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# 1,2-DIHYDROISOQUINOLINES—VIII[1]

## REARRANGEMENT—II

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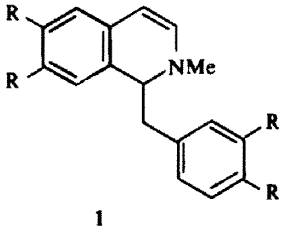
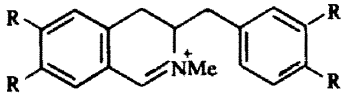
**Abstract**—The acid promoted rearrangement of 1-allyl-2-methyl-1,2-dihydroisoquinoline to the corresponding 3-allyl-2-methyl-3,4-dihydroisoquinoline salt has been observed and the behaviour of 1-benzyl-2-methyl-1,2-dihydroisoquinoline and 2-methyl-1,2-dihydropapaverine towards various conditions of acid concentration and temperature has been studied.

KNABE and Kubitz reported[2] in 1963 that when 2-methyl-1,2-dihydropapaverine (**1**; R = $R^1$ = OMe) was treated with dilute aqueous acid at 100° for a few minutes rearrangement occurred to give the 3-benzyl-3,4-dihydroisoquinolinium salt (**2**, R = $R^1$ = OMe). The mechanism of the rearrangement was shown[3] to involve a migration of the benzyl group from position-1 to position-3 of the isoquinoline system and it was thought initially that the reaction was intramolecular in nature, involving a species such as **3**, formed by the $C_4$-protonation of the 1,2-dihydroisoquinoline.[2,3]

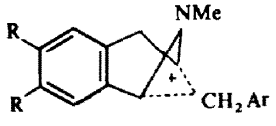


**1**

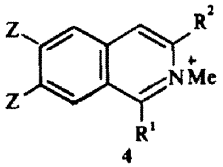


**2**

When, however, a mixture of **1** (R = $R^1$ = OMe) and (R = $R^1$ = OEt) was treated with dilute HCl under the conditions of the rearrangement four 3-benzyl-3,4-dihydroisoquinolinium salts were formed,[4] indicating that cross migration had occurred, and on this evidence Knabe now favours an intermolecular course for the rearrangement. Knabe and Ruppenthal[5] have further shown that rearrangement

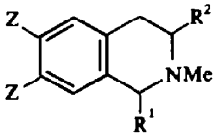


**3**



**4**

followed by disproportionation into **4** (Z = OMe, $R_1$ = H, $R_2$ = *p*-bromobenzyl) and **5** (Z = OMe, $R^1$ = H, $R^2$ = *p*-bromobenzyl) occurs when 1-(4-bromobenzyl) 2-methyl-6,7-dimethoxy-1,2-dihydroisoquinoline is treated with dilute mineral acid, but that disproportionation without rearrangement to give **4** (Z = OMe,

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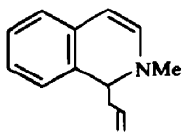


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$R_1$ = Alkyl, $R_2$ = H) and **5** (Z = OMe, $R^1$, = alkyl, $R^2$ = H) is observed when the 1-substituent is methyl, n-butyl and β-phenethyl. A similar result is obtained when the 1-substituent is phenyl.[5,6]

We have now found that when 1-allyl-2-methyl-1,2-dihydroisoquinoline (**6**), prepared by the addition of allyl magnesium bromide to isoquinoline methiodide, is heated with 2N HCl, under the conditions employed for benzyl migration, a quaternary salt, isolated in 60% yield as the pseudocyanide, was formed. A signal at 4·7 ppm in the NMR spectrum of this material (Fig. 1) is assigned to a hydrogen atom

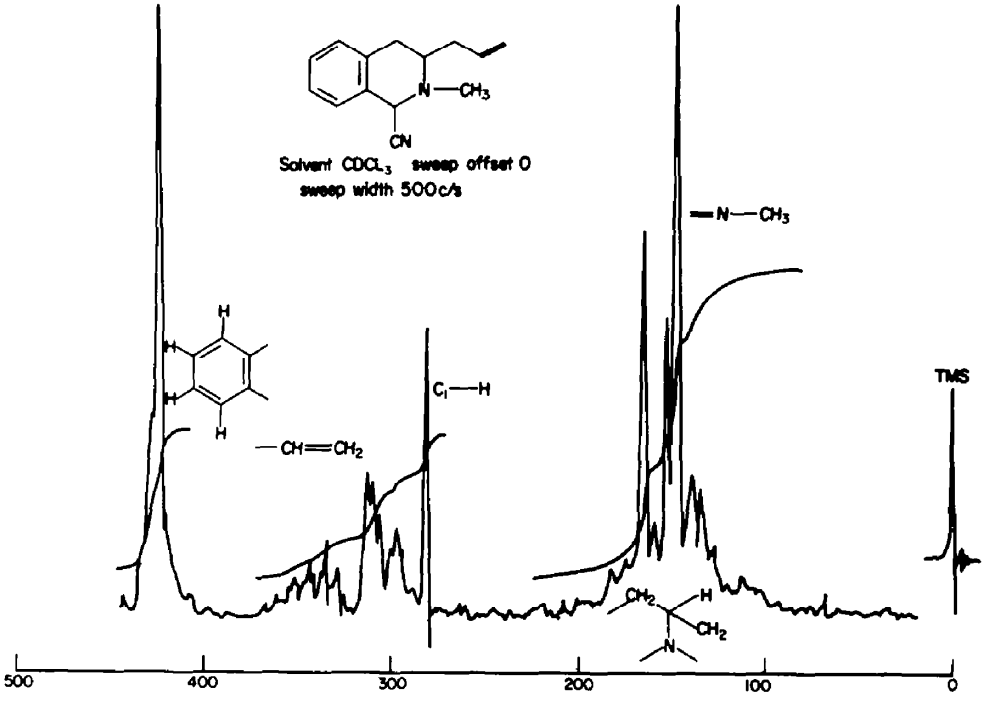



FIG. 1

at $C_1$ of the isoquinoline ring and the three proton complex centred at about 5·3 ppm indicates the presence of the allyl group. Structure **7** for the quaternary salt, which is reformed from the pseudocyanide by treatment with HCl, was established by showing that the product obtained from it by catalytic hydrogenation is identical (superimposable IR and NMR spectra and mixed m.p. of the derived methiodides) with a sample of 2-methyl-3-n-propyl-1,2,3,4-tetrahydroisoquinoline prepared in a standard manner from the amine **8**. The authenticity of the parent 1,2-dihydroisoquinoline (**6**) was confirmed by its characteristic UV and NMR (Fig. 2) spectra

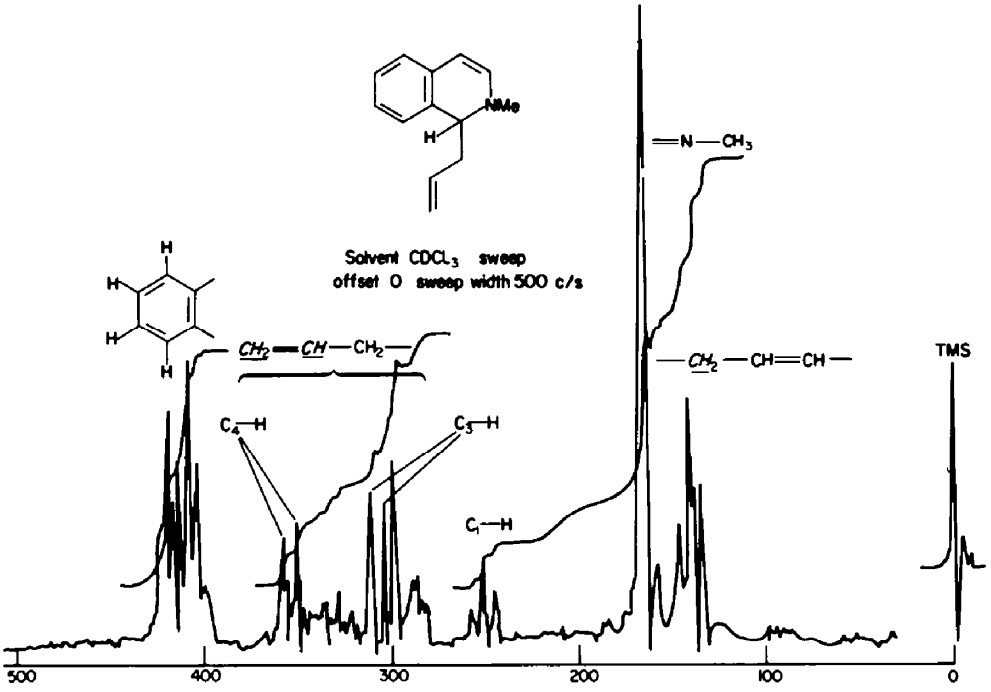
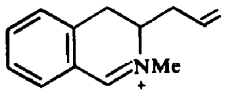



FIG. 2

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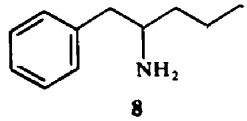


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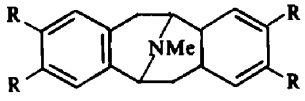
and by the fact that catalytic reduction gave a compound identical (superimposable IR and NMR spectra and mixed m.p. of methiodides) with a synthetic specimen of 1-n-propyl-2-methyl-1,2,3,4-tetrahydroisoquinoline.

Whilst the mild conditions of acid treatment described above brings about the rearrangement of **1** into **2**, more severe conditions have been known for some time to cause cyclization to compounds of the type **9**; for example when **1** (R = $R^1$ = OMe) is heated at 120° with a mixture of orthophosphoric and formic acids for 5 hr, N-methylpavine (**9**, R = OMe) is produced in 72% yield.[7]

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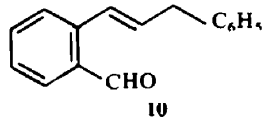


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It was of interest to us to ascertain whether a threshold condition exists between the rearrangement and cyclization reactions of a 1-benzyl-1,2-dihydroisoquinoline and we have examined the behaviour of the parent compound **1** (R = $R^1$ = H) under various conditions of acid treatment. It has already been shown[8] that when **1** (R = $R^1$ = H) is heated at 155° for 48 hr with conc $H_3PO_4$ in a molar ratio of base to acid of 1:48, the pavine-type structure **9** (R = H) is formed in 11% yield.

This structure was proved in a series of degradations. An iodide salt, $C_{17}H_{18}N$ I, m.p. 165–166° was also isolated (9% yield) from the reaction mixture, but a structural assignment was not made.

When **1** (R = $R^1$ = H) was treated with 2N $H_2SO_4$ or 2N $H_3PO_4$ (molar ratio 1:1) at 100° for 2 hr, a new quaternary salt was formed and isolated in 75% yield, iodide m.p. 166–168°. The compound was further characterized by reduction with $NaBH_4$ to the 1,2,3,4-tetrahydroisoquinoline and conversion to the methiodide and the picrate. The UV spectrum of the reaction product was characteristic of a 3,4-dihydroisoquinolinium salt, and the NMR spectrum is consistent with the structure of 2-methyl-3-benzyl-3,4-dihydroisoquinolinium iodide (**2**, R = $R^1$ = H).

Degradation of the quaternary salt with methyl sulphate and alkali yielded a nitrogen-free oil whose NMR spectrum (Fig. 3) confirms the presence of an aldehyde

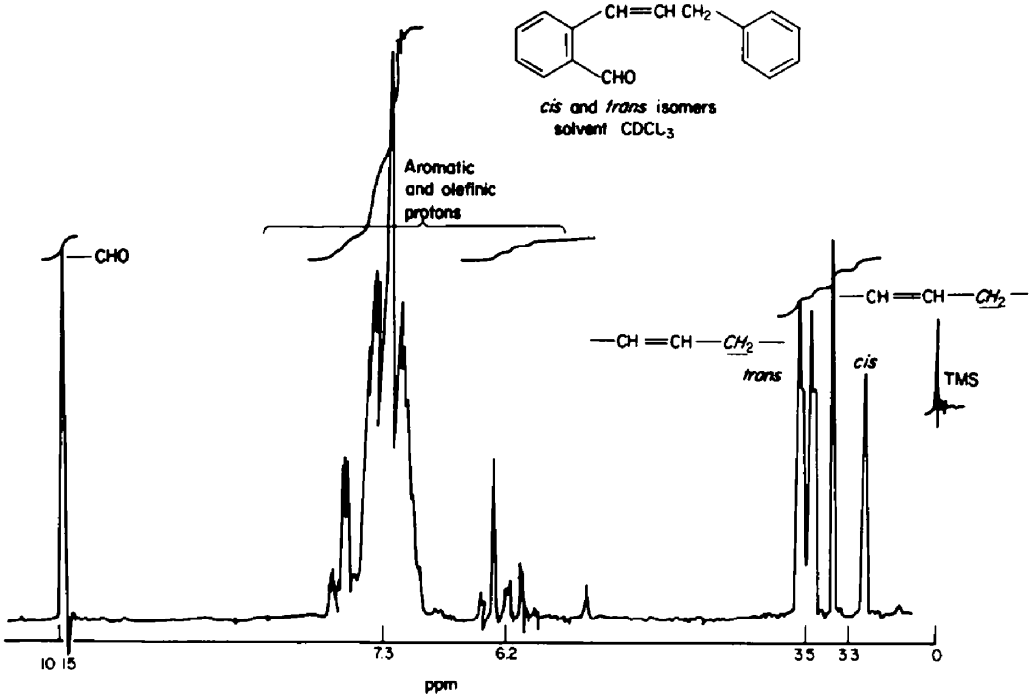


FIG. 3

group (a one proton singlet at 10·15 ppm). The complexity of the signals at 3·3, 3·5 and 6·2 ppm suggests that the compound is probably a mixture of the two geometrically isomeric *o*-formyl styrenes (**10**). Chromatography of the oil on silica gel plates confirms the presence of two closely related compounds. The isolation of an aldehyde in this degradation confirms that rearrangement of **1** (R = $R^1$ = H) has occurred since a 1-substituted-3,4-dihydroisoquinolinium salt would yield a ketone under the degradative conditions employed.[9] The iodide, m.p. 165–166° obtained by Wittig *et al.*[8] was shown, as expected, to be identical with **2** (R = $R^1$ = H).

With a molar ratio of **1** (R = $R^1$ = H) to acid of 1:2, the yield of the cyclized product **9** (R = $R^1$ = H) was raised to 19%, but in this experiment some starting material (4%) was isolated together with a mixture (4%) of two further bases, which

were shown to be 1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (**5**, Z = H, $R^1 = CH_2C_6H_5$, R² = H) and 3-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (**5**, Z = H, $R^1$ = H, $R^2 = -CH_2C_6H_5$), by chromatographic comparison with authentic specimens, and formed presumably by disproportionation. The corresponding fully aromatic compounds **4** (Z = R² = H, $R^1 = -CH_2C_6H_5$ and Z = $R^1$ = H, $R^2 = -CH_2C_6H_5$) were shown to be present in the mixture of quaternary salts also produced by the reaction.

A 57% yield of the rearranged compound **2** (R = $R^1$ = H) was additionally obtained.

Altogether five sets of conditions of acid treatment of **1** (R = $R^1$ = H) were studied (Experimental) and in each case the rearrangement was the major reaction pathway, but whereas under mild conditions of acid treatment the most important secondary reaction seems to be disporportionation of the starting material, at high temperature cyclization to **9** (R = $R^1$ = H) becomes more important.

An attempt was made to carry out a parallel study with 2-methyl-1,2-dihydropapaverine, and to examine the products by reduction and GLC analysis. Unfortunately the retention times of N-methylpavine (**9**, R = OMe) and the tetrahydroisoquinoline (**5**, Z = OMe, $R^1$ = H, $R^2$ = 3,4-dimethoxybenzyl) proved to be so similar, under the conditions which we could employ, that satisfactory resolution of the peaks due to these two components was not achieved. The indications are however that rearrangement persists under vigorous conditions and that N-methylpavine formation diminishes in importance as the concentration of acid and the temperature of the reaction are lowered.

## EXPERIMENTAL

NMR spectra were recorded upon a Varian A-60 spectrometer. Chemical shifts are expressed in ppm downfield from TMS as an internal standard. IR spectra were determined as Nujol mulls upon a Perkin–Elmer 237 instrument and UV spectra were recorded as ethanolic solns upon a Perkin–Elmer 137 spectrometer. All m.ps are uncorrected.

*Acid treatment of* 1-*benzyl*-2-*methyl*-1,2-*dihydroisoquinoline* (*General procedure, see Table* 1). After heating the 1,2-dihydroisoquinoline (5 g) with acid, under $N_2$, the reaction mixture was poured into water (1 l.) and the pH adjusted to 8. Basic components were extracted into ether and separated by thin film chromatography upon $SiO_2$, developing the plates with 1:9 mixture of EtOAc:petrol (60–80). When viewed under UV light three main bands were observed; $R_f$, 0·2–0·3, 1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline and 3-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (which were not resolved), $R_f$, 0·38–0·42, cyclized material (**9**, R = H) and $R_f$ 0·65–0·67, 1-benzyl-2-methyl-1,2-dihydroisoquinoline. The aqueous $NaHCO_3$ soln, after the removal of basic compounds, was treated with KCN and again ether extracted; removal of the solvent gave the pseudocyanide of the rearranged compound **2** (R = $R^1$ = H). Addition of $HClO_4$ to the aqueous phase caused the precipitation of a mixture of the isoquinolinium salts (**4**, Z = $R^2$ = H, $R^1 = CH_2C_6H_5$ and Z = $R^1$ = H, $R^2 = CH_2C_6H_5$).

*Characterization of the rearrangement material* (**2**, R = $R^1$ = H). The pseudocyanide from the above separation was dissolved in 2N HCl (25 ml) and heated for 15 min on a water-bath, KI was then added and the yellow iodide salt collected, and recrystallized from acetone as needles m.p. 168–169°. $\nu^{max}$ $cm^{-1}$, 1663 (>C...N<). $\lambda_{max}$ ($\varepsilon$) mμ, 217 (26,920), 285 (10,720).

NMR ($CDCl_3$) ppm, 9·95 singlet [1] ($C_1H$), ~7·8 complex [4] (aromatic protons), 7·3 singlet [5] (aromatic protons of benzyl group), ~4·55 complex [1] ($C_3$—H), 3·9 singlet [3] (⁺N—$CH_3$), ~3·0 complex [4] ($C_4$ protons plus —$CH_2$—Ph). [Found: C, 56·1; H, 5·3; N, 3·9. $C_{17}H_{18}NI$ requires: C, 56·2; H, 5·0; N, 3·9%]. Reduction of this compound with $NaBH_4$ in aqueous EtOH gave **5** (Z = $R^1$ = H, $R^2$ = $CH_2C_6H_5$) as a pale yellow oil. TLC on alumina using EtOAc and 60–80° pet ether (1:9) showed, under

Table 1

| Acid | Ratio Base:Acid | Temp. °C | Time hr. | % Rearrangement product 2, R = $R^1$ = H) | % Cyclized compound (9, R = H) | % 1- and 3-Benzyl -2-methyl tetra-hydroisoquinolines (5, Z = $R^2$ = H, $R^1$ = —$CH_2$—$C_6H_5$ and 5, 2 = $R^1$ = H, $R^2$ = —$CH_2C_6H_5$) | % 1- and 3-Benzyl -2-methylisoquinolinium salts. (4, Z = $R^2$ = H, $R^1$ = —$CH_2C_6H_5$ and 4, Z = $R^1$ = H, $R^2$ = —$CH_2C_6H_5$ | % Unchanged starting material (1, R = $R^1$ = H) |
|---|---|---|---|---|---|---|---|---|
| 90% $H_3PO_4$ | 1:43 | 155 | 48 | 11* | 9 | — | — | — |
| 90% $H_3PO_4$ | 1:22 | 155 | 48 | 57 | 19 | 4 | 5 | 4 |
| 90% $H_3PO_4$ | 1:2 | 155 | 48 | 59 | 1 | 8 | 8 | 21 |
| 90% $H_3PO_4$ | 1:1 | 100 | 2 | 75 | 0 | — | — | 12 |
| 2N HCl | 1:2 | 100 | 2 | 75 | | | | |

* During this experiment much charring occurred, rendering the work-up procedure difficult.

UV, one spot $R_f$ 0·45. 1-Benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline under the same conditions has $R_f$ 0·55. The methiodide was prepared as colourless needles m.p. 197–198° from aqueous MeOH, mixed m.p. with 1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline methiodide (m.p. 249–253°; lit.,[8] 241–243°) depressed. [Found: C, 57·1; H, 5·7; N, 3·8. $C_{18}H_{22}NI$ requires: C, 57·0; H, 5·9; N, 3·7%].

*Degradation of compound* **2** (R = $R^1$ = H) *with alkaline* $Me_2SO_4$. The pseudocyanide was heated with 2N HCl (20 ml) on a water-bath for 15 min and then made strongly alkaline with 15% NaOH aq (10 ml). $Me_2SO_4$ (6 ml) was then added, together with more NaOH aq (10 ml) and the mixture was heated under reflux for 3 hr. This gave an emulsion, which was extracted with ether (2 × 25 ml); removal of the ether afforded a brown oil, which showed bands at 2870, 2760 and 1695 $cm^{-1}$ in the IR spectrum due to an aldehyde group and a band at 1650 $cm^{-1}$ consistent with an olefinic double bond. TLC on $SiO_2$ showed the presence of two compounds and the NMR spectrum (in $CDCl_3$) indicated an equimolar mixture of *cis* and *trans* isomers of o-formylbenzylstyrene (**10**) the aldehydic proton signals falling together at 10·15 ppm.

*Characterization of cyclized material* (**9**, R = H). The band $R_f$ 0·38–0·42 on the preparative plate was removed and extracted several times with $CHCl_3$; evaporation of the solvent yielded 2-methyl-1-methylene-3-o-benzylene-1,2,3,4-tetrahydroisoquinoline as a pale brown oil, from which the methiodide was prepared. This compound was recrystallized as colourless needles from MeOH had m.p. 306° (lit.,[8] 305–306°). [Found: C, 57·2; H, 5·2; N, 3·7. Calc. for $C_{18}H_{20}NI$: C, 57·3; H, 5·3; N, 3·7%].

1-*Allyl*-2-*methyl*-1,2-*dihydroisoquinoline* (**6**). Allylmagnesium bromide (1 mole) in ether was added in the course of 2 hr to a suspension of isoquinoline methiodide (1 mole) in ether (400 ml), protected by an atmosphere of $N_2$. After stirring overnight, at room temp, water (200 ml) was added and when the initial violent reaction had subsided, the ether layer was separated and rapidly extracted with ice-cold 2N HCl. The combined acid extracts were basified with $NH_4OH$ and re-extracted with ether; after combination and drying the ether extracts were evaporated to give 1-allyl-2-methyl-1,2-dihydroisoquinoline as a pale yellow oil (14% yield); $\nu_{max}$ $cm^{-1}$, 1625, 1620. $\lambda_{max}$ mμ, 240 (Sh), 339. NMR ($CDCl_3$) ppm, ~6·7 complex [4] (aromatic protons on isoquinoline ring), 6·05 doublet [1] $J$ = 9 c/s ($C_4$—H), 6·1–4·7 complex [2] ($CH_2$=CH—$CH_2$—) 5·1 doublet [1] $J$ = 9 c/s ($C_3$—H), 4·15 triplet [1] $J$ = 6 c/s ($C_1$—H), 2·9 singlet [3] (>N—$CH_3$). 2·3 complex [2] (—$CH_2$—CH=$CH_2$).

1-*Propyl*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (**5**, Z = $R^2$ = H, $R^1$ = *propyl*). Catalytic hydrogenation of **6** gave **5** (Z = $R^2$ = H, $R^1$ = propyl) as a colourless oil, characterized as the methiodide, colourless needles m.p. 130–132° from acetone. [Found: C, 50·3; H, 7·0; N, 4·3. $C_{14}H_{22}NI$ requires: C, 50·8; H, 7·0; N, 4·2%].

The free base from the above reaction was shown to be identical with a sample of 1-propyl-2-methyl-1,2,3,4-tetrahydroisoquinoline prepared from 1-propyl-2-methyl-3,4-dihydroisoquinolinium iodide m.p. 134–136° (identical NMR, UV and IR spectra). (lit.,[10] 132–134°) by sodium borohydride reduction. The methiodide of the tetrahydro-base prepared in this way caused no depression in m.p. when mixed with the methiodide (m.p. 130–132°) described above.

*Acid treatment of* 1-*allyl*-2-*methyl*-1,2-*dihydroisoquinoline*. The 1,2-dihydroisoquinoline (3 g) in 2N $H_2SO_4$ (10 ml) was heated on a water-bath for 6 hr and allowed to stand at room temp overnight. After the addition of water (100 ml) the soln was washed with ether, basified with $NaHCO_3$ and extracted with ether. Evaporation of the combined ether extracts gave unchanged starting material (1·4 g) and addition of KCN to the aqueous soln followed by ether extraction afforded a pale yellow oil (1·3 g) NMR ($CDCl_3$) ppm 6·85 complex [4] (aromatic protons), 6·2–4·8 complex [3] ($CH_2$=CH—$CH_2$—), 4·7 singlet [1] ($C_1$—H), 3·1–1·7 complex [5] (Ar.$CH_2$—CH(N=)—$CH_2$—) 2·4 singlet [3] (=N—$CH_3$) 3-allyl-2-methyl-3,4-dihydroisoquinolinium chloride. This compound, an unstable red oil, was hydrogenated at 3 atm press over Adam's catalyst, yielding, after basification, the corresponding tetrahydroisoquinoline as a pale yellow oil (1·0 g), characterized as the methiodide m.p. 173–175° colourless prisms from acetone. [Found: C, 50·4; H, 6·4; N, 4·4; I, 38·9. $C_{14}H_{22}NI$ requires: C, 50·8; H, 7·0; N, 4·2; I, 38·3%].

3-*Propyl*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (**5**, Z = $R^1$ = H, $R^2$ = *propyl*. 1-Phenyl-2-pentanone (12·8 g)[12] was heated with ammonium formate (50 g), 98% formic acid (15 ml) and formamide (15 ml) for 3½ hr at 185°. After cooling, the reaction mixture was poured onto water (400 ml) and extracted with ether (2 × 100 ml). The combined ether extracts were washed with $NH_4OH$ and then dried and evaporated to yield the intermediate amide, which was not purified but heated directly with 90% $H_3PO_4$ (50 ml)

and $P_2O_5$ (90 g) at 200–210° for 3 hr. After standing at room temp overnight the mixture was poured onto crushed ice and extracted with benzene, the aqueous phase was then separated, basified with $Na_2CO_3$ aq and again extracted with benzene. This time the combined extracts were evaporated to give 3-propyl-3,4-dihydroisoquinoline (6·7 g) as a colourless oil, b.p. 4 mm 124–126° (lit.,[11] b.p. 4 mm 120–121°). The methiodide of this compound was prepared and reduced with $NaBH_4$ in aqueous MeOH to yield 3-propyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (4·9 g) as a yellow oil, characterized as the methiodide, m.p. 173–176°, colourless needles from acetone. [Found: C, 50·5; H, 6·9; N, 4·1. $C_{14}H_{22}NI$. Requires: C, 50·8; H, 7·0; N, 4·2%].

A direct comparison of the free base from the above reaction and the tetrahydroisoquinoline from the acid treatment of 1-allyl-2-methyl-1,2-dihydroisoquinoline showed them to be identical (NMR and IR spectra), a conclusion supported by mixed m.ps of the corresponding methiodides.

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