Tetrahedron. Vol. 30. pp. 2623 to 2631. Pergamon Press 1974. Printed in Great Britain

AZABICYCLO CHEMISTRY—V

SYNTHESIS AND STEREOCHEMISTRY OF 7-SUBSTITUTED *CIS*-OCTAHYDROINDOLES PREPARED *VIA* A NITRENIUM INTERMEDIATE[1]

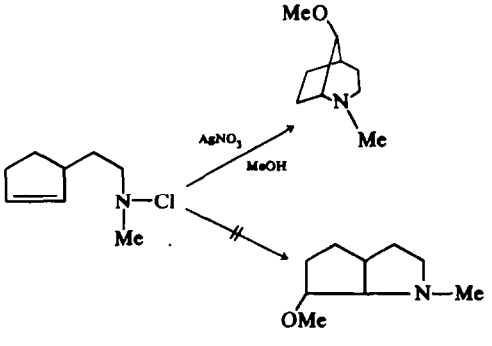
M. MOKOTOFF*[2a] and R. F. SPRECHER[2b]

Contribution from the Department of Medicinal Chemistry, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania 15261 and the Department of Chemistry, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213

(*Received in USA* 10 *January* 1974; *Received in the UK for publication* 12 *March* 1974)

Abstract—As a potential route to 9-functionalized-2-azabicyclo[3.3.1]nonanes we have investigated the silver nitrate catalyzed solvolysis of N-chloro-N-methyl-2-cyclohexene-1-ethanamine (**4a**) in methanol. By this route we obtained 1-methyl-7(a)-methoxy-*cis*-octahydroindole (**5a**), 1-methyl-7-chloro-*cis*-octahydroindole (**6a**), 2-methyl-9-methoxy-2-azabicyclo[3.3.1]nonane (**7a**), and 1-methyl-7(a)-nitrato-*cis*-octahydroindole (**8a**) in the approximate ratio of 75:1:3:23, respectively. The structure proofs of **5a** and **8a** were accomplished by chemical interrelating the two and by double resonance NMR spectroscopy, while the structures of **6a** and **7a** were assigned by mass spectroscopy. Appropriate deuterium studies substantiated the mass spectral fragmentation pathways. Mechanistically we favor the formation of the products by invoking the intermediacy of a nitrenium ion.

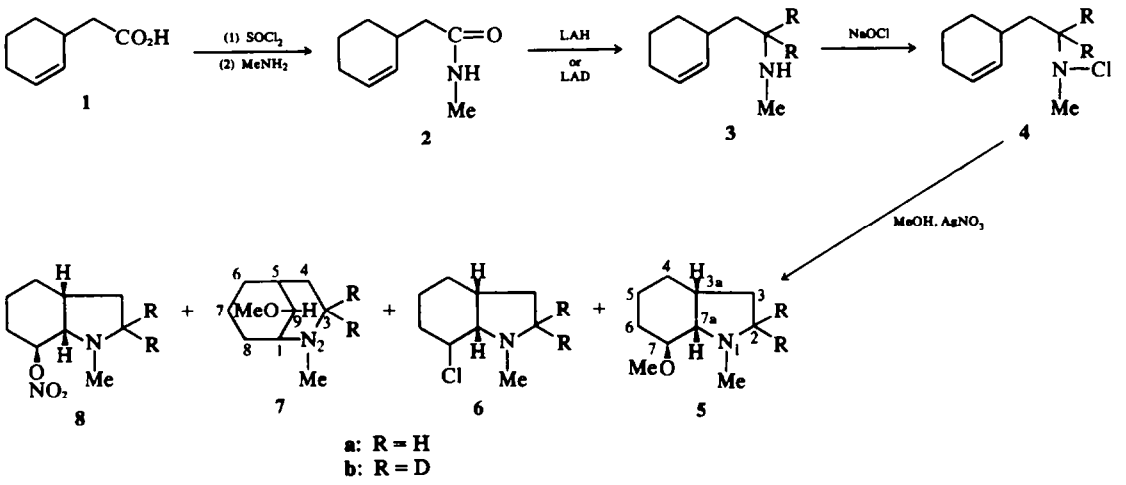
We have been interested in potential synthetic routes to 9-functionalized azabicyclo[3.3.1]nonanes for some time, especially since the literature[3] reports only one rather long approach to this system. However, the recent reports of Gassman *et al.*[4] concerning their solvolytic π-route to azabicyclics seemed attractive to adapt to our needs. Whereas in principle their[4a] solvolysis of a cyclopentene chloroamine could have led to cyclization at either end of the double bond, it was found that only 1,3-cyclization occured. It was therefore felt that perhaps under similar conditions, the solvolysis of a properly positioned cyclohexene chloramine would, *via* a nitrenium ion intermediate, lead to 1,3-cyclization and thus to the desired 2-methyl-9-methoxy-2-azabicyclo[3.3.1]nonane (**7a**). It is the results of this solvolysis which we now wish to report in detail.



RESULTS AND DISCUSSION

trans-1,2-Dibromocyclohexane was readily converted[5] to the known 2-cyclohexene-1-acetic acid 1) in a 60% overall yield. Conversion of **1** to its acid chloride followed by treatment with methylamine gave the corresponding amide **2**. Reduction of **2** with LAH afforded the amine **3a**, which was then converted to the chloramine **4a** with sodium hypochlorite. Heating **4a** in a solution of methanol and silver nitrate gave a brown oil, which on gas chromatographic (GC) analysis indicated the presence of 2 major and 3 minor components. This mixture has been identified (in the order in which they exited from the GC) as recovered starting amine **3a**, methoxy compound **5a**, chloro compound **6a**, azabicyclo compound **7a**, and nitrate **8a** in the approximate ratio (GC peak measurement) 1:75:1:3:23, respectively. The remainder of this text will be concerned with the evidence for these assignments.

Combination GC-mass spectrometry of the mixture gave the molecular weights of **3a**, **5a**, **6a**, and **7a** and an apparent molecular weight of 154 for **8a**. The latter result will later be shown to be that of a fragment ion. The fragmentation pattern of the first minor component was identical to that of starting amine **3a**. Since there was no attempt to establish 100% conversion of **3a** to **4a**, the origin of **3a** in the mixture is possibly[6] due to incomplete conversion to **4a**. Careful chromatography of the mixture on basic alumina afforded two major components **5a** and **8a**, which were further purified through their hydrobromide and picrate salts, respectively. The



minor azabicyclo compound **7a** was obtained by preparative GC and purified by way of its picrate salt.

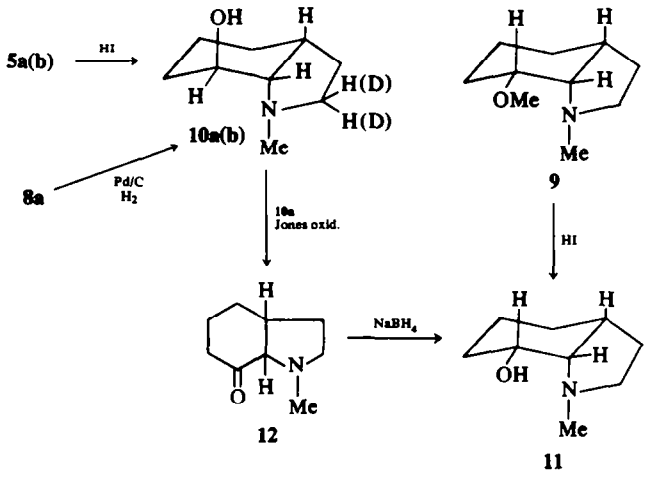
The mass spectrum of **5a** and **7a** gave the same molecular ion, but the fragmentation patterns were quite dissimilar. If cyclization of **4a** occurred at both ends of the double bond, one would expect to obtain both **5a** and **7a**. The NMR spectrum of the major component **5a** did little more than establish the presence of N-Me and O-Me groups. In order to ascertain whether the major component was the structure depicted as **5a** or **7a**, we set out to synthesize a 1-methyl-7-methoxyoctahydroindole by an unequivocal route. This was accomplished by catalytic hydrogenation of 1-methyl-7-methoxyindole and the reduction product identified[7] as the *cis* isomer with the OMe equatorial (**9**). The mass spectral fragmentation of **9** was identical to that of **5a**, but all other physical data (IR, NMR, TLC) were different. This suggested that **5a** and **9** had the same basic ring skeleton but were isomeric with each other. Thus, the major product **5a** is the result of 1,2-cyclization and is contrary to the 1,3-cyclization which Gassman *et al.*[4a] observed on solvolysis of their cyclopentene chloramine.

Initially we attempted to establish the stereochemistry of **5a** by conversion (*via* hydriodic acid cleavage of the OMe group) to its corresponding alcohol **10a** and relating it to the alcohol **11** (obtained from **9**), whose stereochemical structure has been elucidated.[7] Thus **10** was oxidized with Jones reagent to the corresponding ketone **12** (not isolated as it was unstable) and immediately reduced with sodium borohydride. The reduction product was homogeneous on TLC and GC, and identical in the IR with alcohol **11**. Evidently sodium borohydride reduction favors the equatorial product, wherein there is a strong OH–N interaction.[7]

If one assumes that during oxidation of **10a** and subsequent reduction there is no isomerization at C–7a, then a plausible structure for the alcohol **10a**, and thus methoxy **5a**, is as depicted, that is OH and nitrogen *trans*-diaxial and therefore the ring juncture must be *cis*-fused. An interesting observation was the anomalous low field position (δ4·20) for the C–7 axial proton in the alcohol **11** compared to δ3·78 for the equatorial C–7 proton in **10a**. This does not follow the usual trend,[8] i.e., axial protons resonate at higher field than the corresponding equatorial protons. This reversal of the normal course of relative chemical shifts most likely occurs because of two factors, (a) deshielding of axial hydrogens by various electronegative groups in a 1,2-diaxial relationship,[9a] as in **11** and (b) by the shielding of equatorial hydrogens by various electronegative groups in a 1,2-*cis*-relationship,[9b] as in **10a**.

We have been able to confirm the stereochemistry of **10a** (and thus **5a**) by chemically interrelating it with the other major component **8a** and also by high resolution NMR spectroscopy of **8b**. Chemical ionization mass spectrometry* of **8a**-picrate gave the molecular weight of the free amine as 200, and combined with the observation of stong absorption in the IR at 6·15, 7·81 and 11·43 μ confirmed the presence of a nitrate group.[10] The low resolution mass spectrum of **8a** shows the highest ion as the fragment at *m/e* 154 due to loss of NO_2 from the molecular ion, and thereafter the fragmentation pattern is identical to that of **5a**. This suggested that **8a** differed from **5a** in the functional group attached at C–7. Catalytic hydrogenation[11] of **8a** afforded a single alcohol, the free amine and picrate of which was identical in the IR with **10a** obtained by hydriodic acid cleavage of OMe **5a**. Thus, **5a** and **8a** are stereochemically similar and only differ in the group attached at C–7a. When silver perchlorate was substituted for silver nitrate in the solvolysis of **4a**, only **5a**, **6a**, and **7a** were obtained. Although nitrate ion is not considered to be a good nucleophile,[12]

*Isobutane was used as the reactant gas.



it is known[13] that organic nitrates can be prepared from the corresponding halides and silver nitrate. Since Gassman[4] and co-workers did not report obtaining any organic nitrates in their solvolyses, we were somewhat surprised to find **8a** as a major component of our mixture.

The NMR spectrum of the deuterated (see discussion below) free amine **8b** (Fig 1) shows H_7 to be in the equatorial position by reason of the absence of any large couplings. The resonance appears at δ5·14 as a doublet of triplets, with a doublet spacing of 4·9 Hz and a triplet spacing of 3·7 Hz, both of which are consistent with *gauche* couplings. The resonance due to H_{7a} was located at δ2·41 by low power tickling experiments and then strongly irradiated at that frequency to collapse the H_7 resonance to a doublet of doublets. Thus $J_{7,7a}$ was found to be 3·7 Hz.

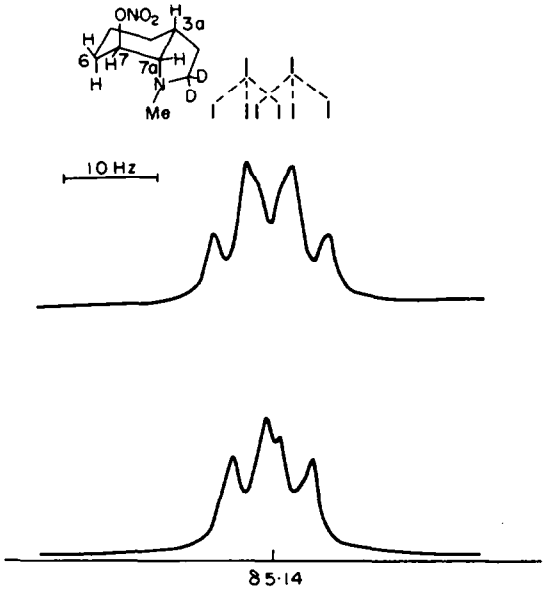


Fig 1. (a) Upper trace: C-7 proton of **8b** in $CDCl_3$ at 250 MHz. (b) Lower trace: double resonance experiment on **8b**; C-7 proton after irradiation at δ2·41.

The NMR spectrum of the picrate of **8b** (Fig 2) shows H_7 to be in the axial position by the presence of large couplings in the resonance due to that proton. The resonance appears at δ5·60 as a doublet of triplets with a doublet spacing of 4·4 Hz and a triplet spacing of 8·9 Hz. The large triplet spacing is consistent with two *trans* couplings and the small doublet spacing with one *gauche* coupling. The resonance due to H_{7a} was located by double resonance at δ3·84 and strongly irradiated at that frequency to collapse the H_7 resonance to a doublet of doublets. The value thus found for $J_{7,7a}$ was 8·9 Hz. Similarly, irradiation at δ5·60 allowed the upfield apparent triplet to collapse to a doublet, thus giving the value for $J_{7a,3a}$ as 7·0 Hz. This latter, rather large, coupling for an axial-equatorial interaction suggests that the six-membered ring is forced into a half-chair conformation.

In each case, strong irradiation at the H_7 resonance produced strong effects in three well separated regions of the rest of the spectrum, thus verifying that the spectra were first order. It seems clear that the free amine **8b** is in a conformation in which the substituent at C-7 and the C–N bond at C-7a are both axial, thus requiring a *cis* ring fusion. The picrate, then, must have the same ring fusion but with the aforementioned groups in equatorial positions. Such a conformational change as we see here would not be possible if the ring fusions were *trans*.

One further observation made with the octahydroindole structures deserves discussion. The NMR spectra of **5a**, **8a** and **10a** all show complex one-proton multiplets at about δ3·2. In the case of **8a** and **10a**, double resonance experiments have shown that irradiation in the vicinity of the C-7 proton does not decouple the resonance at δ3·2 and

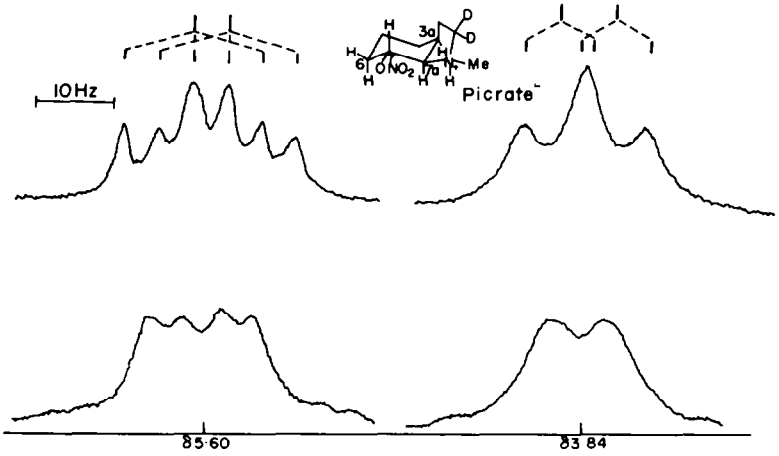


Fig 2. .(a) Upper traces: left, C-7 proton and right, C-7a proton of **8b**-picrate in $CDCl_3$ at 250 MHz. (b) Lower traces: corresponding double resonance experiments, C-7 proton while irradiating at δ3·84 and C-7a proton while irradiating at δ5·60.

thus is not the C-7a proton. We instead interpret this to be one of the C-2 protons, as this downfield location has been observed in the NMR spectra of several alkaloids[14] which have the octahydroindole nucleus. Indeed, other workers[15] have reported similar findings in the decahydroquinoline series. Definitive proof of this assignment was obtained by replacing the C-2 hydrogens with deuterium. This was accomplished by carrying out the reduction of **2** with lithium aluminium deuteride to give **3b**, followed by N-chlorination to **4b** and then solvolysis, the results being identical to that described previously. The NMR spectrum of **5b**, **8b**, and **10b** confirmed our assignment as they all showed the *absence* of complex one-proton resonance at about δ3·2 (see for example Fig 3). We feel that this anomalous position for one of the C-2 protons in octahydroindole derivatives should be recognized as it may lead other workers[7,16] to possible erroneous conformational assignments if this is instead assigned as the C-7a proton.

Mechanistically, the *trans* configuration of the functional groups in the major compounds **5** and **8** is readily rationalized in terms of a nitrenium[4] inter-

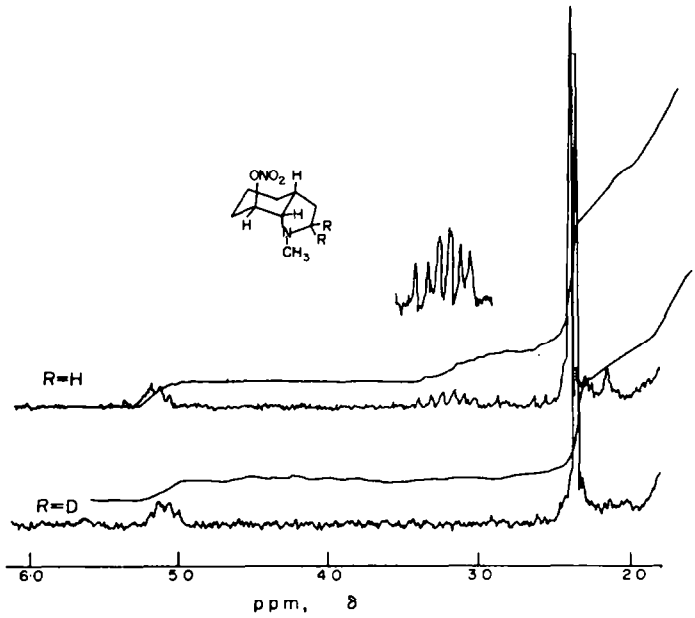


Fig 3. (a) Upper trace: partial NMR spectrum (60 MHz) of **8a** in $CDCl_3$. (b) Lower trace: partial NMR spectrum (60 MHz) of **8b** in $CDCl_3$ showing disappearance of a one proton resonance at about δ3·2.

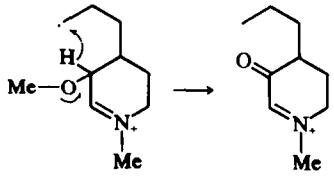
mediate rather than by a radical chain mechanism.[17] By the latter mechanism one would expect to obtain a much larger proportion[17] of amine **3** and chloro **6** than was observed. Furthermore one would not expect to obtain the *trans* configuration in both major compounds but more likely as the *cis* arrangement, as in **9**.

Mass spectral data

The structural assignments for the minor components **6** and **7** are based on mass spectral evidence. The absence of a significant peak at *m/e* 82 in **7a**, an ion generally found in the spectra of azabicyclic compounds containing an N-methylpyrrolidine ring,[17,18] suggested that **7** was not a stereoisomer of **5** but structurally different. A high resolution mass spectral analysis of **7a** was entirely interpretable as the structure previously shown. Further confirmation of the fragment ions was obtained by deuterium labeling, that is, by repeating the solvolysis of **4a** in methanol-d_4, thus affording **13** and **14**, *m/e* 172.

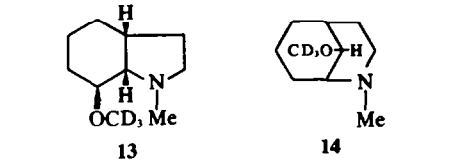
The base peak in the spectrum of **7a** was the dihydropyridinium ion **b**, *m/e* 126·093 (calc 126·092) formed from the ion **a** by transfer to an allylic hydrogen to the radical site and concerted cleavage of the side chain[19] (path 1). A metastable ion at *m/e* 93·9 was observed for this transformation. Alternatively, loss of OMe and cleavage of the side chain would, by path 2, afford the ion **c**, *m/e* 96·082 (calc 96·081). Although the loss of formaldehyde from **b** could also give **c**, this route has been ruled out by the lack of a suitable ion at *m/e* 97 in the spectrum of **14**.

The second most intense ion occurred at *m/e* 154·122 (calc 154·123) and could be visualized as arising from **a** by the loss of a Me radical and hydrogen transfer to the radical site to give the stable pyridone **d**,* which was accompanied by an appropriate metastable peak at *m/e* 140·3. The loss of this Me radical is from oxygen and not nitrogen as shown by the absence of a significant ion at *m/e* 157 in the spectrum of **14**.



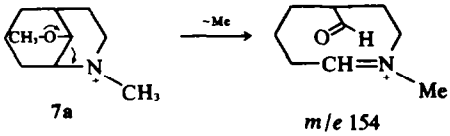
a **d**: *m/e* 154 (97%)

A relatively minor ion was that due to the loss of OMe from the molecular ion to give the nitrenium ion **e**, *m/e* 138·127 (calc 138·128), which was confirmed by the observation of an identical peak due to the loss of OCD_3 in the spectrum of **14**. In effect, this pathway is simply the reverse of the ring closure of **4a** with MeOH, which presumably proceeds through a nitrenium ion intermediate.

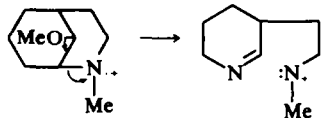


13 **14**

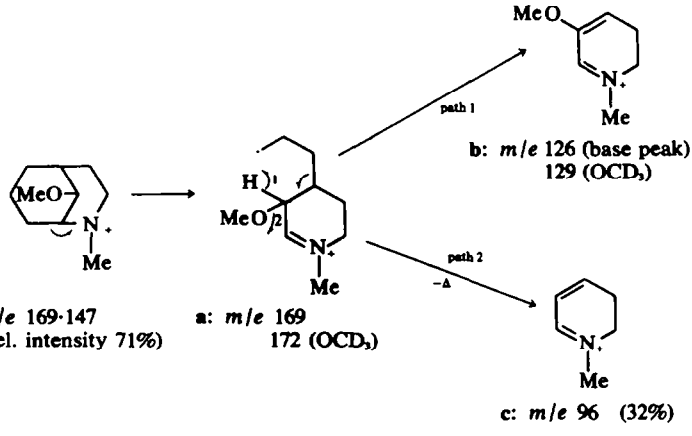
*A referee has suggested an alternative pathway for the loss of methyl radical from **7a**, in analogy with the pathway **5a**→**i**.



7a *m/e* 154

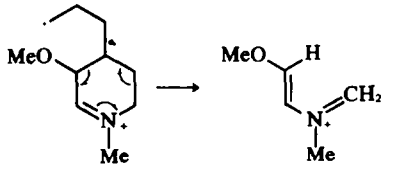


7a **e**: *m/e* 138 (19%)



7a: *m/e* 169·147 (rel. intensity 71%) **a**: *m/e* 169 172 (OCD_3)

The last important ion to be discussed for **7a** is that of **f**, *m/e* 100·076 (calc 100·076). We envisage this ion as occurring from **a** by a *retro* Diels–Alder.[20] This spectrum of **14** shows this ion at *m/e* 103, while **7b** shows this peak at *m/e* 102.



a **f**: *m/e* 100 (42%); 102 (D_2); 103 (OCD_3)

The question of the stereochemical assignment of the OMe in **7a** is still unanswered, however, on purely mechanistic grounds,[4a] we assign it the *anti* configuration, that is, *trans* to the nitrogen. We are presently trying to substantiate this assignment through an X-ray analysis* of **7b**-picrate.

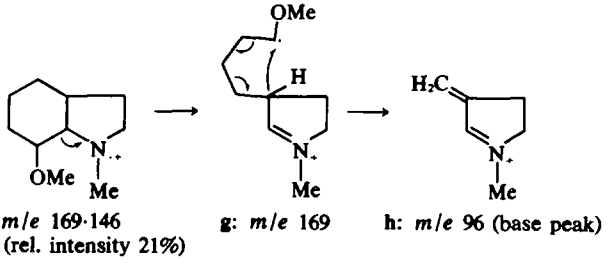
We were not able to isolate a pure sample of chloro **6a** but its mass spectrum showed parent ions at *m/e* 173 and 175. After losing chlorine it shows significant ions at *m/e* 138, 110, 96, 83 and 82, the same pattern as **5a**. We feel that these fragments can be rationalized in the same manner as for **5a** discussed below, and thus assign the chloro compound as the octahydroindole **6a**.

The high resolution mass spectrum of **5a** has been fully interpreted as the octahydroindole nucleus and the fragments further confirmed by way of the deuterated compounds **5b** and **13**. The most abundant ion in the spectrum arises by α-cleavage to **g** followed by transfer of an allylic hydrogen to the radical site and concerted rupture of the side chain[19] to give ion **h** *m/e* 96·082 (calc 96·081). A metastable ion at *m/e* 54·5 was observed for this transformation.

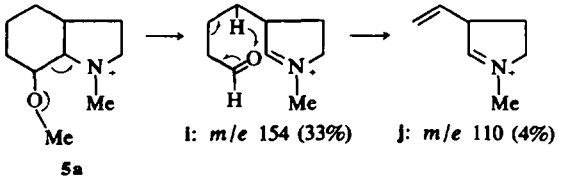
The next most intense ion, *m/e* 154·123 (calc 154·123), was formed directly from the molecular ion (metastable at *m/e* 140·3) by the loss of a methyl radical and α-cleavage to the aldehyde **i**. The loss of Me was from oxygen as shown by the absence of a suitable peak at *m/e* 157 in the spectrum of **13**. A McLafferty rearrangement from **i** could account for the ion **j** observed at *m/e* 110·096 (calc 110·097).

The ion **k** at *m/e* 83·072 (calc. 83·074) may be considered to have been formed by a concerted, homolytic fission[21] of the 6-membered ring and which upon loss of a hydrogen radical gives **1**, *m/e* 82·006 (calc. 82·006). In the spectrum of deuterated **5b**, one observes peaks at *m/e* 85, 84 and 83. This would indicate that in the process **k** → **1** the loss of a hydrogen radical can occur from more than one position. The fact that *m/e* 84 in **5b** is more intense than *m/e* 83 indicates the importance of the structure **1**.

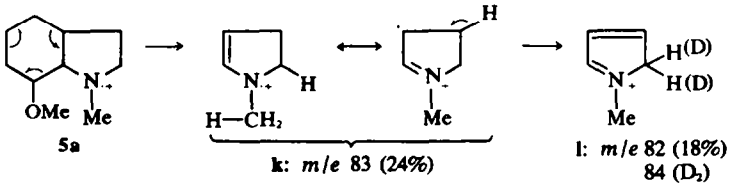
*Initial photographs indicate that **7b**-picrate crystallizes in space group $P\bar{1}$. The completed results of the crystal study will be published elsewhere.



5a: *m/e* 169·146 (rel. intensity 21%) **g**: *m/e* 169 **h**: *m/e* 96 (base peak)

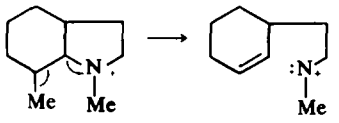


5a **i**: *m/e* 154 (33%) **j**: *m/e* 110 (4%)



5a **k**: *m/e* 83 (24%) **l**: *m/e* 82 (18%); 84 (D_2)

Finally, the loss of OMe from the molecular ion of **5a** followed by opening of the pyrrolidine ring would give the same nitrenium ion **e**, *m/e* 138·128 (calc 138·128), for the same reason as previously discussed for **7a**.



5a **e**: *m/e* 138 (4%)

EXPERIMENTAL

M.ps were determined on a Fisher–Johns apparatus and are not corrected. NMR spectra were recorded on a Varian A-60D or the Mellon Institute 250 MHz spectrometer in $CDCl_3$ with TMS as internal standard, and IR spectra were recorded in $CHCl_3$ either on a Beckman IR-8 or Perkin-Elmer 267 grating spectrometer, unless stated otherwise. TLC (Analtech, Inc) and preparative TLC (1·0 mm, Quantum Industries) were carried out with silica gel GF and the spots located by spraying with a 4% soln of I_2 in EtOH. GC analyses were performed on a Varian Aerograph series 1800 gas chromatograph with a 6 ft × 1/8 in column of 3% OV-1 on Supelcoport 80/100. For preparative GC, a 12 ft × 3/8" column of 3% of OV-1 on ABS 50/60 was used isothermally at 155°. Low resolution mass spectra were determined on an LKB model 9000 spectrometer at 70 eV. The high resolution data were obtained on a Consolidated Electrodynamics 21-110B spectrometer, while the chemical ionization data were obtained on an A.E.I. MS-9 spectrometer. The organic layers were dried with Na_2SO_4 prior to concentration. Microanalyses were performed by Spang, Microanalytical Laboratory, Ann Arbor, Michigan and Galbraith Laboratories, Inc., Knoxville, Tennessee. The light petroleum used had b.p. 30–60°, unless stated otherwise.

2-Cyclohexene-1-acetic acid (**1**). *trans*-1,2-Dibromocyclohexane (25·0 g, 103 mmole, Aldrich Chemical) was converted by known procedures[5] to **1** (8·6 g, 60% overall), obtained as a colorless oil, b.p. 83–95° (0·25 mm), n^{24}D 1·4799 [lit[5] b.p. 101·5–104° (1 mm), n^{24}D, 1·4800; b.p. 150–152° (24 mm), n^{25}D 1·4787]; NMR (CCl_4) δ5·3–5·9 (m, 2, vinyl H); 12·13 (s, 1, CO_2H).

N-Methyl-2-cyclohexen-1-acetamide (**2**). A mixture of (8·83 g, 63 mmol) and $SOCl_2$ (15·0 g, 126 mmol) was refluxed for 3 h and then distilled to give 9·87 g (98%) of the colorless oily acid chloride, b.p. 40–41° (0·25 mm) n^{25}D 1·4830 [lit[5] b.p. 58–60 (1 mm), n^{25}D 1·4860; b.p. 98° (25 mm), $n^{22.5}$D 1·4835]. The acid chloride was dissolved in 50 ml anhydrous ether, cooled and added portionwise to a cold soln (75 ml) of excess $MeNH_2$ in ether. The precipitated $MeNH_2$.HCl was removed by filtration, the filtrate concentrated to dryness and the solid product crystallized from benzene–light petroleum, giving 7·1 g (73%) of **2**, m.p. 54–55°; IR 5·97 μ (amide CO); NMR (CCl_4) δ2·70 (d, 3, N–Me); 5·3–5·8 (m, 2, vinyl H); 7·83 (m, 1, NH); mass spectrum *m/e* (rel intensity) 153 (26), 95 (17), 81 (50), 73 (100). (Found: C, 70·60; H, 9·78; N, 9·10. Calcd for $C_9H_{15}NO$: C, 70·55; H, 9·87; N, 9·14%).

N-Methyl-2-cyclohexen-1-ethanamine (**3a**) *and N-methyl 2-cyclohexen-1-ethanamine-α-d_2* (**3b**). An ethereal soln of LAH (60 ml, 1 M) was placed in a 500 ml 3-neck flask equipped with a reflux condenser and a dropping funnel. The flask was cooled in ice and treated dropwise while stirring, with a soln of **3a** (5·0 g, 33 mmol) in ether (120 ml). The soln was then refluxed for 2·5 h, cooled and the excess LAH decomposed by the dropwise addition of a 10% NaOH aq. The salts were removed by filtration, washed with ether and the combined organic layers were concentrated to about 100 ml. The ethereal soln was extracted 3 times with 5% HCl, the combined acidic solns basified with 10% NaOH aq and the liberated amine extracted into CH_2Cl_2. Evaporation of the solvent and distillation of the residue gave 3·2 g of pale yellow amine **3a**, b.p. 78–80° (12 mm); NMR (CCl_4) δ2·37 (apparent s, 3, N–Me), 2·58 (apparent t, 2, CH_2–N), 5·57 (m, 2, vinyl H). All of **3a** was converted to its HBr salt and recrystallized from acetone to give 4·2 g (58%) of **3a**. HBr, m.p. 181–183°; mass spectrum *m/e* (rel intensity) 139 (16), 108 (13), 96 (6), 93 (11), 79 (16), 44 (100, $CH_2=\overset{+}{N}HMe$). (Found: C, 49·30; H, 8·32; N, 6·45. Calcd for $C_9H_{18}NBr$: C, 49·10; H, 8·24; N, 6·36%).

When the above was repeated using LAD (Alfa Inorganics) the corresponding deuterated amine **3b** was obtained; NMR δ2·42 (apparent s, 3, N–Me), 5·57 (m, 2, vinyl H); mass spectrum *m/e* (rel intensity) 141 (14) 110 (14), 79 (15), 46 (100, $CD_2=\overset{+}{N}HCH_3$).

1-Methyl-7(a)-methoxy-cis-octahydroindole (**5a**), *1-methyl-7-chloro-cis-octahydroindole* (**6a**), *2-methyl-9-methoxy-2-azabicyclo[3.3.1]nonane* (**7a**), *and 1-methyl-7(a)-nitrato-cis-octahydroindole* (**8a**) *and deuterated counterparts* **5b**, **6b**, **7b** *and* **8b**

A soln of **3a**–HBr (1·00 g, 4·6 mmol) in water (2·0 ml) was brought to a pH of 7–8 with 10% NaOH and then treated, while cooling in ice, with a NaOCl aq (15 ml, Purex Commercial bleach, 6%). The mixture was vigorously stirred for 60 min and then extracted with 3 portions of ether. The combined ethereal solns were washed once with cold water, dried and concentrated *in vacuo* to the oily chloroamine **4a** (0·75 g) whose GC analysis indicated that only a trace of starting amine **3a** was present. An NMR analysis of **4a** showed the N–Me resonance as a singlet at δ2·87 and the two vinyl protons as a multiplet at δ5·55. The amine **4a** was dissolved in 20 ml of a methanolic soln of $AgNO_3$ (1·2 g, 7·0 mmol) and then refluxed for 1 h. The resulting dark mixture was filtered, concentrated to a smaller volume, diluted with water and made acidic with 10% HCl. The precipitated AgCl was removed by filtration with the aid of Celite, the filtrate basified with 25% NaOH and the product extracted into CH_2Cl_2. The organic layer was washed once with a satd NaCl aq, dried, and concentrated to a crude brown oil (0·77 g). A TLC examination (10% CH_3OH–$CHCl_3$ + 1% NH_4OH) of the oil indicated 3 spots and by a combination of preparative TLC and GC-mass spectrometry it was found that the upper R_f component was a mixture of **6a** and **8a**, the middle component (major spot) a mixture of **5a** and **7a**, while the lower spot was the starting amine **3a**. A portion of the crude oil (0·44 g) was chromatographed on a column (1·5 × 19 cm) of basic Al_2O_3 (Woelm, Grade 1) packed in ether. Development with ether gave 0·11 g of an oil which was the nitrate **8a**. Purification of **8a** was accomplished through its picrate and recrystallization from benzene gave the analytical sample, m.p. 153–154·5°; high resolution mass spectrum, calcd *m/e* (Found) 154·123 (154·122, $C_9H_{16}NO$, M^+–NO_2), 138·128 (138·129, $C_9H_{16}N$, M^+–ONO_2), 96·081 (96·081, $C_6H_{10}N$), 83·074 (83·072, C_5H_9N), 82·066 (82·065, C_5H_8N). (Found: C, 41·92; H,

4·48; N, 16·33. Calcd for $C_{15}H_{19}N_5O_{10}$: C, 41·95; H, 4·46; N, 16·31%).

The eluting solvent was changed to 25% $CHCl_3$–ether and the fractions analyzed by GC and combined, thus affording 0·1 g as a mixture of **5a** and **7a**, and 0·1 g of an oil which was mostly **5a**. The latter was purified as its HBr salt and recrystallized from EtOAc, m.p. 116·5–117·5°; NMR (free base) δ2·33 (s, 3, N–Me), 3·0–3·3 (m, 1, C–2 H), 3·37 (s, 4, O–Me and C–7 H). (Found: C, 48·17; H, 7·66; N, 5·73. Calcd for $C_{10}H_{20}BrNO$: C, 47·99; H, 8·06; N, 5·60%).

A pure sample of **7a** was obtained by preparative GC of the above mixture of **5a** and **7a**, converted to its picrate and crystallized from benzene–light petroleum, m.p. 188–192°.

Repeating the above ring closure with **3b** (1·00 g, 7·1 mmol) gave 0·87 g of a brown oil which on analysis by GC-mass spectrometry indicated identical results to above except that the parent ions were all 2 mass units higher. Purification was more easily accomplished by preparative TLC than by column chromatography. Thus a portion (0·20 g) of the crude oil was purified on 3 preparative plates (10% MeOH–$CHCl_3$ + 1·5% NH_4OH). The material in the upper band was converted to its picrate and crystallized from benzene to give, in 2 crops, 0·09 g of **8b**-picrate m.p. 153–155°. The pure free base was readily obtained by passing a $CHCl_3$ soln of **8b**-picrate through a short column of Woelm basic alumina. The middle band from the preparative plates (0·044 g) was a mixture of **5b** and **7b** and was further purified by preparative GC. The first peak off the column was **5b**, which was isolated as its picrate (0·055 g), and crystallized from isopropyl alcohol, m.p. 82–83°; NMR (free amine) δ2·32 (s, N–Me), 3·33 (s, 4, O–Me and C-7 H). The second peak was that of **7b** which also was isolated as its picrate (0·011 g) and recrystallized from benzene–light petroleum (b.p. 60–68°), m.p. 190–194°.

1-Methyl-7(a)-hydroxy-cis-octahydroindole (**10a**) *and 1-methyl-7(a)-hydroxy-cis-octahydroindole-2-d_2* (**10b**)

(a) A soln of **5a** (0·093 g, 0·55 mmol) in HI (Fisher, 57%, 0·22 ml, 1·65 mmol) was refluxed for 1 h, cooled, diluted with H_2O and basified with 25% NaOH. The mixture was saturated with NaCl and then extracted with CH_2Cl_2. The combined organic layers were washed once with satd NaCl aq, and concentrated, affording **10a** as an oil (0·075 g); NMR δ2·50 (s, 3, N–Me), 3·1–3·4 (m, 1, C-2 H), 4·32 (s, 1, OH which disappears upon shaking with D_2O). The alcohol **10a** was purified through its picrate and crystallized from benzene, m.p. 166–168°.

The above cleavage was repeated with **5b** (0·07 g, 0·44 mmol) and **10b** isolated as its picrate (0·09 g, 52%), m.p. 170–172°. Several recrystallizations from acetone–ether gave the analytical sample, m.p. 171–173°. (Found: C, 46·74; H, D, 5·71; N, 14·60. Calcd for $C_{15}H_{18}D_2N_4O_8$: C, 46·61; H, D, 5·74; N, 14·50%).

(b) A soln of **8a** (0·010 g, 0·05 mmol) in EtOH (3 ml) was hydrogenated in the presence of 10% Pd/C (0·020 g, Englehard Industries) at atmospheric pressure. After 30 min the theoretical amount of H_2 was consumed. The reaction was stopped after 70 min, the catalyst removed by filtration, and the bulk of EtOH removed *in vacuo*. Since the alcohol **10a** was resonably volatile, the remaining ethanolic soln was rendered acid with 10% HCl and then all of the EtOH removed *in vacuo*. The acid soln was made basic with 25% NaOH, the product extracted into CH_2Cl_2, and the organic layer concentrated to give **10a** (0·005 g), which was identical in the IR with **10a** prepared as above. This was converted to its picrate and crystallized from ether–light petroleum, m.p. 165–167°, identical in the IR (KBr) with **10a**-picrate prepared as above.

1-Methyl-7(e)-hydroxy-cis-octahydroindole (**11**)

A soln of **10a** (0·009 g) in acetone (2 ml) was cooled in an ice bath and treated with 6 drops of freshly prepared[22] Jones reagent. The ice bath was removed and the initially clear soln allowed to stir at room temp for 30 min. Water was added to the mixture (this dissolved the precipitated salts) and the acetone was removed in a stream of N_2. The aqueous soln was made alkaline with 10% NaOH and the ketone immediately (it was unstable) extracted into ether. The organic layer was concentrated, the residue dissolved in MeOH (3 ml) and treated with a soln (1 ml) of $NaBH_4$ (0·03 g) in MeOH. After 60 min several drops of H_2O were added, the soln was acidified with 10% HCl, and the MeOH removed *in vacuo*. The aqueous soln was made alkaline with 25% NaOH aq and the product extracted into ether. Concentration of the ethereal soln gave **11** as an oil, the IR spectrum of which was identical to that of **11** prepared as described previously.[7]

Acknowledgements—For the mass spectral data, the authors wish to thank Mr. J. Naworal, University of Pittsburgh, low resolution, performed under Grant RR-00273; Dr. Philip Levins, A. D. Little, Inc., high resolution, performed under Contract No. NIH-69-225; and Dr. Roger Foltz, Battelle Columbus Laboratories, chemical ionization, performed under Contract No. NIH-71-2483, all from the National Institutes of Health. For the 250 MHz NMR results we thank Mr. Brian Aufderheide, Carnegie–Mellon University, performed under Grant RR-00202 from the National Institutes of Health. For some of the deuterium syntheses, we thank Mr. Peter D. Alt.

REFERENCES

[1a] Part IV. M. Mokotoff and R. C. Cavestri, *J. Org. Chem.* **39**, 409 (1974); [b] This work was supported in part by Grant RR-05455-11 from the National Institutes of Health, Bethesda, Maryland

[2a] University of Pittsburgh; [b] Carnegie–Mellon University

[3] F. Ramirez and J. W. Sargent, *J. Am. Chem. Soc.* **77**, 6297 (1955)

[4a] P. G. Gassman, F. Hoyda and J. Dygos, *Ibid.* **90**, 2716 (1968); [b] P. G. Gassman and J. H. Dygos, *Tetrahedron Letters* 4745, 4749 (1970); [c] P. G. Gassman, *Accounts Chem. Res.* **3**, 26 (1970)

[5] R. B. Moffett, C. A. Hart and W. M. Hoehm, *J. Am. Chem. Soc.* **69**, 1854 (1947); A. T. Blomquist, J. Verdol, C. L. Adami, J. Wolinski and D. D. Philips, *Ibid.* **79**, 4976 (1957); H. O. House, R. G. Carlson and H. Babad, *J. Org. Chem.* **28**, 3359 (1963); M. Julia, J. M. Surzur, L. Katz and F. Le Goffic, *Bull. Soc. Chim. Fr.* 1119 (1964)

[6] For an alternative mechanism for the formation of **3a** see Ref 4*b*

[7] The results of this work and the stereochemical proof by NMR was the subject of a separate paper, M. Mokotoff, *J. Heterocycl. Chem.* **10**, 1063 (1973)

[8] N. Bhacca and D. H. Williams, *Application of NMR Spectroscopy in Organic Chemistry* p. 77. Holden-Day, San Francisco, California (1964)

[9a] Ref 8, p. 184, type D shift; [b] Ref 8, p. 184, type A shift

[10] R. A. G. Carrington, *Spectrochim. Acta* **16**, 1279 (1960)

[11] L. P. Kuhn, *J. Am. Chem. Soc.* **68**, 1761 (1946); I.

Tanasescu, F. Hodoson and M. Terdic, through *Chem. Abstr.* **58**, 4618f (1963)
[12]J. B. Hendrickson, D. J. Cram and G. S. Hammond, *Organic Chemistry*, (3rd edition), p. 393. McGraw-Hill, New York (1970)
[13]N. Kornblum and D. E. Hardies, *J. Am. Chem. Soc.* **88**, 1707 (1966); and refs therein
[14]P. W. Jeffs, J. F. Hansen, W. Dopke and M. Bienert, *Tetrahedron* **27**, 5065 (1971); H. Taguchi, T. Oh-ishi and H. Kugita, *Tetrahedron Letters* 5763 (1968); *Chem. Pharm. Bull.* **18**, 1008 (1970); P. W. Jeffs, R. L. Hawks and D. S. Farrier, *J. Am. Chem. Soc.* **91**, 3831 (1969)
[15]H. Booth and A. H. Bostock, *Chem. Commun.* 177 (1967); E. E. Smissman and G. S. Chappell, *J. Med. Chem.* **12**, 432 (1969); H. Booth and A. H. Bostock, *J. Chem. Soc.* Perkin II, 615 (1972)
[16]M. P. Mertes, S. A. Nerukar and W. J. Walszek, *J. Med. Chem.* **11**, 106 (1968); M. Langlois, C. Guillonneau, J. Meingan and J. Maillard, *Tetrahedron* **27**, 5641 (1971)
[17]J. W. Bastable, J. D. Hobson and W. D. Riddell, *J. Chem. Soc.* 2205 (1972)
[18]E. C. Blossey, H. Budzikiewicz, M. Ohashi, G. Fodor and C. Djerassi, *Tetrahedron* **20**, 585 (1964); W. M. Bryant, H. O. House, C. G. Pitt and B. A. Tefertiller, *J. Org. Chem.* **31**, 3120 (1966); P. W. Jeffs, G. Ahmann, H. F. Campbell, D. S. Farrier, G. Ganguli and R. L. Hawks, *Ibid.* **35**, 3512 (1970)
[19]H. Budzikiewicz, C. Djerassi and D. H. Williams, *Mass Spectrometry of Organic Compounds*, pp. 304, 358. Holden-Day, San Francisco, California (1967)
[20]F. W. McLafferty, *Interpretation of Mass Spectra*, p. 141. W. A. Benjamin, New York (1967); Ref 19, p. 316
[21]Ref 19, p. 307
[22]R. G. Curtis, I. Heilbron, E. R. H. Jones and G. F. Woods, *J. Chem. Soc.* 457 (1953)