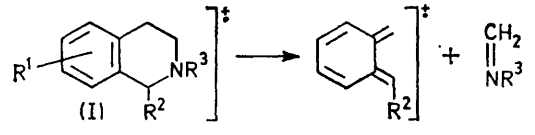
# Mass Spectra of Tetrahydroisoquinolines: A Novel Concerted Fragmentation

By G. A. Charnock and A. H. Jackson,*† Robert Robinson Laboratories, University of Liverpool

An unusual fragmentation of 92 mass units from the parent ion of an 8-benzyloxytetrahydroisoquinoline is due to loss of the elements of toluene by concerted cleavage of the benzyl group and a hydrogen atom from the 1-position; this is confirmed both by the appearance of a metastable ion for the overall process, by deuterium labelling of the 1-position, and by the absence of a corresponding peak in the spectrum of a 7-benzyloxytetrahydroisoquinoline. Deuterium labelling also confirms that the $M-1$ peak commonly observed in the mass spectra of tetrahydroisoquinolines is due to cleavage of a hydrogen atom from the 1-position; high-resolution measurements have confirmed the nature of the other major primary fragmentation processes.

THE main features of the mass spectra of tetrahydroisoquinolines (I) were first described several years ago.[1] The molecular ion is usually of low intensity, and the major fragmentation is often due to the loss of a substituent from the 1-position, or to loss of a hydrogen atom. If, however, a benzylic ether substituent is present in the benzene ring then cleavage of the benzyl group may well be the predominant fragmentation process. Loss of the nitrogen atom and the 3-carbon atom together with substituents at these positions also appears to be a common feature of tetrahydroisoquinoline mass spectra, and this has been attributed to a reverse Diels–Alder type reaction as shown below. (A similar process is also observed in the mass spectra of tetrahydro-β-carbolines [2]).




In our earlier work in the isoquinoline field we observed the effects of steric hindrance on the mass spectra of a series of aporphines [3] and we now report another type of steric effect, encountered in the mass spectrum (Figure 1) of an 8-benzyloxytetrahydroisoquinoline (IIa), which had been prepared as an intermediate in a projected synthesis of the isoquinoline alkaloid cularine.[4] The base peak at $m/e$ 191 corresponded to the loss of 92 mass units from the molecular ion at $m/e$ 283, rather than 91 as expected from cleavage of the benzyl group. It seemed likely that this was due to loss of toluene in a concerted process involving the 8-benzyloxy-group and one of the hydrogen atoms at the neighbouring 1-position. This hypothesis was supported by the appearance of a metastable ion at $m/e$ 129 corresponding to the 283 ⟶ 191 transition, and although an $M-1$ peak was observed at $m/e$ 282, there was no metastable peak corresponding to subsequent loss of 91 mass units.

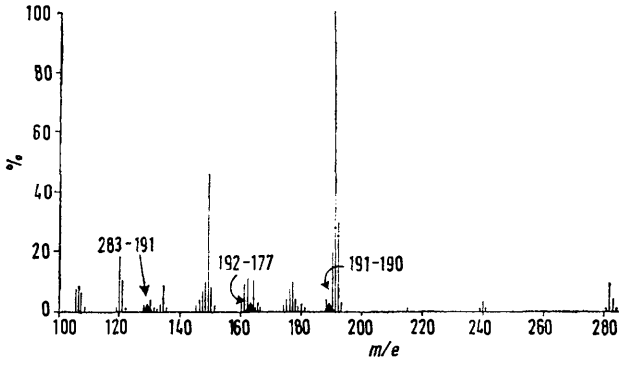



FIGURE 1 Mass spectrum of compound (IIa)

It is now, of course, recognised [5] that the appearance

† *Present address:* Department of Chemistry, University College, Cardiff.

[1] C. Djerassi, J. M. Wilson, and H. Budzikiewicz, *J. Amer. Chem. Soc.*, 1962, **84**, 3210.

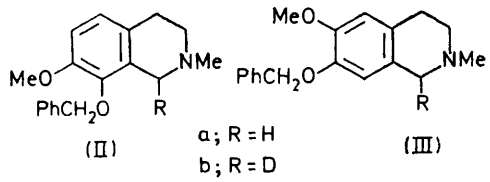
[2] L. D. Antonaccio, N. A. Pereira, B. Gilbert, H. Vorbrueggen, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *J. Amer. Chem. Soc.*, 1962, **84**, 2161; B. Gilbert, J. A. Brissolese, N. Finch, W. I. Taylor, H. Budzikiewicz, J. M. Wilson, and C. Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, 1523.

[3] A. H. Jackson and J. A. Martin, *J. Chem. Soc.*, 1966, 2181.

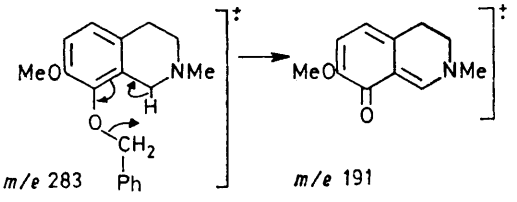
[4] G. A. Charnock, Ph.D. Thesis (Liverpool, 1968); *cf.* also A. H. Jackson and G. W. Stewart, *Chem. Comm.*, 1971, 149.

[5] A. H. Jackson, G. W. Kenner, K. M. Smith, R. T. Aplin, H. Budzikiewicz, and C. Djerassi, *Tetrahedron*, 1965, **21**, 2913; J. Seibl, *Helv. Chim. Acta*, 1967, **50**, 263; A. H. Jackson, G. W. Kenner, and D. R. A. Ridyard, unpublished work (D. R. A. Ridyard, M.Sc. Thesis, Liverpool, 1966).

of a metastable ion is not necessarily an indication that the overall fragmentation process takes place in a single




step but may result from two or more cleavages taking place in very rapid succession. However, in the present instance we felt justified in concluding that the loss of 92 mass units was concerted owing to the proximity of the groups concerned and because ejection of toluene could occur *via* a 6-membered cyclic transition state as shown below.




Circumstantial evidence in favour of this proximity effect was provided by the mass spectrum (Figure 2) of the isomeric 7-benzyloxyisoquinoline (IIIa) which showed the normal benzylic fragmentation from the parent ion to give a base peak at *m/e* 192, with a corresponding metastable ion peak at *m/e* 130·2. Furthermore, the proportion of the total ion current carried by the molecular ion of (IIa) is much smaller than the proportion carried by the molecular ion of (IIIa), and the $M - 92$ ion of (IIa) clearly carries a much greater proportion of the total ion current, than the $M - 91$ ion of (IIIa). Thus the $M - 92$ ion of (IIa) appears to be relatively more stable, and loss of toluene as shown above would facilitate its formation. The mass spectrum of the 8-methoxytetrahydroisoquinoline (V) prepared by sodium borohydride reduction of cotarnine chloride (IV) was also determined but its fragmentation pattern was quite normal (Table 1).

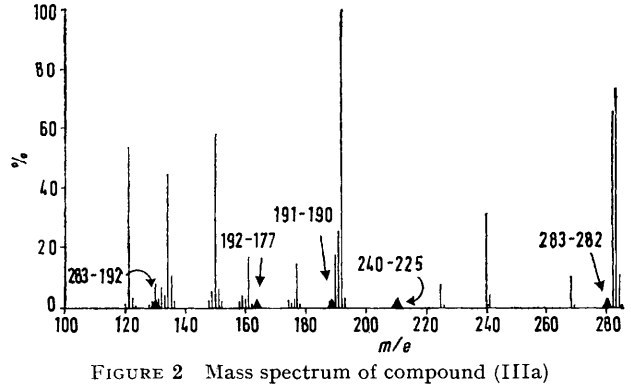
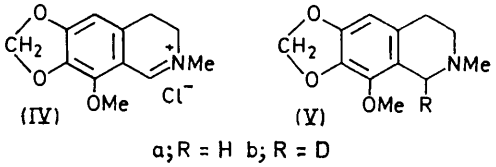



FIGURE 2 Mass spectrum of compound (IIIa)

The origin of the hydrogen atom lost in association with the benzyl group in the mass spectrum of (IIa) was confirmed by deuterium labelling experiments. The 1-deuteriated analogues (IIb) and (IIIb) of the tetrahydroisoquinolines (IIa) and (IIIa) were prepared by sodium borodeuteride reduction of the corresponding 3,4-dihydroisoquinoline salts. The structures of the




monodeuteriated products were confirmed by n.m.r. spectrometry, and their mass spectra are tabulated in Table 1. The spectrum of the 1-deuterio-8-benzyloxy-

TABLE 1

Mass spectra of tetrahydroisoquinolines

(IIb) 284 (6), 283 (10), 282 (5), 241(6), 226 (2), 193 (41), *192* (*100*), 191 (66), 190 (13), 178 (12), 177 (10), 165 (15), 163 (10), 162 (14), 151 (7), 150 (60), 149 (6), 134 (15), 122 (12), 121 (15), 92 (7), 91 (42). $m^*$: 189 (191→ 190), $m^*$: 129·8 (284→ 192)

(IIIb) 285 (22), *284* (*100*), 283 (58), 282 (24), 269 (3), 242 (8), 241 (45), 226 (5), 224 (6), 209 (4), 194 (8), 193 (52), 192 (14), 191 (12), 178 (3), 165 (3), 163 (4), 162 (4), 150 (6), 134 (3), 123 (3), 122 (13), 121 (3), 92 (5), 91 (60). $m^*$: 212 (241→ 226)

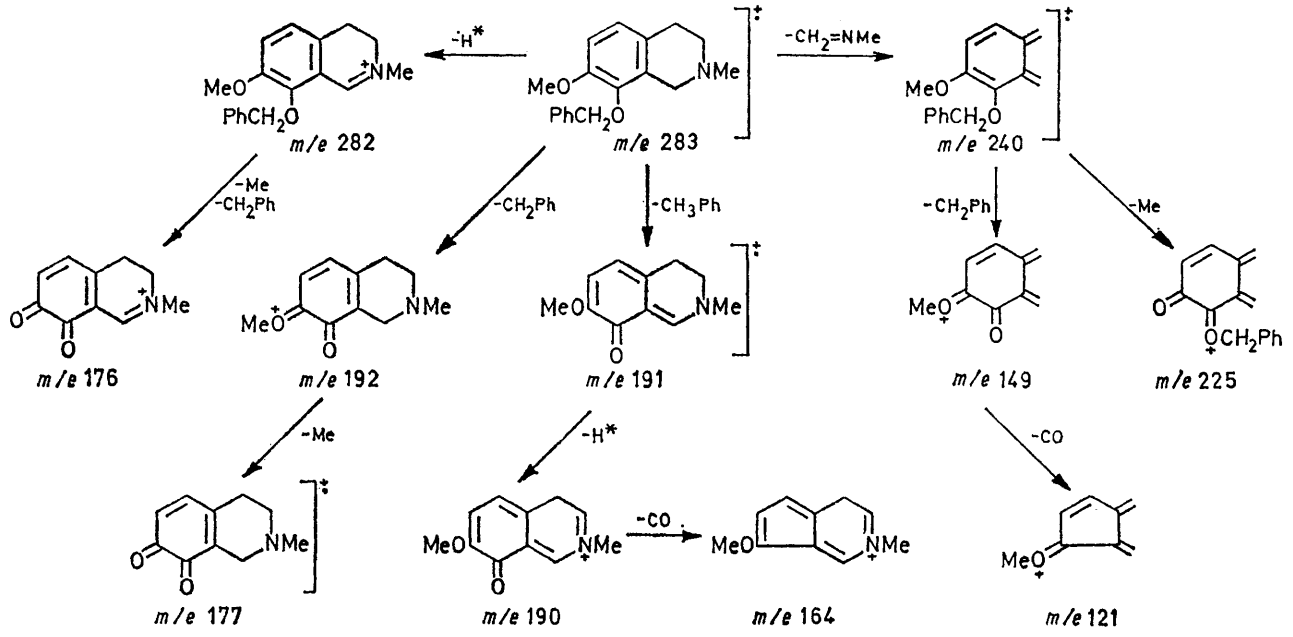
(Va) 222 (6), 221 (67), *220* (*100*), 205 (17), 192 (3), 190 (3), 179 (10), 178 (61), 177 (10), 164 (3), 163 (16), 149 (4), 148 (11), 147 (4), 133 (8), 120 (3). $m^*$: 219 (221→ 220), $m^*$: 191 (200→ 205), $m^*$: 176 (205→ 190)

(Vb) 223 (9), 222 (53), 221 (62), 220 (28), 207 (5), 206 (21), 205 (18), 191 (6), 180 (18), *179* (*100*), 178 (29), 177 (8), 165 (4), 164 (32), 163 (7), 151 (5), 150 (7), 148 (8), 149 (26), 134 (21), 121 (6), 120 (6). $m^*$: 192 (221→ 206), $m^*$: 191 (220→ 205), $m^*$: 177 (206→ 191), $m^*$: 109·5 (164→ 134)

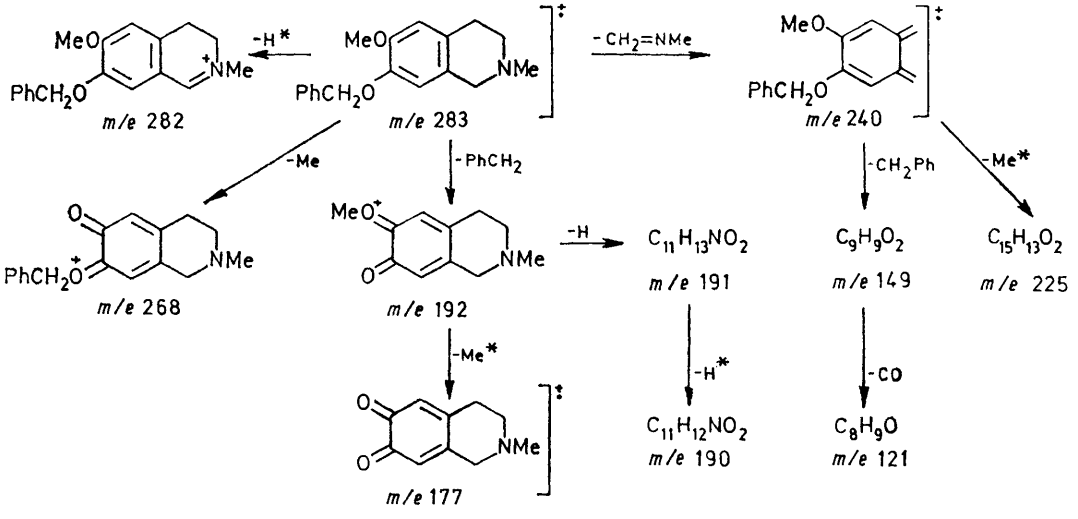
derivative (IIb) showed intense peaks at *m/e* 192 and 191 due to the loss of 92 and 93 mass units from the parent ion, whereas the 7-benzyloxy-isomer manifested a major ion at *m/e* 193 ($M - 91$), and less intense ions at *m/e* 192 ($M - 92$) and 191 ($M - 93$). The fact that the ion at *m/e* 192 [from (IIb)] is more intense than that at *m/e* 191 shows that a small isotope effect is operating, and that there is a slight preferential cleavage of hydrogen (rather than deuterium) from the 1-position, comcomitantly with the benzyl group.

The mass spectra of the 1-deuteriated compounds also confirmed that the $M - 1$ peak commonly observed in the mass spectra of tetrahydroisoquinolines is due to the loss of a hydrogen atom from the 1-position; an isotope effect is again observed, and the latter two compounds show preferential loss of hydrogen rather than deuterium from the molecular ion. (Other workers have previously demonstrated by deuterium labelling that the $M - 1$ peak in the spectra of the structurally similar tetrahydro-β-carbolines is due to the loss of hydrogen from the 1-position [2]).

Accurate mass measurements of the major ions in the mass spectra of the two benzyloxytetrahydroisoquinolines (IIa) and (IIIa) are given in Tables 2 and 3, and possible fragmentations are outlined below. The high




SCHEME 1 Mass spectral fragmentation of compound (IIa)




SCHEME 2 Mass spectral fragmentation of compound (IIIa)

TABLE 2

High-resolution mass spectral data for (IIa)

| | Accurate mass | | |
|---|---|---|---|
| *m/e* | Found | Calculated | Formula |
| 283 | 283·1555 | 283·1572 | $C_{18}H_{21}NO_2$ |
| 282 | 282·1494 | 282·1494 | $C_{18}H_{20}NO_2$ |
| 240 | 240·1155 | 240·1150 | $C_{16}H_{16}O_2$ |
| 192 | 192·1010 | 192·1024 | $C_{11}H_{14}NO_2$ |
| 191 | 191·0943 | 191·0946 | $C_{11}H_{13}NO_2$ |
| 190 | 190·0868 | 190·0868 | $C_{11}H_{12}NO_2$ |
| 177 | 177·0790 | 177·0790 | $C_{10}H_{11}NO_2$ |
| 164 | 164·1075 | 164·1075 | $C_{10}H_{14}NO$ |
| 162 | 162·0922 | 162·0919 | $C_{10}H_{12}NO$ |
| 161 | 161·0841 | 161·0841 | $C_{10}H_{11}NO$ |
| 149 | 149·0612 | 149·0602 | $C_9H_9O_2$ |
| 135 | 135·0446 | 135·0446 | $C_8H_7O_2$ |
| 134 | 134·0584 | 134·0606 | $C_8H_8NO$ |
| 121 | 121·0653 | 121·0653 | $C_8H_9O$ |
| 120 | 120·0811 | 120·0813 | $C_8H_{10}N$ |

resolution data confirms the identity of the atoms and groups lost in the primary fragmentation processes summarised briefly at the beginning of this paper.

The two tetrahydrobenzyloxyisoquinolines were prepared by the Bobbitt modification [6] of the Pomerantz–Fritzsch isoquinoline synthesis as shown schematically in the accompanying chart. The *N*-methyl group was introduced in each case by *N*-formylation followed by lithium aluminium hydride reduction. After the preparative work on the isomer (IIa) had been completed other workers reported [7] a synthesis along similar lines, but differing in points of detail. We found iodine to

[6] J. M. Bobbitt, J. M. Kiely, K. L. Kharma, and R. Ebermann, *J. Org. Chem.*, 1965, **30**, 2247.

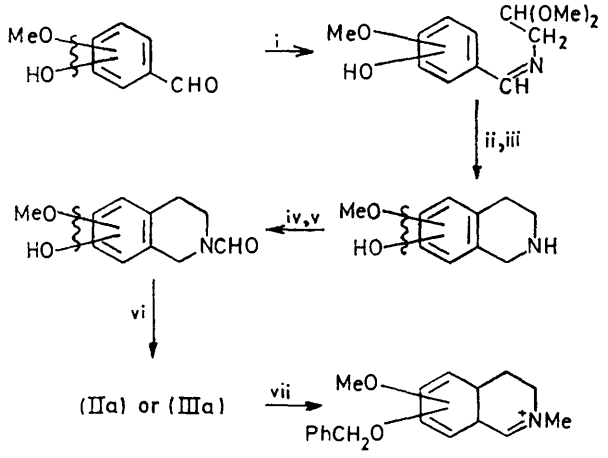
[7] G. Grethe, M. Uskokovic, and A. Brossi, *J. Org. Chem.*, 1968, **33**, 2500.

TABLE 3

High-resolution mass spectra data for (IIIa)

| | Accurate mass | | |
|---|---|---|---|
| *m/e* | Found | Calculated | Formula |
| 283 | 283·1565 | 283·1571 | $C_{18}H_{21}NO_2$ |
| 282 | 282·1487 | 282·1493 | $C_{18}H_{20}NO_2$ |
| 268 | 268·1342 | 268·1337 | $C_{17}H_{18}NO_2$ |
| 240 | 240·1146 | 240·1149 | $C_{16}H_{16}O_2$ |
| 225 | 225·0937 | 225·0915 | $C_{15}H_{13}O_2$ |
| 192 | 192·1033 | 192·1024 | $C_{11}H_{14}NO_2$ |
| 191 | 191·0954 | 191·0945 | $C_{11}H_{13}NO_2$ |
| 190 | 190·0882 | 190·0868 | $C_{11}H_{12}NO_2$ |
| 177 | 177·0765 | 177·0790 | $C_{10}H_{11}NO_2$ |
| 162 | 162·0913 | 162·0918 | $C_{10}H_{12}NO$ |
| 150 | 150·0682 | 150·0680 | $C_9H_{10}O_2$ |
| 149 | 149·0821 | 149·0840 | $C_9H_{11}NO$ |
| | 149·0592 | 149·0601 | $C_9H_9O_2$ |
| 148 | 148·0748 | 148·0762 | $C_9H_{10}NO$ |
| | 148·0539 | 148·0523 | $C_9H_8O_2$ |
| 135 | 135·0451 | 135·0446 | $C_8H_7O_2$ |
| 134 | 134·0977 | 134·0969 | $C_9H_{12}N$ |
| 121 | 121·0662 | 121·0653 | $C_8H_9O$ |
| 120 | 120·0820 | 120·0813 | $C_8H_{10}N$ |

be a better dehydrogenating agent than mercuric acetate (*cf.* ref. 7) for conversion of the tetrahydroisoquinolines to the 3,4-dihydroisoquinolines; reduction




Reagents: i, $NH_2CH_2CH(OMe)_2$; ii, $H^+$; iii, $H_2$–Pt; iv, $HCONH_2$; v, $PhCH_2Cl$–$Na_2CO_3$; vi, $LiAlH_4$; vii, $Hg(OAc)_2$ or $I_2$.

of the latter with sodium borodeuteride gave the required 1-deuterio-2,3,4-trihydroisoquinolines.

## EXPERIMENTAL

M.p.s were determined on a Kofler micro-hot stage. The reactions were investigated by t.l.c. using silica gel containing an u.v. absorber at 354 nm; 1% potassium permanganate in 10% potassium carbonate solution, or iodine, were used for making the spots visible. N.m.r. spectra were determined with Varian A60 and HA100 instruments, and mass spectra were determined at 70 eV and 50 μA with an A.E.I. MS9 spectrometer, using a direct inlet at 200°.

1,2,3,4-*Tetrahydro*-8-*hydroxy*-7-*methoxyisoquinoline*.— 2-Hydroxy-3-methoxybenzaldehyde (24·3 g) and aminoacetaldehyde dimethyl acetal (16·8 g) were heated under reflux in ethanol (640 ml) for 1 h. The bright orange solution was then immediately hydrogenated over platinum oxide (0·5 g) until uptake of hydrogen was complete (4—6 h). The catalyst was filtered off and the filtrate was evaporated to dryness under reduced pressure. The oily residue crystallised slowly and was recrystallised from benzene–light petroleum (b.p. 60—80°) to give the *benzylamino-acetal* (33·8 g, 90%) as cubes, m.p. 75—76° (Found: C, 59·8; H, 8·1; N, 5·8. $C_{12}H_{19}NO_4$ requires C, 59·7; H, 7·9; N, 5·8%), τ ($CDCl_3$) 3·2—3·5 (m, Ar*H*), 3·9br (O*H* and N*H*), 5·54 (t) and 6·66 [C*H*(OC$H_3$)$_2$], 6·03 (ArC$H_2$N), 6·17 (ArOC$H_3$), and 7·25 (d, NC$H_2$).

The foregoing acetal (30 g) was dissolved in hydrochloric acid (900 ml, 6N) and the solution was washed once with ether (450 ml) to remove traces of 2-hydroxy-3-methoxybenzaldehyde. After 15 h the resulting bright yellow solution was hydrogenated over palladium–charcoal (15 g; 5%) until uptake was complete (9—12 h). At this stage part of the product had begun to crystallise out and it was filtered off together with the catalyst. It was leached from the catalyst with the quantity of hot water; it slowly crystallised from the cooling solution. The mother liquors from this recrystallisation were combined with the original filtrate and the solution was evaporated under reduced pressure. The solid product was recrystallised twice from aqueous ethanol and combined with other material to give the tetrahydroisoquinoline hydrochloride (21·9 g, 75%) as needles, m.p. 281—282·5° (lit.,[6] m.p. 282—283°) (Found C, 55·5; H, 6·6; N, 6·35. Calc. for $C_{10}H_{14}ClNO_2$; C, 55·7; H, 6·5; N, 6·5%), τ ($D_2O$) 3·02 (d) and 3·22 (d) (6,7-*H*), 5·72 (1-C$H_2$), 6·14 (OC$H_3$), 6·53 (t) and 6·96 (t) (3,4-C$H_2$·C$H_2$).

An alternative method of obtaining the product was to take the hydrogenation solution before the catalyst had been filtered off and to heat this until the hydrochloride of the tetrahydroisoquinoline dissolved; the solution was then filtered whilst hot. Evaporation of the filtrates followed by recrystallisation as above then gave the tetrahydroisoquinoline in similar yield.

1,2,3,4-*Tetrahydro*-7-*hydroxy*-6-*methoxyisoquinoline* was prepared by an analogous method to the isomer above and in comparable overall yield starting from 3-hydroxy-4-methoxybenzaldehyde. The intermediate *dimethyl acetal* crystallised from benzene–light petroleum (b.p. 60–80°) as needles, m.p. 73—75° (Found: C, 59·6; H, 7·8; N, 5·7. $C_{12}H_{19}O_4$ requires C, 59·7; H, 7·8; N, 5·8%). The tetrahydroisoquinoline hydrochloride crystallised from ethanol and had m.p. 254—256°. (lit.,[6] m.p. 256—258°) (Found: C, 59·6; H, 6·7; N, 6·3. Calc. for $C_{10}H_{14}ClNO_2$: C, 55·7; H, 6·5; N, 6·5%), τ ($D_2O$) 2·94 and 3·01 (5,8-*H*), 5·75 (1-C$H_2$), 6·06 (OC$H_3$), 6·92 (NC$H_3$), and 6·4 (m) and 6·7 (m) (3,4-C$H_2$·C$H_2$).

2-*Formyl*-1,2,3,4-*tetrahydro*-8-*hydroxy*-7-*methoxyisoquinoline*.— 1,2,3,4-Tetrahydro-8-hydroxy-7-methoxyisoquinoline hydrochloride (20 g) was heated in formamide (40 ml) at 140° for 1 h. The resulting light brown solution was cooled and poured into water (100 ml). With time buff coloured crystals separated out and were collected, washed with water, and dried. The solid was recrystallised from ethanol and gave the 2-formylisoquinoline (18·5 g, 97%) as rods m.p. 177—178° (lit.,[7] m.p. 177—179°) (Found: C, 63·7; H, 6·3; N, 6·6. Calc. for $C_{11}H_{13}NO_3$: C, 63·75; H, 6·3; N, 6·8%). The n.m.r. spectrum ($CDCl_3$) showed the presence of two conformers in approximately equal amounts presumably due to restricted rotation of the N–CO bond: τ 1·81 and 1·88 (C*H*O), 3·3—3·5 (m, Ar*H*),

5·42 and 5·56 (ArC$H_2$N), 6·21 (OC$H_3$), 6·2—6·6 (m) and 7·15—7·4 (m) (3,4-C$H_2$C$H_2$), and 4·15 br (O$H$).

2-*Formyl*-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxyisoquinoline* was prepared in a similar fashion and crystallised from ethanol as needles, m.p. 145—147° (Found: C, 64·0; H, 6·3; N, 6·6. $C_{11}H_{13}NO_3$ requires C, 63·75; H, 6·3; N, 6·8%). The n.m.r. spectrum ($CDCl_3$) showed the presence of two conformers: τ 1·80 and 1·84 (NC$H$O), 3·34 and 3·40 (5,8-$H$), 3·82 (O$H$), 5·44 and 5·58 (ArC$H_2$N), 6·15 (OC$H_3$), and 6·2—6·5 (m) and 7·22 (t) (3,4-C$H_2$C$H_2$).

8-*Benzyloxy*-2-*formyl*-1,2,3,4-*tetrahydro*-7-*methoxyisoquinoline*.—The foregoing amide (15·0 g) and benzyl chloride (10·5 g) in dimethylformamide (100 ml) were heated in presence of potassium carbonate (7·5 g) under nitrogen at 100° for 4 h. The brown solution was cooled, poured into water (250 ml); the emulsion formed was extracted with benzene (3 × 50 ml). The combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The *product* (18·5 g, 81%) could not be crystallised but was shown by t.l.c. to be largely one compound. It was further purified on neutral alumina (grade III) to give a light brown oil (one spot on t.l.c.) (Found: C, 72·4; H, 6·6; N, 4·55. $C_{18}H_{19}NO_3$ requires C, 72·7; H, 6·4; N, 4·7%). The n.m.r. spectrum ($CDCl_3$) showed the presence of two conformers: τ 1·87 and 2·04 (C$H$O), 3·20 (5,6-H), 2·66 and 4·93 ($C_6H_5CH_2O$), 5·40 and 5·76 (ArC$H_2$N), 6·14 and 6·16 (OC$H_3$), and 6·2—6·6 (m), and 7·1—7·4 (m) (3,4-C$H_2$C$H_2$).

7-*Benzyloxy*-2-*formyl*-1,2,3,4-*tetrahydro*-6-*methoxyisoquinoline* was obtained as an oil (like the 8-benzyloxy-isomer) and the crude product was used directly for the next stage.

8-*Benzyloxy*-1,2,3,4-*tetrahydro*-7-*methoxy*-2-*methylisoquinoline*.— 8-Benzyloxy-2-formyl-1,2,3,4-tetrahydro-7-methoxyisoquinoline (15 g) in dry tetrahydrofuran (150 ml) was added slowly to a suspension of lithium aluminium hydride (2·8 g) in tetrahydrofuran (50 ml). After completion of the addition the reaction mixture was boiled under reflux for 2 h and then excess of lithium aluminium hydride was decomposed by a cautious addition of a saturated solution of Rochelle salt to the cool mixture. The organic layer was decanted and the thick pasty residue was washed several times with fresh solvent; the organic fractions were combined and evaporated to dryness. The oily residue was taken up in chloroform, extracted with hydrochloric acid (3 × 30 ml; 10%) and the aqueous extracts were basified with sodium hydroxide. Extraction with chloroform (3 × 30 ml) followed by washing with water and drying ($MgSO_4$) yielded a pale yellow solution which was evaporated to dryness under reduced pressure. The pale yellow oily amine (13·9 g, 97%) was characterised as its *hydrochloride* which crystallised from ethanol–ether as needles, m.p. 184—186° (Found: C, 67·5; H, 6·6; N, 4·1. $C_{18}H_{22}NO_2Cl$ requires C, 67·6; H, 6·9; N, 4·4%), τ ($D_2O$) 2·75 (s, 5,6-Ar$H$), 2·40 and 4·82 ($C_6H_5CH_2O$), 6·02 ($CH_3O$), 5·80 (1-C$H_2$), 6·97 (NC$H_3$), and 6·50 (t) and 6·72 (t) (3,4-C$H_2$·C$H_2$), τ ($CDCl_3$) 2·68 and 4·95 ($C_6H_5CH_2O$), 3·13 (5,6-$H$), 6·04 (ArC$H_2$N), 6·14 (OC$H_3$), 6·7—7·0 (m, 3,4-C$H_2$·C$H_2$), 7·32 (NC$H_3$), τ (free base in $CDCl_3$) 2·5—2·8 (m) and 5·01 ($C_6H_5CH_2O$), 3·21 (5,6-$H$), 6·17 (OC$H_3$), 6·48 (ArC$H_2$N), 7·18 (t) and 7·39 (t) (3,4-C$H_2$·C$H_2$) and 7·60 (NC$H_3$).

7-*Benzyloxy*-1,2,3,4-*tetrahydro*-6-*methoxy*-2-*methylisoquinoline hydrochloride* was prepared in the same fashion as its isomer and crystallised from ethanol as needles, m.p. 213·5—215° (Found: C, 67·4; H, 6·9; N, 4·3. $C_{18}H_{22}NO_2Cl$ requires C, 67·6; H, 6·9; N, 4·4%), τ ($D_2O$) 2·95 (5-$H$), 3·03 (8-$H$), 2·45 and 4·80 ($C_6H_5CH_2O$), 6·06 ($CH_3O$), 5·52 (1-C$H_2$), 6·85 (NC$H_3$), 6·33 (m) and 6·72 (m) (3,4-C$H_2$·C$H_2$).

8-*Benzyloxy*-3,4-*dihydro*-7-*methoxy*-2-*methylisoquinoline Salts*.—(i) *Oxidation of the tetrahydroisoquinoline with mercuric acetate*. The tetrahydroisoquinoline hydrochloride (670 mg) and mercuric acetate (3·4 g) were dissolved in acetic acid (15 ml; 10%) and the resulting colourless solution was heated at 100°. After *ca.* 30 min crystalline mercuric acetate began to separate from the solution which became pale yellow. The progress of oxidation was monitored by u.v. spectroscopy until no further increase was observed in the absorption at $\lambda_{max.}$ 379 nm (about 4—8 h). The precipitated mercuric acetate was filtered off and washed with dilute acetic acid and then with acetone. The filtrate and washings were saturated with hydrogen sulphide and the precipitate was removed by filtration through Highflow supercel. The bright yellow solution was basified by gradual addition of aqueous potassium carbonate and extracted with chloroform. The organic extracts were evaporated to dryness under reduced pressure and the residue was dissolved in ethanol containing a little ether. The solution was slowly acidified by addition of aqueous perchloric acid (72%) in ethanol (1/1 : v/v). The bright yellow solution which formed, slowly deposited the dihydroisoquinoline perchlorate (313 mg, 41%) as yellow needles, m.p. 181—182·5° (lit.,[5] m.p. 181—183°) (Found: C, 56·6; H, 5·4; N, 3·6. Calc. for $C_{18}H_{20}NO_6Cl$: C, 56·6; H, 5·2; N, 3·7%).

(ii) *Oxidation with iodine*. The tetrahydroisoquinoline hydrochloride (2 g) was dissolved in ethanol (50 ml) and potassium acetate (1·31 g) were added to the solution. The resulting suspension was heated under reflux and a solution of iodine (1·76 g) in ethanol (15 ml) was added with stirring. The iodine solution was added at about the same rate as reaction occurred, and the solution became bright yellow in colour. The addition was complete in 30 min and the reaction mixture was boiled for a further 30 min to complete the reaction. Monitoring was carried out as before by following the increase in absorption at 379 nm. The hot reaction mixture was filtered through Highflow supercel and the filtrate was treated with sulphur dioxide to discharge the slight excess of iodine. On cooling the 3,4-dihydroisoquinoline hydriodide (1·76 g, 70%) crystallised out as bright yellow needles, m.p. 135—136°. Recrystallisation was difficult owing to liberation of iodine by decomposition and a satisfactory elemental analysis could not be obtained. However, conversion into the perchlorate salt gave a product identical with that prepared by the mercuric acetate method above. N.m.r. spectrum of the hydriodide ($CDCl_3$): τ 1·25 (1-$H$), 2·65 and 4·70 ($C_6H_5CH_2O$), 2·72 (d, 5,6-$H$), 6·11 (OC$H_3$), 6·20 (NC$H_3$), and 6·02 (t) and 6·84 (t) (3,4-C$H_2$·C$H_2$). Mass spectrum, *m/e* (%): 282($M^+$,2) 230(7), 229(5), 218(24), 192(25), *191*(100), 190(43), 167(17), 149(3). *m**: 189(191 ⟶ 190), 129·4(282 ⟶ 191).

7-*Benzyloxy*-3,4-*dihydro*-6-*methoxy*-2-*methylisoquinoline hydriodide* was prepared in a similar manner by iodine oxidation of the corresponding 1,2,3,4-tetrahydroisoquinoline. The hydriodide had m.p. 189—191° but like its isomer did not have a satisfactory analysis. The *perchlorate*, however, crystallised from ethanol–water as yellow needles, m.p. 172—175° (Found: C, 56·45; H, 5·2; N, 3·4. $C_{18}N_{20}$-

$ClNO_6$ requires C, 56·6; N, 5·2; N, 3·7%). N.m.r. spectrum of the hydriodide ($CDCl_3$): τ 1·22 (1-*H*), *ca.* 2·6 (m) and 4·80 ($C_6H_5CH_2O$), 2·27 and 3·06 (5,8-*H*), 5·97 ($OCH_3$) 6·07 ($NCH_3$), and 5·95 (m) and 6·6 (m) (3,4-$CH_2CH_2$).

8-*Benzyloxy*-1-*deuterio*-1,2,3,4-*tetrahydro*-7-*methoxy*-2-*methylisoquinoline*.—A solution of the corresponding dihydroisoquinoline salt (19 mg) in methanol (15 ml) was cooled and treated with a solution of sodium borodeuteride (100 mg) in water (5 ml) containing 2M-sodium hydroxide (5 ml); the bright yellow colour of the solution was discharged almost immediately. Stirring was continued for 10 min amd the solution was then made strongly alkaline and extracted with ether. The dried ($MgSO_4$) ethereal extracts were treated with hydrogen chloride, and the 1-deuteriotetrahydroisoquinoline hydrochloride (70 mg, 80%) formed was recrystallised from ethanol to give plates, m.p. 195—196°. The n.m.r. spectrum showed that one deuterium atom had been introduced at the 1-position as the resonance at τ 5·80 was diminished by 50%, and this was confirmed by the mass spectrum.

7-*Benzyloxy*-1-*deuterio*-1,2,3,4-*tetrahydro*-6-*methoxy*-2-*methylisoquinoline* was prepared in a similar manner and formed colourless plates, m.p. 220—222° from ethanol. The n.m.r. spectrum confirmed that one deuterium atom had been introduced.

1,2,3,4-*Tetrahydro*-8-*methoxy*-2-*methyl*-6,7-*methylenedioxyisoquinoline* was prepared in 80% yield by sodium borohydride reduction of 3,4-dihydro-8-methoxy-2-methyl-6,7-methylenedioxyisoquinoline in hydrochloride (cotarnine chloride). The hydrochloride crystallised from ethanol and had m.p. 247—249° (decomp.). N.m.r. ($D_2O$): 3·50 (5-*H*), 4·06 ($OCH_2O$), 5·70br ($N{-}CH_2Ar$), 5·97 ($OCH_3$), 6·88 ($NCH_3$), and 6·47(t) and 6·90(t) (3,4-$CH_2{\cdot}CH_2$). N.m.r. spectrum of the corresponding free base, 1,2,3,4-tetrahydro-1-hydroxy-8-methoxy-2-methyl-6,7-methylenedioxyisoquinoline in $CDCl_3$: τ 3·69 (5-*H*), 4·12 ($OCH_2O$), 4·61 (1-*H*), 5·97 ($OCH_3$), 7·43 ($NCH_3$), 7·0—7·6 (m, 3,4-$CH_2{\cdot}CH_2$), and 8·05br (O*H*).

The 1-deuterio-analogue was prepared by sodium borodeuteride reduction of cotarnine chloride, and its hydrochloride had m.p. 249—251° (decomp.). The resonance at τ 5·70 in its n.m.r. spectrum ($D_2O$) was only 50% of that in the non-deuteriated analogue showing that one atom of deuterium had been introduced.

[1/2090 *Received*, 9*th November*, 1971]