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MASS SPECTRA OF DECAHYDROQUINOLINES

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Abstract—The mass spectra of *cis*- and *trans*-decahydroquinoline, their N-methyl and their N-benzoyl derivatives have been examined. Several deuterated derivatives of the N-methyl compounds and one C-methyl derivative have been prepared and a study of their spectra has aided in the interpretation of the mechanism of fragmentation. The major fragment ions are formed by loss of two, three and four carbon fragments from the homocyclic ring.

THE MASS spectra of quinolines and tetrahydroquinolines have been the subject of several recent studies.[1,2,3] To our knowledge, the mass spectra of simple decahydroquinolines have not been extensively investigated. A recent report of the spectra of 2,4-disubstituted derivatives has, however, appeared.[4] The main emphasis in the latter work was directed towards the determination of the relative configuration of substituents at C-2 and C-4. The authors noted, however, that in the spectra of all the compounds which they studied there was an [M − 43] ion. They postulated that this ion was formed by extrusion of C_3H_7 from the molecular ion and that the three carbon atoms were derived from C_6–C_8 inclusive. Our work in which we have used deuterium labelling has confirmed this finding for the case of decahydroquinoline and several of its derivatives. The labelling studies have also shed light on the origin of peaks at [M − 29], [M − 56] and [M − 57] in the spectra of all the compounds studied.

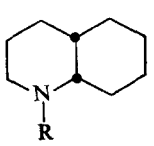
Cis- and *trans*-decahydroquinolines (Ia and IIa) are readily available and are easily converted to their N-methyl derivatives (Ib and IIb) and their N-benzoyl derivatives (Ic and IIc) but deuterated derivatives of these compounds have not been reported. The 2,2-d_2, 3,3-d_2, 4,4-d_2, 6,6-d_2, N-methyl-d_3 and 7-methyl derivatives of N-methyldecahydroquinoline were prepared in this investigation. These syntheses will be described before considering the mass spectra of the compounds.

The 2,2-d_2 analogue (IIIb) was prepared by the reduction of the lactam, octahydrocarbostyril (IV), to IIIa with lithium aluminum deuteride. In the preparation of the lactam only the *trans*-isomer is formed.[5] The N-methyl derivative (IIIb) was prepared by treatment of IIIa with formaldehyde and formic acid.[6]

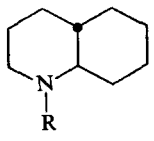
When compound IV was treated with sodium methoxide in CH_3OD the hydrogens at C-3 were exchanged for deuterium. Reduction of octahydrocarbostyril-3,3-d_2 with lithium aluminum hydride followed by N-methylation gave compound V.

N-methyl-decahydroquinoline-4,4-d_2 (VI), was prepared in two steps from compound VII.[7] When VII was reduced with $LiAlD_4$ it yielded an octahydroquinoline which was converted to its perchlorate and reduced with $NaBH_4$ to yield the desired compound VI.

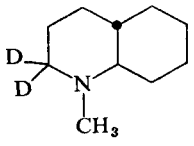
The 6,6-d_2 derivative (VIII) was obtained in a series of steps from 5-aza-1-tetralone (IX). The hydrogens alpha to the keto group in IX were exchanged for deuterium in basic medium and the keto group reduced to methylene by prolonged treatment



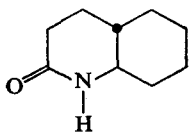
(Ia) R = H
(Ib) R = CH_3
(Ic) R = —COC_6H_5



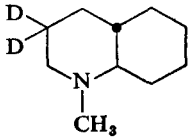
(IIa) R = H
(IIb) R = CH_3
(IIc) R = COC_6H_5



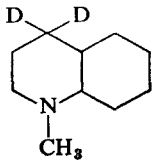
(IIIa) R = H
(IIIb) R = CH_3



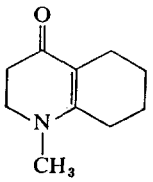
(IV)



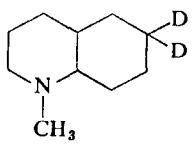
(V)



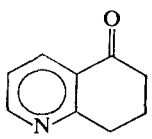
(VI)



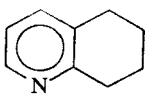
(VII)



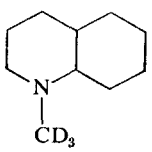
(VIII)



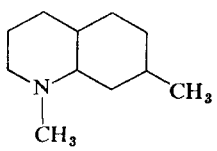
(IX)



(X)



(XI)



(XII)

with $LiAlH_4$ in tetrahydrofuran.[2] The resulting 5,6,7,8-tetrahydroquinoline-6,6-d_2 was converted to its methiodide and reduced with sodium borohydride yielding an octahydroquinoline. The location of the double bond in this compound was not established, but in analogy with the reduction of pyridine methiodide[8] it is likely that it is in the 3,4 position. The octahydro compound was converted to the fully saturated system by reduction with hydrogen over Adam's catalyst. Some exchange occurred in the reduction step but by using a small ratio of catalyst to compound a product was obtained which was predominantly a dideuterated derivative.

The N-methyl-d_3 compound was prepared from IX. Upon Wolff-Kishner reduction[9] compound IX was converted to X which in turn was converted to its methiodide by treatment with CD_3I. Conversion of the resulting methiodide to compound XI was accomplished by the method used in the preparation of VIII.

N-methyl-7-methyldecahydroquinoline (XII) was obtained in several steps from orcinol. The intermediate 7-methyl-5,6,7,8-tetrahydroquinoline was prepared by using a procedure similar to that reported for the preparation of 5,6,7,8-tetrahydroquinoline.[9] The tetrahydro compound was converted to the N-methyl decahydro compound as in the preparation of VIII.

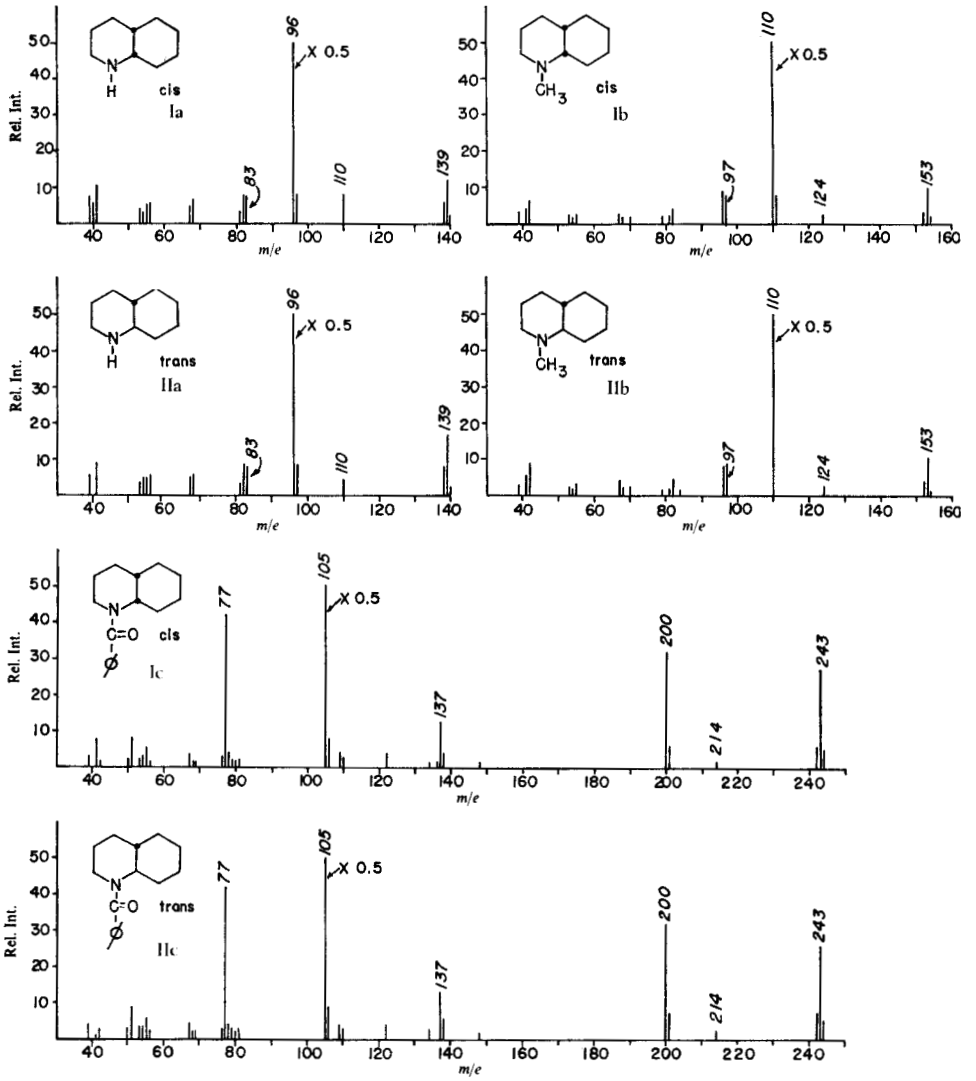
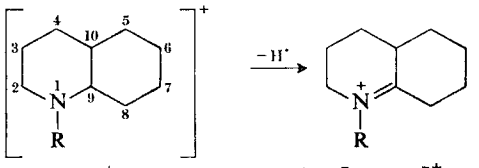


FIG. 1. Mass spectra of *cis*- and *trans*-decahydroquinoline and their N-methyl and N-benzoyl derivatives.

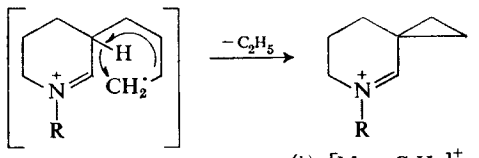
The configuration of VI, VIII, XI and XII has not been established. There seems little doubt however that IIIa IIIb and V have the *trans*-configuration for IIIa like IIa but unlike Ia is a solid at room temperature. Pure *trans*- and *cis*-isomers Ia and Ib, IIa and IIb, and the benzoyl derivatives Ic and IIc of Ia and IIa have been prepared. The mass spectra of the *cis*- and *trans*- isomers shown in Fig. 1 are virtually identical and, therefore, it seemed of little consequence from the mass spectrometric point of view to concern ourselves with the stereochemistry of VI, VIII, XI and XII.

The spectra of Ia and IIa, Ib and IIb are easily rationalized in terms of the fragmentation depicted in Scheme 1. In Ia and IIa the major fragment ion appears at *m/e* 96 [M − 43]. Ions of lower intensity are found at *m/e* 138 [M − 1], *m/e* 110



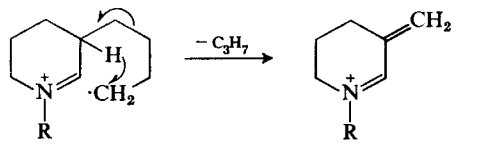
$[M]^+$ (a) $[M - H]^+$

ion *a* *m/e* 138 in Ia and IIa
ion *a* *m/e* 152 in Ib and IIb
ion *a* *m/e* 154 in IIIb, V, VI and VIII
ion *a* *m/e* 155 in XI



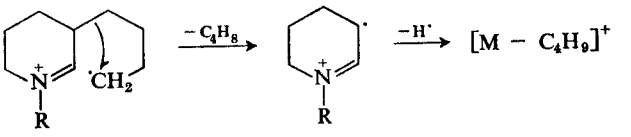
(b) $[M - C_2H_5]^+$

ion *b* *m/e* 110 in Ia and IIa
ion *b* *m/e* 124 in Ib and IIb
ion *b* *m/e* 126 in IIIb, V, VI and VIII
ion *b* *m/e* 127 in XI



(c) $[M - C_3H_7]^+$

ion *c* *m/e* 96 in Ia and IIa
ion *c* *m/e* 110 in Ib, IIb and VIII
ion *c* *m/e* 112 in IIIb, V and VI
ion *c* *m/e* 113 in XI



(d) $[M - C_4H_8]^{+\cdot}$ (e)

ion *d* *m/e* 83 in Ia and IIa
ion *d* *m/e* 97 in Ib, IIb and VIII
ion *d* *m/e* 99 in IIIb, V and VI
ion *d* *m/e* 100 in XI
ion *e* *m/e* 82 in Ia and IIa
ion *e* *m/e* 96 in Ib, IIb and VIII
ion *e* *m/e* 98 in IIIb, V and VI
ion *e* *m/e* 99 in XI

SCHEME 1

[M — 29], *m/e* 83 [M — 56] and *m/e* 82 [M — 57]. A metastable peak is observed for the transformation $[M]^{+\cdot} \rightarrow [M - 43]$ in all the compounds examined. A similar pattern is observed for Ib and IIb with all peaks shifted upward by 14 mass units. These ions are considered to arise by loss of fragments exclusively from the homocyclic ring, a fact confirmed by the deuterium labelling (*vide infra*). The N-benzoyl compounds Ic and IIc also show peaks at [M — 1], [M — 29] and [M — 43] as found in the four bases. Ions at [M — 56] and [M — 57] are also present but their intensity is <1 % of the base peak at *m/e* 105 and do not appear in the Figures. The spectra, as expected, show strong ions at *m/e* 105 and 77 for $[C_6H_5CO]^+$ and $[C_6H_5]^+$. There are

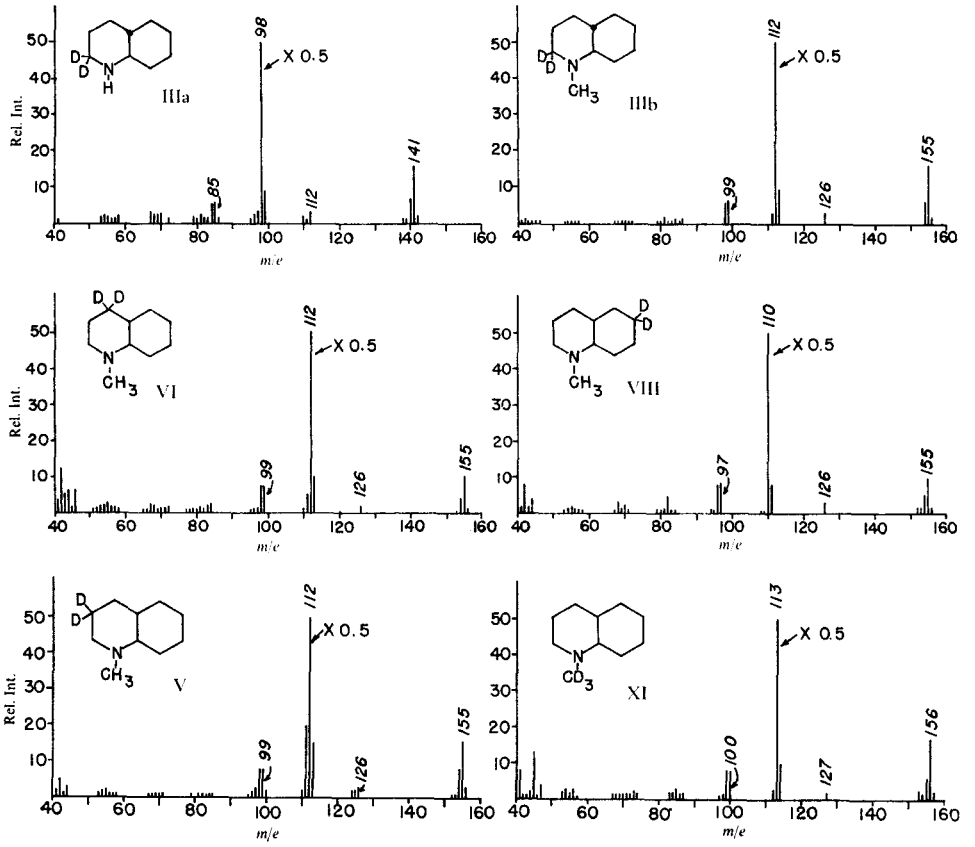


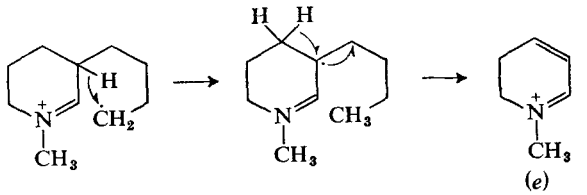
FIG. 2. Mass spectra of deuterated decahydroquinolines.

also peaks formed by loss of benzoyl and benzoyl + H from $[M]^{+\cdot}$ at *m/e* 138 and 137, respectively.

The spectra of the deuterated compounds are shown in Fig. 2. These spectra lend support to the fragmentation mechanism proposed in Scheme 1. The spectra of IIIb, V and VI show that all fragment ions discussed previously appear 2 mass units higher confirming that the heterocyclic ring remains intact. In compounds IIIb, V and VI ion *e* also appears two mass units higher than in the undeuterated analogue IIb inferring that the hydrogen lost in the [M − 56] → [M − 57] process does not come from C-2, C-3 or C-4. It seemed, therefore, very likely that it came from the N-methyl group. Upon preparation* of the N-methyl-d_3 compound we were much surprised to find that the [M − 56] and [M − 57] ions in the spectrum were shifted upward by three mass units with no apparent loss of deuterium from the N-methyl group.

The genesis of ion *e* must, therefore, remain unresolved. If it arises from *d* by loss of H there must be a large isotope effect favouring loss of H over D and the loss of H must be random in view of the labelling results. An alternative route to '*e*' is from the molecular ion as indicated below. In this scheme ion *e* is derived from the same intermediate that yields ions *b* and *c* but an additional hydrogen migration is involved. This

* The preparation of this compound and of the 3,3-d_2 compound were undertaken at the suggestion of the referee.



mechanism explains the retention of deuterium in ion *e* in the compounds deuterated at N-methyl, C-2, C-3 and C-4. Similarly, examination of the spectrum of IIIa shows that the hydrogen is not lost specifically from C-2.

In compound VIII both deuteriums are lost in the elimination of the three and four carbon fragments but retained in the loss of the two-carbon fragment. The hydrogen atom transferred in the formation of ions *b* and *c* is assumed to come from C-10.* Although there is no direct evidence that this is the case it is clear from the spectra of IIIb, V and VI that it does not arise from C-2, C-3 or C-4.

The deuterium labelling results are substantiated in the spectrum of N-methyl-7-methyldecahydroquinoline (XII) shown in Fig. 3. In the spectrum of this compound the [M − 29] ion observed in Ib and IIb is shifted to [M − 43] and the base peak of [M − 43] in Ib and IIb is shifted to [M − 57]. There is also an ion of low intensity at [M − 15]. The results obtained with XII suggest that it should be possible to assign a single C-methyl substituent to the homocyclic or the heterocyclic ring in the decahydroquinolines by mass spectrometry. Similarly, it should be possible to differentiate C-methylated decahydroquinolines substituted at C-5 and C-6 from those substituted at C-7 and C-8 and to assign definitely a substituent to C-5 or C-6.

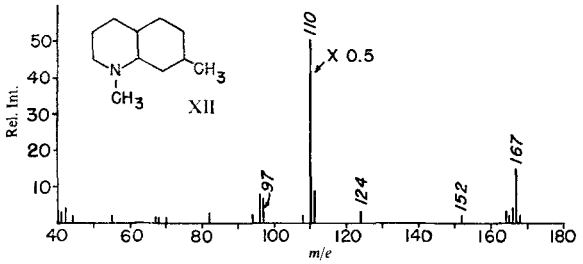


FIG. 3. Mass spectrum of *N*,7-dimethyldecahydroquinoline.

EXPERIMENTAL

Apparatus, Methods and Materials

The bases were purified and identified by gas-liquid-chromatography (g.l.c.) using a 12′ × 0·25″ O.D. stainless steel column packed with chromosorb-W which was coated with 5% potassium hydroxide and 20% carbowax 20 M.[10] The column temperature was maintained at 150°.

The mass spectra were recorded on an Hitachi–Perkin–Elmer RMU-6A mass spectrometer with the inlet system maintained at 200°C and at an ionization potential of 80 eV and an ionizing current of 50 μA. All spectra are plotted relative to the most abundant peak in the spectrum (base peak) which is given the value of 100%. All peaks with an intensity of 2% or more of the base peak are recorded.

* An alternative mechanism for the formation of *b* suggested by a referee involves abstraction of H from C-5 instead of C-10. This mechanism cannot be ruled out on the basis of the labelling evidence at hand.

A mixture of *cis*- and *trans*-decahydroquinoline and pure *trans*-decahydroquinoline were obtained commercially.

Cis- and trans-N-methyldecahydroquinoline. Pure *cis*-decahyroquinoline was obtained from the *cis-trans* mixture by the method of Armarego.[11] *Cis* and *trans*-decahydroquinolines were converted to the corresponding N-methyldecahydroquinolines by treating them with formaldehyde and formic acid[6] and purified by preparative g.l.c.

Cis- and trans-N-benzoyl decahydroquinoline. These compounds were prepared by standard procedures[12] and recrystallized several times from ligroin (b.p. 80 to 90°). The *cis* compound melted at 94 to 96° (Lit. 95°C)[11] and the *trans* compound at 54 to 55° (Lit. 56°C).[13]

Decahydroquinoline-2,2-d_2 *and N-methyl-decahydroquinoline*-2,2-d_2. A solution of octahydrocarbostyril (50 mg), prepared by the method of Kost *et al.*[5] in dry dioxane (10 ml), was added slowly to a solution of lithium aluminum deuteride (40 mg) in dry dioxane (10 ml). The solution was heated gently under reflux for 12 hrs. Excess lithium aluminum deuteride was destroyed by addition of water (1 ml) and the mixture poured into 2·5 M sulphuric acid (50 ml). The resulting solution was extracted several times with ether. The aqueous solution was made alkaline (sodium hydroxide solution) and extracted with ether. The ether extract was washed with water, dried, (calcium chloride) and the ether removed leaving a yellow oil which was purified by g.l.c. The white crystalline solid so obtained melted at 45 to 46°, (Lit. 48°).

The composition of the product determined by low voltage mass spectrometry was: $d_0 = 2\%$, $d_1 = 3\%$, $d_2 = 94\%$, $d_3 = 1\%$. This compound was N-methylated as previously described and purified by g.l.c. The composition of the product determined by low voltage mass spectrometry was: $d_1 = 3\%$, $d_2 = 96\%$, $d_3 = 1\%$.

N-methyl-decahydroquinoline-3,3-d_2. Octahydrocarbostyril (116 mg) was dissolved in CH_3OD (2 ml), treated with sodium methoxide (40 mg) and refluxed for 4 hrs. The solvent was evaporated and another 1 ml of CH_3OD was added and the mixture heated under reflux for another 3 hrs. The solvent was then evaporated and the residue triturated with $CHCl_3$. The chloroform solution was dried over sodium sulfate and evaporated to dryness to yield a white residue. Without further purification the residue was dissolved in dioxane (20 ml) and added to a suspension of $LiAlH_4$ (100 mg) in dioxane (10 ml) and the mixture heated under reflux for 12 hrs. This mixture was worked up as in the previous procedure and N-methylated and purified as described above. The composition of the product determined by low voltage mass spectrometry was: $d_0 = 2\%$, $d_1 = 16\%$, $d_2 = 82\%$.

N-methyldecahydroquinoline-4,4-d_2. 1-Methyl-4-keto-1,2,3,4,5,6,7,8-octahydroquinoline was prepared by the method of Horii *et al.*[7] The yellow oil obtained in this reaction formed a crystalline picrate, m.p. 154°; (Lit. 156°).[7]

The quinolone VII (245 mg) was dissolved in dry ether (10 ml) and a solution of lithium aluminum deuteride (49 mg) in dry ether (15 ml) was added slowly to the organic solution at such a rate that the solution gently boiled. The solution was heated under reflux for 30 mins. Excess lithium aluminum deuteride was destroyed by addition of ethyl acetate (2 ml) and the mixture poured into 2·5 M sulphuric acid (20 ml). The product was isolated in the same manner as the reduction product of octahydrocarbostyril. Yield: 175 mg. A perchlorate was prepared by addition of perchloric acid to an ether solution of the base. After recrystallization from ethanol it melted at 185 to 188°.

The perchlorate (200 mg) was dissolved in methanol (5 ml) and sodium borohydride (100 mg) was added gradually. After the vigorous exothermic reaction had subsided the solution was heated under reflux for 10 mins. The methanol was removed, water (5 ml) added, and the aqueous solution extracted with ether. The extract was dried (calcium chloride) and the ether removed yielding VI as a yellow oil. The oil was purified by g.l.c. The composition of the product determined by low voltage mass spectrometry was: $d_0 = 2\%$, $d_1 = 4\%$, $d_2 = 93\%$, $d_3 = 1\%$.

N-methyldecahydroquinoline-6,6-d_2. 5,6,7,8-tetrahydroquinoline-6,6-d_2 prepared by the method of Draper and MacLean[2] was converted to its methiodide by treatment of an acetone solution of the base with methyl iodide. The yellow crystalline methiodide was dissolved in methanol and treated with an excess of sodium borohydride. The solution was stirred for 30 mins after addition of the reducing agent, the methanol removed, water added and the solution extracted with ether. The ether solution was washed, dried and evaporated giving a colourless oil in 74% yield. Without further purification the oil was dissolved in dry ethanol (25 ml) and the solution hydrogenated over Adam's catalyst at 60 p.s.i. for 2 hrs. The solution was filtered and the solvent evaporated. The residue was purified

by g.l.c. before recording its mass spectrum. The composition of the product determined by low voltage mass spectrometry was: $d_0 = 9\%$, $d_1 = 12\%$, $d_2 = 78\%$, $d_3 = 1\%$.

N-methyl-d_3-tetrahydroquinoline. Compound X was prepared from IX by the procedure described by Zymalkowski and Rimek.[9] Compound X (240 mg) was dissolved in acetone (10 ml) and treated with CD_3I (40 mg) and the mixture allowed to stand for 12 hrs. The crystalline methiodide so obtained was converted to XI by the procedure described in the preceding section. The product was purified by g.l.c. Its composition determined by low voltage mass spectrometry was: $d_1 = 4\%$, $d_2 = 5\%$, $d_3 = 91\%$.

N-methyl-7-methyldecahydroquinoline. 5-methyl-1,3-cyclohexanedione, prepared by the same method as 1,3-cyclohexadione[14] by using orcinol as starting material instead of resorcinol (Yield. 85%, m.p. 79 to 82°), was converted to 5-methyl-3-amino-2-cyclohexen-1-one in the following way. 5-methyl-1,3-cyclohexadione (12·2 g) was dissolved in 100 ml benzene and heated to boiling. A stream of NH_3 was bubbled through the solution, and the water formed was constantly removed by a Dean-Stark apparatus. After 1·5 hrs the reaction mixture was cooled and the yellow precipitate was filtered off. After recrystallization from acetone (2 ~ 3% H_2O) the compound melted at 165 to 167°. Yield: 60%. The amino compound was then converted to 3-methyl-5-aza-1-tetralone.

Freshly prepared propargyl aldehyde[15] (2·6 g), dissolved in 5 ml benzene, was added slowly to a suspension of 4·2 g of 3-methyl-1-amino-1-cyclohexene-3-one in 10 ml benzene and the mixture was stirred for 8 hrs. The red brown precipitate was filtered and dried. The crude product was heated to 140° for 2 hrs. Upon cooling the crude product was purified on an alumina column. The column was eluted first with 400 ml ligroin (b.p. 30 to 60°) and then a mixture of 600 ml ligroin and benzene (1:1). The product was obtained from the latter fraction as white crystals. Yield: 1·9 g (38%). After recrystallization from ether and petroleum ether (b.p. 30 to 60°) the compound melted at 51 to 52° (Lit. 56·5°).[16] Through a Wolff-Kishner reduction this ketone was converted to 7-methyl-5,6,7,8-tetrahydroquinoline. Thus, 0·56 g KOH and 0·40 g of 3-methyl-5-aza-1-tetralone were mixed with 20 ml triethylene glycol, 2 ml NH_2NH_2 was added and the mixture heated to 80 to 90° in an oil bath for 1 hr, then at 150° for 1 hr and finally at 180° for 1·5 hrs. Water, 20 ml, was added to the cooled reaction mixture and it was extracted with ether. The ether extract was washed with water and dried (K_2CO_3). After evaporation of the solvent, an almost quantitative yield of product was obtained (0·36 g). The compound was converted to its perchlorate by treating an ether solution of the base with perchloric acid. Recrystallization from methanol gave the perchlorate of 7-methyl-5,6,7,8-tetrahydroquinoline, m.p. 132 to 133°. (Found : C, 48·7; H, 5·6; N, 5·9. $C_{10}H_{14}NO_4Cl$ requires C, 48·5; H, 5·7; N, 5·7%).

The tetrahydro compound prepared above was converted to the N-methyldecahydro compound by the procedure described earlier in this section. The decahydro base was converted to its picrate by treating a solution of the base in ether with a solution of picric acid in ether. Recrystallization from ether–methanol gave the picrate of N-methyl-7-methyldecahydroquinoline melting at 184 to 186°. (Found: C, 51·2; H, 6·1. $C_{17}H_{24}N_4O_7$ requires C, 51·5; H, 6·1%.

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