vbh)	2·55 (at, J 8Hz)	6·03 (s, CH_2O_2)
	Acetone-d_6[a]	—	6·70 (s)	6·87 (s)	3·20–4·10 (vbh)	2·60 (at, J 8Hz)	6·00 (s, CH_2O_2)
	Benzene	8·10 (t, J, 2Hz)	6·30 (s)	6·42 (s)	3·62 (tf, J 8Hz)	2·25 (at, J 8Hz)	5·70 (s, CH_2O_2)
2	$CDCl_3$[a]	7·00–8·00 (vbh)	6·83 (s)	6·85 (s)	3·70–4·30 (vbh)	2·65 (bt, J 8Hz)	3·87, 3·88 (2s, OCH_3)
	$CDCl_3$[a] + CF_3COOH	8·97 (bs)	6·95 (s)	7·35 (s)	3·98 (bt)	3·15 (t, J 8Hz)	3·92, 4·02 (2s, OCH_3)
3	$CDCl_3$[a]	—	6·70 (s)	6·83 (vbs)	—	2·00–3·50 (vbh)	3·87 (s, OCH_3) 5·15 (s, $C_6H_5C\underline{H}_2$) 7·20–7·70 (m, C_6H_5)
	CCl_4[g]	—	6·58 (s)	6·75 (vbs)	—	2·00–3·50 (vbh)	3·80 (s, OCH_3) 5·05 (s, $C_6H_5C\underline{H}_2$) 7·20–7·50 (m, $\underline{C_6H_5}$)
4	$CDCl_3$[a]	—	6·67 (s)	6·83 (bs)	—	2·40–3·00 (bh)	3·87 (s, OCH_3) 5·12 (s, $C_6H_5C\underline{H}_2$) 7.20–7·60 (m, $\underline{C_6H_5}$)
5	$CDCl_3$[a] + DMSO-d_6	—	6·67 (s)	6·83 (bs)	—	2·00–3·00 (vbh)	3·85 (s, OCH_3)

6	$CDCl_3$[a]	9·20 (s)	—	—	8·52 (J 6Hz)	—	7·10–7·80 (m, C-4, C-5, C-6, C-7, C-8H)
	$CDCl_3$[a] + NH_3	9·20 (s)	—	—	8·52 (d, J 6Hz)	—	7·10–7·80 (m, C-4, C-5, C-6, C-7, C-8H)
7	$CDCl_3$[a]	—	7·00 (s)	7·13 (s)	8·20–8·70 (vbh)	7·45 (vbd)	6·10 (s, CH_2O_2)
	CCl_4[g]	8·88 (bs)	6·95 (s)	7·08 (s)	8·28 (bd, J, 6Hz)	7·33 (d, J 6Hz)	6·03 (s, CH_2O_2)
8	$CDCl_3$[a]	9·30 (vbs)	7·30 (s)	—	8·37 (vbd, J 6Hz)	7·50 (bd, J 6Hz)	6·17 (s, CH_2O_2) 7.30 (s, C-6H)
	CF_3COOH	9·60 (bd)	7·95 (s)	—	8·37 (bs)	8·37 (bs)	6·53 (s, CH_2O_2) 7·95 (s, C-6H)
9	$CDCl_3$[a]	7·80–8·50 (vbh)	6·58 (s)	6·72 (s)	3·20–4·00 (vbh)	2·30–2·90 (m)	1·38 (d, CH_3) 5·92 (s, CH_2O_2)
10	D_2O	8·67 (bs)	6·90 (s)	7·15 (s)	3·95 (at, J 8Hz)	3·13 (at, J 8Hz)	3·68 (s, NCH_3) 6·07 (s, CH_2O_2)
11	$CDCl_3$[a]	7·95 (bs)	6·72 (d, J 8Hz)	7·32 (d, J 1·5Hz)	3·80 (at, J 8Hz)	2·95 (t, J 8Hz)	5·83 (s, CH_2O_2) 7·17 (s, C_6H_5) 7·00 (dd, J8, 1.5Hz, C-10H)

Source of solvent:
a—Switzerland *b*—Poona *c,d*—USA *e*—England *f*—India-commercial reagent *g*—India-redistilled
Abbreviations for signal shapes:
s—singlet; d—doublet; t—triplet; m—multiplet; h—hump; b—broad; v—very; f—fine structure; a—approximate.

spectrum of norhydrastinine (1, 3,4-dihydro-6,7-methylene-dioxyisoquinoline) in a sample of $CDCl_3$ and obtained strange and wholly unexpected results (figure 1). While the signals due to the aromatic and methylenedioxy protons were seen as sharp singlets at 6·73, 6·60 and 5·95 ppm respectively, there was no visible signal below 7·5 ppm as would have been expected for the azomethine proton, nor between 3 and 5 ppm for the protons on C-3, although integration revealed the presence of less than 25% of one proton in the former and about one proton in the latter regions. The benzylic protons (on C-4) were seen as a very broad hump between 2·2 and 3 ppm and integrated nearly correctly. Intrigued by these observations, we extended the study to some other dihydroisoquinolines and related compounds and our findings are reported in this paper.

2. NMR spectra of 3,4-dihydroisoquinolines

^1H NMR spectra of 1 and its 6,7-dimethoxy (2), 6-benzyloxy-7-methoxy (3), 6-methoxy-7-benzyloxy (4) and 6-methoxy-7-hydroxy (5) analogues were run in the same sample of $CDCl_3$ and the results are presented in table 1. They are all obviously anomalous to varying degrees, 3 (figure 2) perhaps being conspicuously so. In the spectrum of the 3-methyl-3,4-dihydroisoquinoline 9, the signals due to the methine protons at C-1 and C-3 were again found to be very broad humps. But the spectrum of an acyclic analogue, the schiff base 11, in this sample of $CDCl_3$, was perfectly normal (figure 3), with all protons displaying sharp signals with expected multiplicity. The spectrum of 1 was studied in $CDCl_3$ from the same batch on several occasions over a period of two years and remained consistently mysterious. However, normal spectra were obtained in $CDCl_3$ received from four other sources; abnormality was restored on addition of the first sample of $CDCl_3$ to these solutions.

The NMR spectrum of 1 in a commercial reagent grade of CCl_4 was again normal (figure 4) but became fairly 'abnormal', when the solvent was used after further purification. Similar spectra were obtained in DMSO-d_6 and acetone-d_6. In the last three

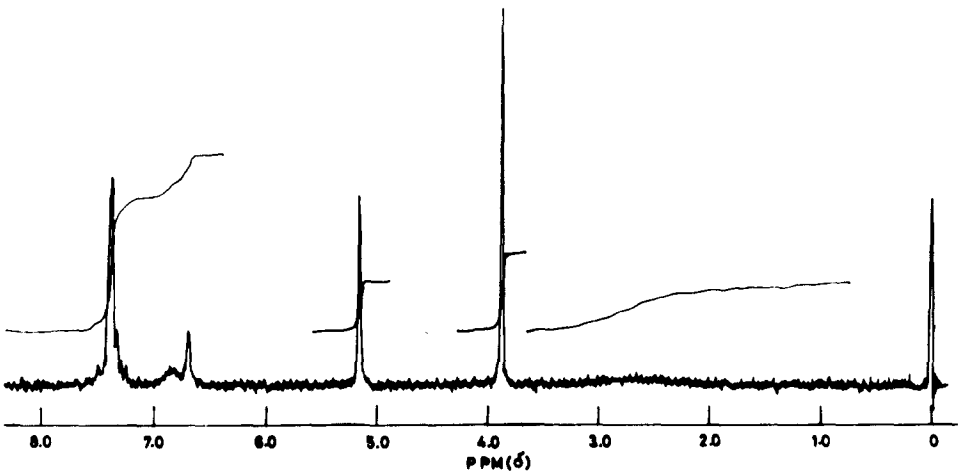


Figure 2. NMR spectrum of 3 in $CDCl_3$.

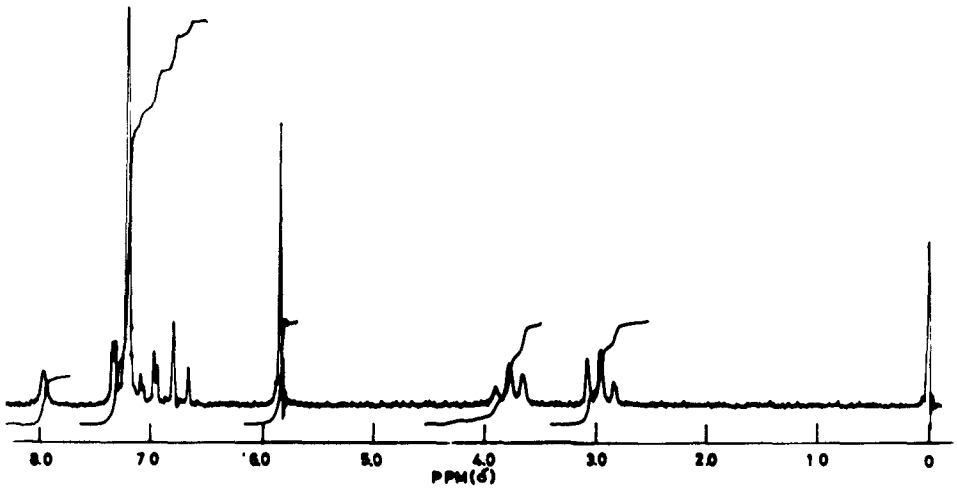


Figure 3. NMR spectrum of 11 in $CDCl_3$.

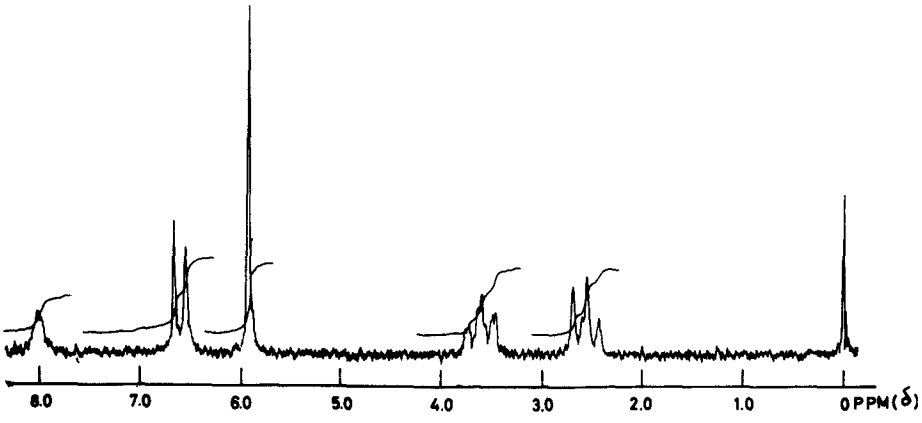


Figure 4. NMR spectrum of 1 in CCl_4.

cases, the signal due to the azomethine proton was still invisible, but the signal of the NCH_2 group was picked up as a broad hump between 3·2 and 4·1 ppm, while the $ArCH_2$ signal sharpened up to an approximate triplet. The spectrum of 1 in ordinary benzene displayed signals due to all the protons, but protons at C-4, C-5 and C-8 had suffered upfield shifts of 0·3–0·4 ppm, due perhaps to the complexation of 1 with the solvent in an appropriate orientation. The spectrum clearly revealed the signals at C-1 and C-3 and their mutual coupling.

The NMR spectrum of 3 in CCl_4 was as abnormal (figure 5) as in $CDCl_3$ with total absence of signals due to protons at C-1 and C-3, a very broad hump for protons at C-4 and a very broad singlet for C-8 proton.

The anomaly in the NMR spectrum of 1 in $CDCl_3$ persisted upon addition of D_2O,

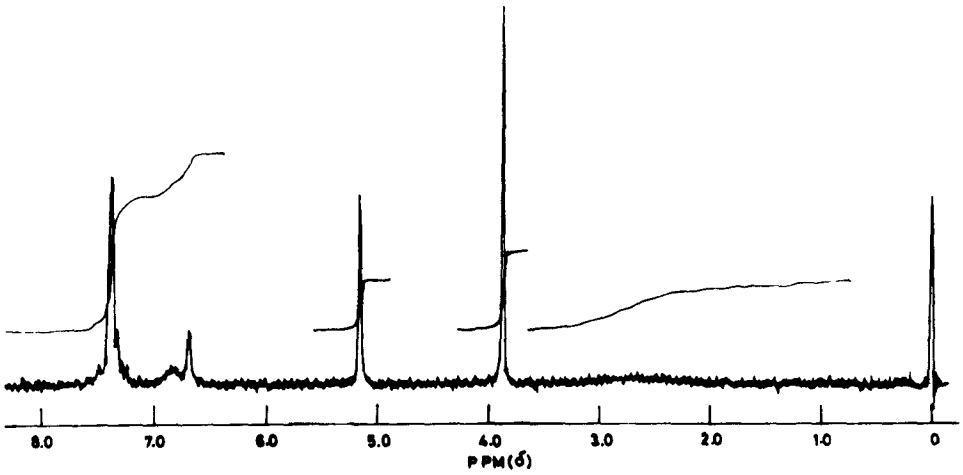


Figure 5. NMR spectrum of 3 in CCl_4.

and further a little trifluoroacetic acid, but normality could be attained by the addition of more trifluoroacetic acid, or hydrogen chloride to the original solution, as evidenced by the appearance of signals with appropriate shape for protons at C-1 and C-3, with some acid-induced shifts. As a logical corollary, the spectrum of the quaternary salt 10 of 1 was run in D_2O and found to possess the appropriate features, with some signals displaced to low field, consistent with the presence of a full charge on the nitrogen atom.

3. NMR spectra of isoquinolines

The spectrum of the parent 3,4-dihydroisoquinoline could not be run due to the difficulty in the synthesis, but we could study isoquinoline 6 itself in the original sample of $CDCl_3$ alone or in the presence of ammonia (to remove traces of acid if present). Both spectra displayed sharp signals for all the protons. However, abnormality appeared to some extent in the spectrum of the 7,8-methylenedioxy derivative (8), and to a greater extent in that of 6,7-methylenedioxyisoquinoline (7). Thus the signal due to the proton at C-1 in 7 was not visible (figure 6) and that of the proton at C-3 was a very broad hump. Even the doublet of the proton at C-4 was visibly broadened. However, normalcy appeared in the spectrum of 7 in CCl_4 and 8 in TFA.

4. Discussion of results

The anomalous nature of spectra of 3,4-dihydroisoquinolines which was apparently a case of extreme line broadening was observed for quite a few 6,7-dialkoxy derivatives, but not for the schiff base 11, in one sample of $CDCl_3$. This was true for 1 and 3 in CCl_4 and for 1 in DMSO-d_6 and acetone-d_6 solution. It was present, perhaps to a lesser extent, for the isoquinolines 7 and 8. These observations prompted us in the first instance to consider that the phenomenon was due to an unusual broadening effect of the coupling of the nitrogen (^{14}N), although two bonds were intervening. In the fluorine NMR

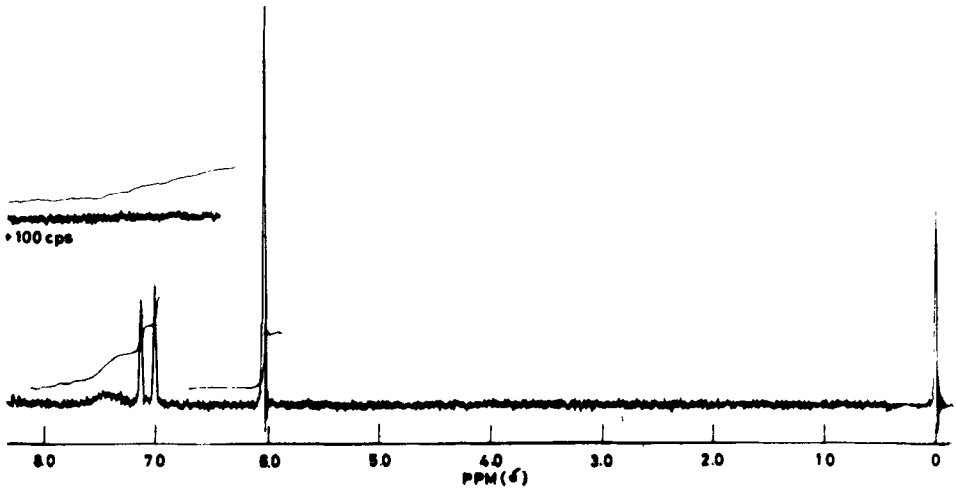


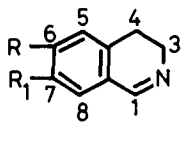
Figure 6. NMR spectrum of 7 in $CDCl_3$.

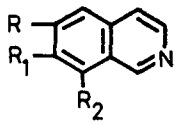
spectrum of the azomethine 12, the –CF=N absorption has been reported (Cavalli and Piccandi 1969) to be a broad band. It has been speculated that this could be due to such an effect. However, the spectrum of 1 in $CDCl_3$ with simultaneous irradiation at ^{14}N frequency did not revert to normalcy.

We considered the possibility that dissolved oxygen could be responsible for line broadening, but bubbling oxygen into a solution of 1 in a sample of $CDCl_3$ that had given a 'normal' spectrum did not lead to any line broadening. However, addition of crystals of nickel acetate to this solution caused a dramatic effect and produced the 'familiar' 'anomalous' spectrum. When solutions giving rise to anomalous spectra of 1 at usual probe temperatures, were cooled to $-40°$ to $-60°$, the expected signals of *all* the protons in 1 appeared with appropriate line shapes. Thus it seemed possible that the 'anomalous' spectra were caused by a slow equilibrium of 1 as a ligand with some complexing agent, which need not of course necessarily be paramagnetic. However, the low temperature spectrum showed *only one* species, 1 to be present—and hence it would have to be argued that at these temperatures the equilibrium was very much in favour of 1 with the complex present in undetectable proportions. Raising the temperatures should increase the rate of exchange and produce sharp signals, but in $CDCl_3$ upto 50° (the maximum temperature obtainable) this did not happen.

The complexing extraneous impurity could be present in the solvent, (*e.g.* traces of acid). This was considered unlikely since anomaly had occurred in $CDCl_3$, CCl_4, DMSO-d_6 and acetone-d_6. Further, this persisted even in $CDCl_3$ that had been distilled over norhydrastinine (1). It could be present in the solute, but this hypothesis had to be ruled out because similar phenomena were realized with dihydroisoquinolines 1–5 and 9 and isoquinolines 7 and 8. Again a carefully recrystallised sample of 1 behaved similarly towards the truant $CDCl_3$. Lastly we had to reckon with the possibility of tetramethylsilane (internal reference) as the culprit, but with or without this, an anomalous spectrum of 1 in $CDCl_3$ continued to be so.

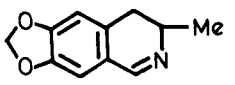
Having practically exhausted 'extraneous' possibilities, we turned our attention to





1 $RR_1 = CH_2O_2$
2 $R = R_1 = OMe$
3 $R = PhCH_2O$; $R_1 = OMe$
4 $R = OMe$, $R_1 = PhCH_2O$
5 $R = OMe$; $R_1 = OH$

6 $R = R_1 = R_2 = H$
7 $RR_1 = CH_2O_2$; $R_2 = H$
8 $R = H$; $R_1R_2 = CH_2O_2$



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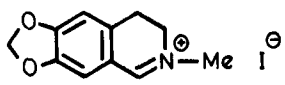

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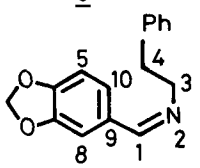

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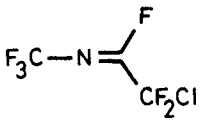

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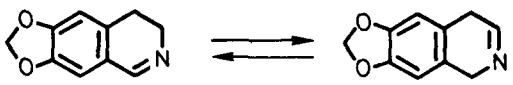
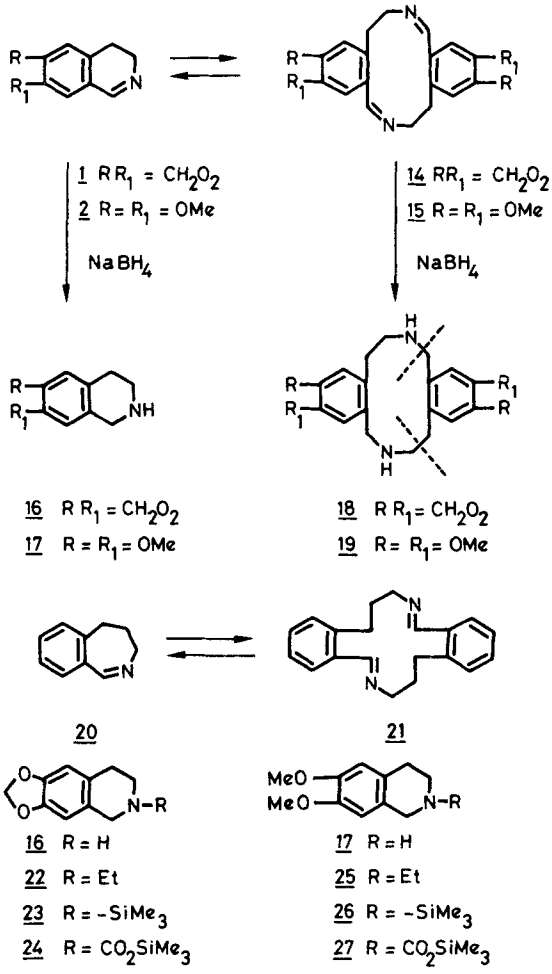


1 13

examine the unlikely possibility of an 'internal' 'slow' equilibrium*, 1 ⇄ 13. This was considered extremely unlikely. But we could rule it out firmly also since exposure of a solution of 1 in a sample of $CDCl_3$ giving a 'normal' spectrum to D_2O for 5 days did not show any change in the signals due to protons at C-1, C-3 and C-4. Further spectra of 1 and 2 in acids showed separate signals for *protons at both C-1 and C-3*.

We considered one last possibility that dihydroisoquinolines of type 1 and 2 could exist in a slow equilibrium* with dimers 14 and 15 respectively. The concentration of 14 and 15 may be so small at low temperatures that the insensitive NMR technique may not pick up their signals. Such a speculation has supportive precedent in the literature (Goldman *et al* 1969) in the case of the benzazepine 20 which has been shown to go over to 21 on prolonged storage. We failed in our efforts to detect the presence of 14 and 15 in the NMR spectra of 1 and 2 respectively and turned our attention to using mass spectrometry to unmask the 'culprits'. Our efforts were unsuccessful but provided unexpected and interesting diversions. These are reported in the next section.

* We, of course, make the assumption that this happens fortuitously in some solvents favouring this process, but not in others. These possibilities are unlikely to be applicable to 7 and 8.



5. Mass spectral studies

Carefully run high resolution mass spectra of 1 showed no mass peaks above $M^{+\bullet}$ at m/z 175 ($C_{10}H_9NO_2$), as the most abundant peak, followed by important fragments at m/z 174, 149, 116 and 89. The dimeric species 14 was not detectable in the sample vaporized from the probe of the mass spectrometer at 50°. It was still possible that traces of 14 and 15 were formed in solution. We considered that reduction would be a sure method of trapping such fugitive species irreversibly. Accordingly 1 was reduced with $NaBH_4$ in ethanol and the product worked up by dilution with water, extraction with ether and evaporation of the dried extract. Low resolution mass spectrum of the crude product 16 showed as expected, prominent peaks at m/z 177 ($M^{+\bullet}$ of 1) and 176 $(M\text{-}H)^{+\bullet}$. Additional small peaks were seen at m/z 205, 204 and 190, but none above 205. Thus although *a priori* there was no evidence for the formation of 18, conceivably the peak at m/z 205 could be explained as arising from the fragmentation of 18 as

shown, with $M^{+\bullet}$ of the intact dimer itself not being seen. However, the mass spectrum of the trimethyl silyl (TMS) derivative of crude 16 discredited the speculation, and indicated the major impurity to be the ethyl derivative, 22. Thus the spectrum still showed the peak at m/z 205 ($M^{+\bullet}$ of 22), besides a major one at m/z 249 ($M^{+\bullet}$) of 23, the TMS derivative of 16. A small peak at m/z 293 should be due to $M^{+\bullet}$ of 24, the TMS derivative of the N-carboxylic acid of 16 formed by the exposure of 16 to aerial CO_2. The presence of the ethyl species 22 was confirmed by the 360 MHz ^1H NMR spectrum of crude 16. Characteristic signals due to the N-ethyl species were seen at 1.15 (triplet) and 2.6 (quartet) ppm, integration revealing that 22 was present to the extent of about 10%.

The crude reduction product 17 of 2 in EtOH (work-up by dilution with water and extraction with ether) was examined in greater detail. The 360 MHz spectrum in $CDCl_3$ of crude 17 showed the presence of the N-ethyl derivative 25-triplet at 1·15 and quartet at 2 ppm. High resolution electron impact (EI) mass spectrum showed $M^{+\bullet}$ for 17 at m/z 193 ($C_{11}H_{15}NO_2$), $M^{+\bullet}$ for 25 at m/z 221 ($C_{13}H_{19}NO_2$), and its $(M-CH_3)^{+\bullet}$ fragment at m/z 206 ($C_{12}H_{16}NO_2$). After deuterium exchange, peaks at m/z 221 and 206 remained unshifted but the one at m/z 193 moved up to 194. Thus fragmentation of 19 as shown would not be the source of the ion at m/z 221. Field desorption (FD) mass spectrum of crude 17 showed mass peaks only at 193 and 221 and none in the higher mass region. The TMS derivative of crude 17 displayed in its EI spectrum, peaks at m/z 265 ($M^{+\bullet}$ of 26), 309 ($M^{+\bullet}$ of 27) and 221 ($M^{+\bullet}$ of 25). High resolution accurate mass measurements indicated, in addition, the presence of boron complexes as minor constituents.

Interestingly the same ethylated species 22 and 25 were respectively formed when the reduction of 1 and 2 with $NaBH_4$ was performed in *methanol* solution, further work-up constituting dilution with water and extraction with ether. The products were identified by resort to both mass and NMR spectrometry. At the moment, we are obliged to postulate that N-ethylation occurred by reaction of 16 or 17 with ether (or its peroxide) during extraction in the presence of unused excess sodium borohydride. The same ethylated species 25 was formed when the reduction of 2 with sodium borohydride was conducted in water and the product extracted with ether. The involvement of ether in the formation of 25 was confirmed when benzene was used to extract the reduction product from the aqueous solution. The mass spectrum of crude 17 was devoid of any peaks above the one at m/z 193. On the other hand, the products obtained by reducing 2 in methanol, ethanol or water and extracting with methylene chloride again showed peaks at m/z 221. High resolution mass spectra revealed this species to be due to $C_{12}H_{15}NO_3$ ions, corresponding probably to the molecular ion of the N-formyl derivative of 17. Additionally peaks were also seen at m/z 207 and 206, corresponding to $C_{12}H_{17}NO_2$ and $C_{12}H_{16}NO_2$ respectively, arising probably from the N-methyl derivative of 17. We speculate that the reaction of 17 with methylene chloride would lead to a N-chloromethyl derivative which as such (or as the hydroxy methyl compound) can lead to the two products by oxidation-reduction mechanisms. These were however present in trace amounts and not detectable in the NMR spectra. We next studied the reaction of 1-phenyl-3,4-dihydro-6,7-dimethoxyisoquinoline with sodium borohydride under various conditions, especially using ether for extraction. There was again no evidence for the formation of dimeric reduction products, nor was there any suggestion of the presence of compounds with additional mass of 28 units. The various reduction experiments thus served to rule out the possibility of a slow equilibrium of 1

and 2 with 14 and 15 respectively, as the cause for the observed line broadening in the NMR spectra of 3,4-dihydroisoquinolines in certain solvents.

6. Experimental

Dihydroisoquinolines and related compounds studied in this work were prepared by known procedures. ^{1}H NMR spectra were run mostly on a Varian A 60 NMR spectrometer with TMS as internal reference. Probe temperature was generally around 40° unless otherwise stated. Chemical shifts are quoted in ppm downfield from TMS.

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