533. *Alkaloid Studies. Part XLV.[1] Mass Spectrometry in Structural and Stereochemical Problems. Part XLII.[2] Some Aspects of the Chemistry and Mass Spectrometry of Uleine.*

By J. A. Joule and Carl Djerassi.

The chemistry of uleine (Ia) as an analogue of gramine has been studied. It has been found possible to open the D-ring of uleine under very mild conditions by treatment of its methiodide with reagents such as methoxide, cyanide, or lithium aluminium hydride, or by exposure of uleine itself to acetic anhydride–pyridine, attachment of the nucleophile always occurring at C-4 with concomitant fission of the bond between the benzylic C-4 carbon atom and N_b. The mass spectra of uleine, dihydrouleine, and several of its ring-D-opened derivatives are discussed.

In continuation of our systematic studies of the alkaloidal constituents of *Aspidosperma* species,[3] we have isolated [4] from five of them a new alkaloid, apparicine.* In connection
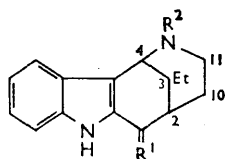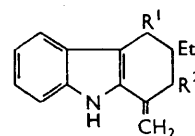

	R¹	R²
a:	CH_2	Me
b:	CH_2	Et
c:	CH_2	Ac
d:	CH_2	H
e:	O	Me
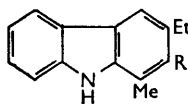
(I)

	R
a:	$CH_2 \cdot CH_2 \cdot NMe_2$
b:	CHO
c:	H
d:	$CH_2 \cdot CH_2 \cdot N(Me)Ac$
e:	$CH_2 \cdot CH_2 \cdot N(Me)H$

(II)

	R¹	R²
a:	MeO	$CH_2 \cdot CH_2 \cdot NMe_2$
b:	CN	$CH_2 \cdot CH_2 \cdot NMe_2$
c:	H	$CH_2 \cdot CH_2 \cdot NMe_2$
d:	$C_5H_5N^+$	$CH_2 \cdot CH_2 \cdot N(Me)Ac$
e:	MeO	$CH_2 \cdot CH_2 \cdot N(Me)Ac$
f:	D	$CH_2 \cdot CH_2 \cdot NMe_2$

(III)
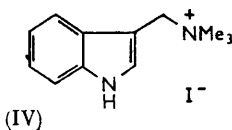
(IV)
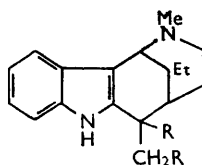
(Va: R = H)
(Vb: R = D)
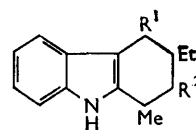
(VI)

	R¹	R²
a:	MeO	$CH_2 \cdot CH_2 \cdot NMe_2$
b:	CN	$CH_2 \cdot CH_2 \cdot NMe_2$
c:	H	$CH_2 \cdot CH_2 \cdot NMe_2$
d:	MeO	$CH_2 \cdot CH_2 \cdot N(Me)Ac$
e:	D	$CH_2 \cdot CH_2 \cdot NMe_2$

with the structural elucidation of apparicine, and as a model for its chemistry, we have investigated some reactions of uleine (Ia), with which apparicine co-occurs and which it resembles structurally. We now report on the chemistry and mass spectrometry of uleine and some of its derivatives, since this information is of intrinsic interest and relevant to subsequent discussions [4] of alkaloids related to uleine.

* Named after the distinguished Brazilian botanist, Apparicio Duarte, whose help in the collection and identification of the many *Aspidosperma* species has been indispensable in our work.

[1] Part XLIV, Djerassi, Nakagawa, Wilson, Budzikiewicz, Gilbert, and Antonaccio, *Experientia*, 1963, **19**, 467; through an error this Paper was numbered XLI.
[2] Part XLI, Williams, Budzikiewicz, and Djerassi, *J. Amer. Chem. Soc.*, 1963.
[3] For latest article, see Ferreira, Gilbert, Owellen, and Djerassi, *Experientia*, 1963, **19**, 585.
[4] Djerassi, Gilbert, Owellen, Joule, and Brissolese, unpublished results.

4 X

Uleine was assigned structure (Ia) mainly on the basis of its n.m.r. spectrum [5] and of the Hofmann degradation [6] of its methiodide. The latter gave a carbazole (IIa), the substitution pattern of which was elucidated [5] by converting it into the aldehyde (IIb) by a second Hofmann degradation followed by oxidation of the vinyl group thus produced. The carbazole aldehyde (IIb) was decarbonylated to (IIc) which was synthesized.[5] The point of closure of the D-ring was indicated by the doublet corresponding to one proton at 4·11 p.p.m. ($J = 3$ c./sec.) in the n.m.r. spectrum of the alkaloid. This signal was assigned to the unique benzylic proton (at C-4) which was also adjacent to N_b.[5] * The n.m.r. spectrum [5] clearly showed the presence of an exocyclic methylene group as well as a C-ethyl and an N-methyl substituent. In order to explain the production of a carbazole during the Hofmann degradation, it was only necessary to postulate a double-bond migration into conjugation, entirely unexceptional under the conditions of the reaction (150°; potassium hydroxide in ethylene glycol).

We have now found that these vigorous conditions are unnecessary for the opening of the piperidine ring; fission of the C_4–N_b bond can be achieved under conditions sufficiently mild that isomerization to a carbazole does not occur. Thus treatment of uleine (Ia) methiodide with sodium methoxide in methanol at room temperature for a short time produced a substance (IIIa) which could be converted into the previously obtained dimethylamino-carbazole (IIa) by treatment with mineral acid at room temperature.

Consistent with the structure (IIIa) were its ultraviolet spectrum (essentially identical with that of uleine), its mass spectrum (see below), and, most important, its n.m.r. spectrum, which clearly showed the presence of an aliphatic methoxyl (3·52 p.p.m.), a dimethyl-amino (2·20 p.p.m.), and an exocyclic methylene (5·00 and 5·37 p.p.m.) substituent, as well as the C-ethyl group, four aromatic protons, and the indolic NH. A two-proton triplet ($J = 6$ c./sec.) centred at 2·38 p.p.m. was assigned to the methylene hydrogens next to N_b. The unique benzylic proton, now next to oxygen, was shifted to 4·46 p.p.m. and was a broad singlet.

(A)   (B)
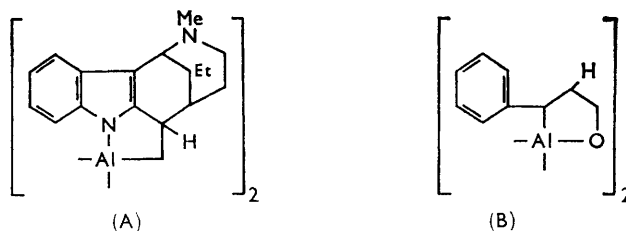
The displacement of N_b^+ from C-4 by methoxide corresponds to the nucleophilic displacements [8] which can be effected at the benzylic position of the simple analogue of uleine, gramine methiodide (IV).[8a] Similarly, uleine methiodide reacted with cyanide ion to give (IIIb), the n.m.r. spectrum of which was very similar to that of the methoxy-analogue (IIIa) except for the absence of the methoxyl signal and the fact that the benzylic proton yielded a doublet at 4·13 and a singlet at 3·92 p.p.m., the two signals together integrating for one proton.† Displacement was even possible with hydride, since lithium aluminium

* Hydrogen atoms similarly situated in yohimbine and ajmalicine type molecules have been shown to exhibit a downfield signal only when equatorial to the piperidine ring.[7] It is noteworthy that the C-4 proton of uleine is also equatorial with respect to the piperidine ring.

† This seems to indicate a mixture of C-4 isomers, a result to be expected from the postulated [8c] mechanism for such displacements. In only one of the isomers is the C-4 hydrogen correctly oriented for coupling with the C-3 proton and thus only one of the signals is split.

[5] Büchi and Warnhoff, *J. Amer. Chem. Soc.*, 1959, **81**, 4433.
[6] Schmutz, Hunziker, and Hirt, *Helv. Chim. Acta*, 1957, **40**, 1189.
[7] Wenkert, Wickberg, and Leicht, *J. Amer. Chem. Soc.*, 1961, **83**, 5037.
[8] (a) Snyder, Smith, and Stewart, *J. Amer. Chem. Soc.*, 1944, **66**, 200; (b) Brewster and Eliel, *Org. React.*, 1953, **7**, 99; (c) Geissman and Armen, *J. Amer. Chem. Soc.*, 1952, **74**, 3916; (d) Albright and Snyder, *ibid.*, 1959, **81**, 2239.

treatment provided (IIIc) which had n.m.r. features analogous to those of (IIIa) and (IIIb) except for the absence of a benzylic proton at a unique position (it no longer being adjacent to nitrogen or oxygen).

Presumably the relative facility of the reaction of uleine methiodide reflects a certain release of strain on opening ring D. This strain factor might have been expected to facilitate nucleophilic attack on the free base [8b] itself, but when uleine (Ia) was treated with sodium methoxide in refluxing methanol, no reaction occurred. Also, the expected ring-opening did not take place on treatment of uleine with lithium aluminium hydride; instead, dihydrouleine (Va) was isolated in moderate yield, identical with a sample obtained by catalytic hydrogenation [6] of uleine.

The reduction of the conjugated double bond cannot proceed through an intermediate (A) which would be formally similar to that (B) postulated [9] for the reduction of the double bond of cinnamyl alcohol. Reduction of cinnamyl alcohol was shown [9] to involve incorporation of one hydrogen from the reducing agent and one from the water used to work up the reaction. In the reduction of uleine (Ia), both hydrogens come from the complex metal hydride and none from the water used in work-up. Thus the mass-spectrometrically determined molecular weight of dihydrouleine (Va), produced by reduction of uleine with lithium aluminium hydride and work-up with either water or deuterium oxide, was 268, whilst a shift to 270 (Vb) was noted upon reduction with lithium aluminium deuteride and work-up with water or heavy water. The most reasonable scheme to explain this novel reduction appears to be:
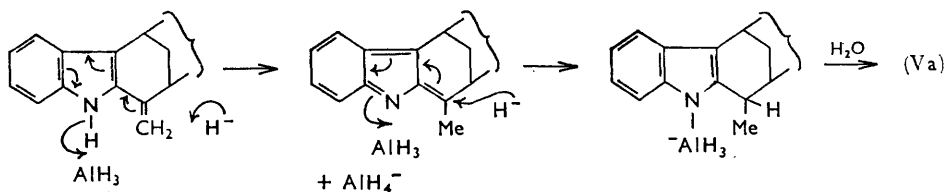
Perhaps more surprising than the gramine-type nucleophilic displacements described above are the results of treatment of uleine (Ia) under acetylation conditions, though they too can be rationalized along similar lines. Uleine with acetic anhydride–pyridine gave a crystalline N-acetyl (amide carbonyl band at 6·10 μ) acetate, the analysis of which corresponded to the acetate salt of the quaternary pyridinium compound (IIId). The salt must be formed by nucleophilic displacement at C-4, by pyridine, of an initially formed $N_b{}^+$-acyl ion.* This salt, on attempted crystallization from methanol, underwent facile nucleophilic displacement by solvent, again of the gramine type, to give (IIIe), mild acid treatment of which resulted in loss of methanol, migration of the exocyclic double bond into conjugation, and production of the carbazole (IId). The latter was converted into the known [5,6] carbazole (IIa) by stronger acid hydrolysis to (IIe) followed by N-methylation. The physical characteristics of the methoxy-amide (IIIe) agreed with the assigned structure. The ultraviolet spectrum was identical with that of uleine (Ia), and the n.m.r. spectrum showed the presence of the following protons: exocyclic methylene (5·00 and 5·37 p.p.m.), C-ethyl, 4 aromatic protons, NH, N-acetyl (2·05 p.p.m.), N-methyl (2·88 p.p.m.), and aliphatic O-methyl (3·55 p.p.m.). The benzylic proton signal was a broad singlet at 4·46 p.p.m.†

Treatment of uleine (Ia) with acetyl chloride in benzene in the presence of anhydrous potassium carbonate led directly to the carbazole (IId), which had been obtained earlier by a stepwise procedure (Ia ⟶ IIId ⟶ IIIe ⟶ IId).

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* Geissman described [8c] the reaction of gramine with refluxing acetic anhydride. The product, 3-acetoxymethyl-N-acetylindole, was visualized as being formed by nucleophilic displacement, by acetate, on the benzylic carbon atom, of an initially generated $N_b{}^+$ acylium ion.

† It is not clear why (IIIb) should occur as two C-4 isomers (see footnote on p. 2778) whereas (IIIa) and (IIIe) do not.

[9] Hochstein and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3484.

The possibility that these facile ring-openings were in some way connected with the exocyclic double bond was discounted by carrying out analogous ring-openings on dihydro-uleine (Va) methiodide. The products (VIa—d) from such ring-openings could be obtained by hydrogenation of their dehydro-counterparts (IIIa, b, c, and e). The two methoxylated derivatives (VIa and VId) were very unstable, and when left for a short time in air or more especially in acid solution in the presence of air were converted into the corresponding carbazoles (IIa and IId).

Mass Spectra

The mass spectrum (Fig. 1) of uleine (Ia) contains major peaks at m/e 237, 223, 222, 209, a group from 208 to 204, 194, and 180, as well as the molecular ion, an $(M - CH_3)$ peak $(m/e$ 251), and a peak at m/e 167. The last occurs in the spectra of all uleine derivatives and presumably represents the carbazole ion. The mass of each fragment was increased by one unit in the spectrum of uleine run in the presence of heavy water, *i.e.*, when the indolic proton had been exchanged for deuterium, showing that the indole portion of the molecule is present in each fragment. Only one of the peaks under consideration $(m/e$ 237—180) was altered in position in the spectrum of the homologue (Ib),[*] namely, a 14 mass-unit shift from m/e 237 to 251. Thus, the ion corresponding to m/e 237 in Fig. 1 is the only major fragment which retains the N-methyl group. Substantiating this is the spectrum of N_b-acetyl-N-demethyluleine (Ic),[*] in which, again, only the peak corresponding to m/e 237 in uleine is altered in position (to m/e 265). The spectrum of the amide (Ic) also shows the expected [10] peaks corresponding to loss of acetyl $(m/e$ 251) and acetamide $(m/e$ 235).

A clue to the fragmentation process leading to some of the peaks in Fig. 1 comes from the spectrum (Fig. 2) of the carbazole (IIe) which is an isomer of uleine and could be derived from it under electron-impact by unexceptional changes. One of the changes, homolytic fission of the benzylically activated C-4–N_b bond with rearrangement of the C-3 hydrogen atom (arrows in the molecular ion †), leads to the intermediate (*a*), which would readily lose the allylic methyl group, giving rise to the $(M - CH_3)$ peak $(m/e$ 251 in Fig. 1). Migration of the exocyclic double bond into the ring of (*a*) can yield the carbazole (IIe). The peaks at m/e 223 and 222, and the group from 208 to 204, common to the spectra of (Ia) (Fig. 1), (Ib), (Ic), and (IIe) (Fig. 2), can then be explained in terms of the fragmentation behaviour of the carbazole (IIe). Thus, homolytic fission at the benzylic carbon atom would give species (*b*) $(m/e$ 222), whilst bond cleavage (arrows in IIe) with transfer of the N_b-hydrogen atom would yield (*c*) $(m/e$ 223). Allylic loss of the methyl groups from (*b*) and (*c*) would then produce (*d*) $(m/e$ 208) and (*e*) $(m/e$ 207). It is noteworthy that ions of m/e 223 and 208 occur to a much smaller extent in the spectra of the carbazoles (IIa) and (IId) (Fig. 3) in which there is no N_b-hydrogen. The group of peaks from m/e 206 to 204 appears to represent further formal loss of up to three hydrogen atoms from (*e*).

Five major peaks remain to be rationalized in the spectra of uleine (Fig. 1) and its relatives (Ib) and (Ic), which do not occur appreciably for the carbazoles (IIa), (IId),

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[*] N-Demethyl-N-ethyluleine (Ib) was obtained by lithium aluminium hydride reduction of the N-acetyl derivative (Ic) of N-demethyluleine (Id), which was isolated (ref. 4) from *A. dasycarpon*.
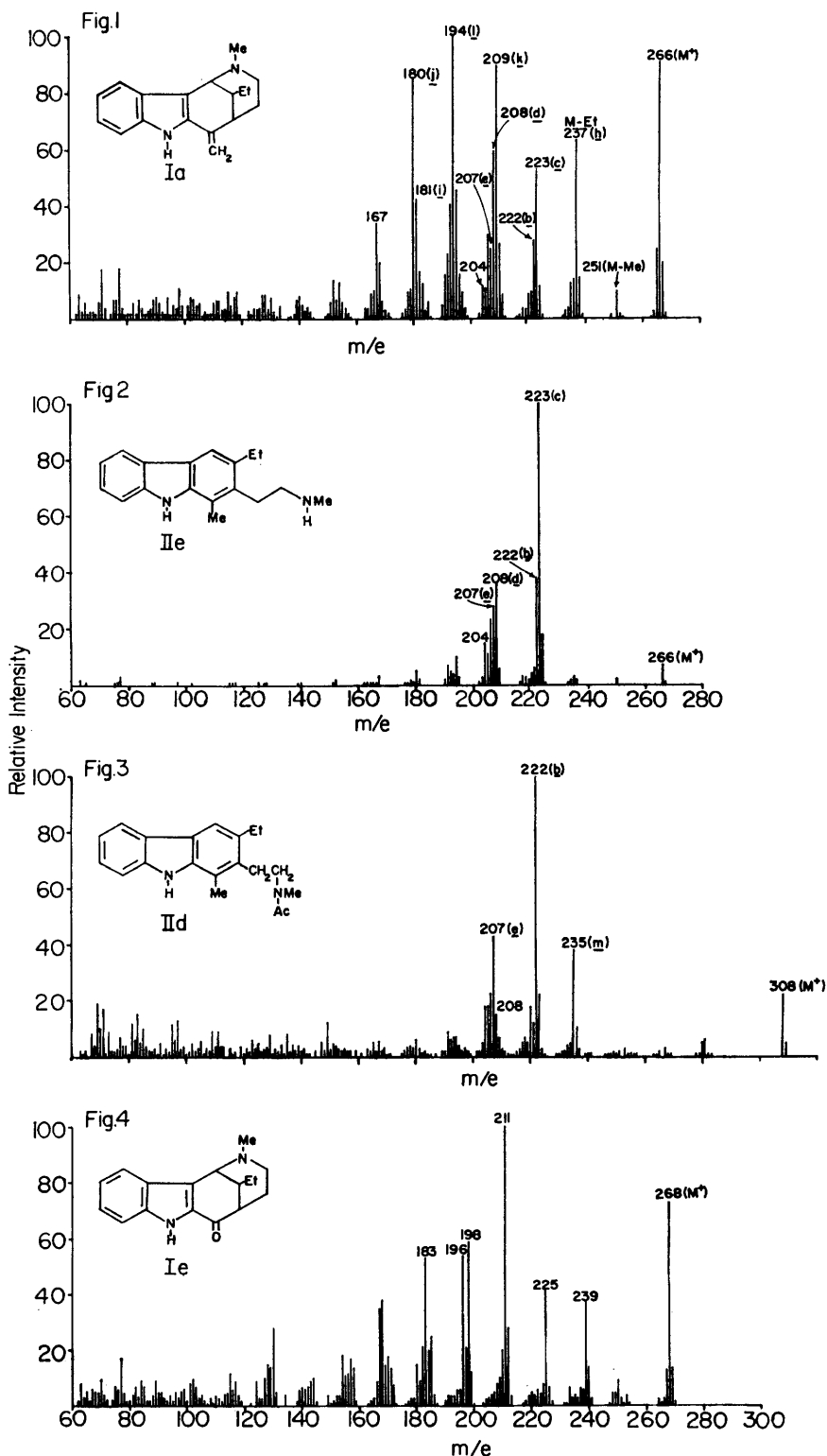
† While certainly not established, we believe that it is convenient for the rationalization of the fragmentation processes to represent the molecular ion as that species in which one of the non-bonded electrons from N_a has been abstracted. We selected N_a rather than N_b because the latter is lost in most fragment ions and it would be necessary to postulate electron shifts in order to switch the positive charge from such a molecular ion to the charge-retaining species. In order to avoid confusion with two-electron shifts, commonly depicted in organic chemistry by an arrow, we are using " fish hooks " to denote single-electron movements, *e.g.*, change from C:C to C· + ·C. See Budzikiewicz, Djerassi, and Williams, " Interpretation of Mass Spectra of Organic Compounds," Holden-Day, San Francisco, 1964, p. xii.
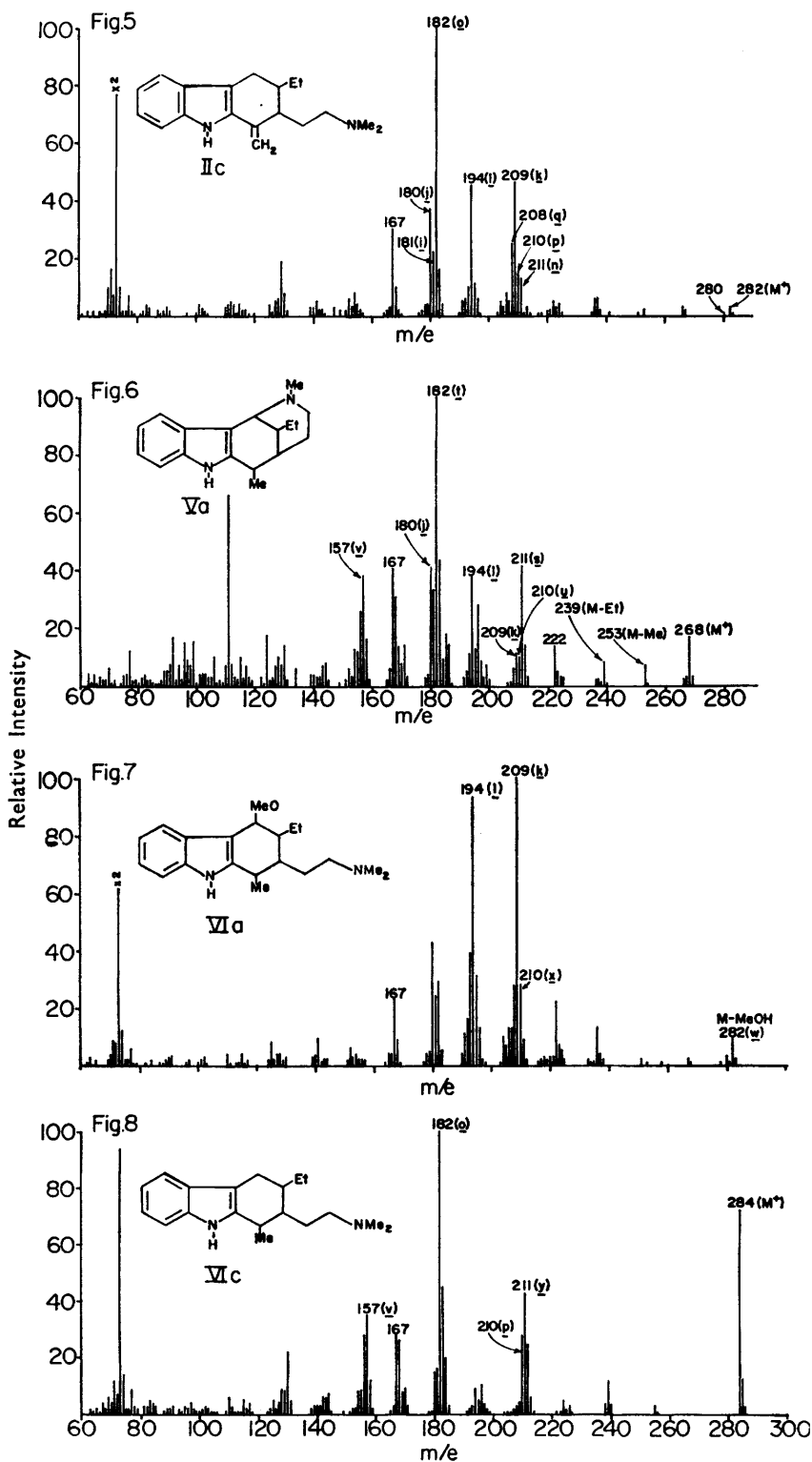
[10] See Pelah, Kielczewski, Wilson, Ohashi, Budzikiewicz, and Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, 2470, and references therein.

Mass spectra.   FIG. 1.   Uleine (Ia).   FIG. 2.   3-Ethyl-1-methyl-2-(2-methylamino-ethyl)carbazole (IIe).   FIG. 3.   2-(2-Acetylmethylaminoethyl)-3-ethyl-1-methyl-carbazole (IId).   FIG. 4.   1-Demethylene-1-oxouleine (Ie).

4 x 2

Mass spectra. Fig. 5. 2-(2-Dimethylaminoethyl)-3-ethyl-1,2,3,4-tetrahydro-1-methyl-
enecarbazole (IIIc). Fig. 6. Dihydrouleine (Va). Fig. 7. 2-(2-Dimethylamino-
ethyl)-3-ethyl-1,2,3,4-tetrahydro-4-methoxy-1-methylcarbazole (VIa). Fig. 8.
2-(2-Dimethylaminoethyl)-3-ethyl-1,2,3,4-tetrahydro-1-methylcarbazole (VIa).

(Fig. 3), or (IIe) (Fig. 2). The M — C_2H_5 fragment (m/e 237 in Fig. 1) is readily explained if some initial bond-cleavage ion takes place in the allylically activated 2—10 position, to give (f), which then loses an ethyl radical to give (g) and permit eventual formation of
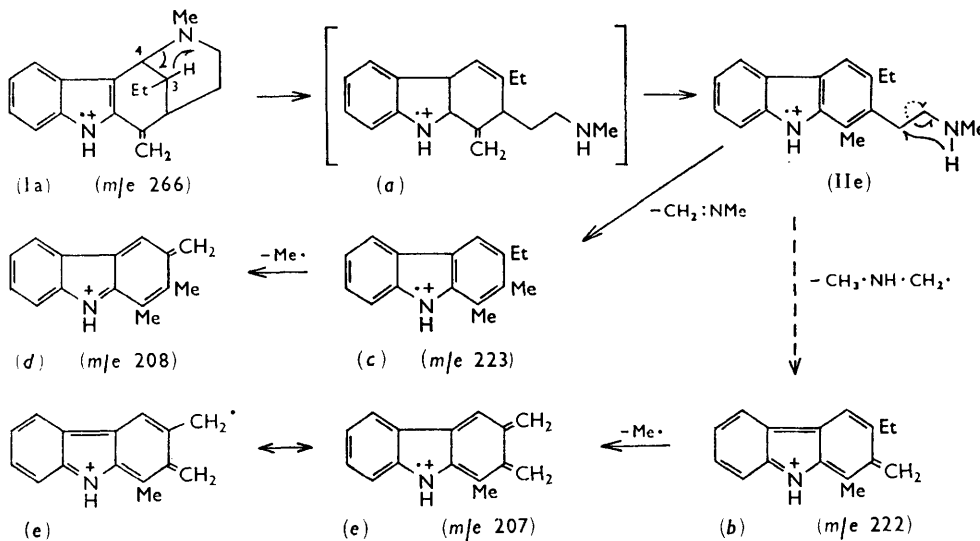
(h) (m/e 237). Alternatively, loss of the C-4 substituent with transfer of an N_b-methyl hydrogen atom from (g) would give (i) (m/e 181); subsequent benzylic loss of hydrogen from (i), or the amino-side-chain from (g), would yield a fully conjugated species (j) (m/e 180).
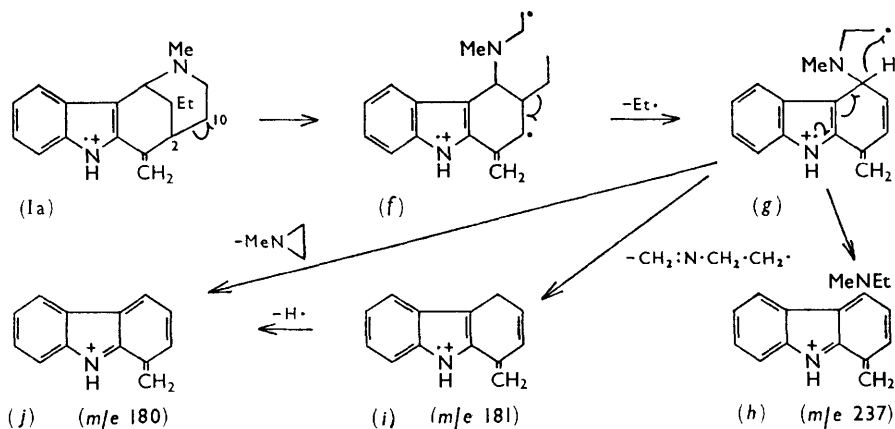

The important ion (k) (m/e 209) may arise by a hydrogen rearrangement through a six-membered intermediate [arrows in (a)] further fission of the benzylic bond with loss of a methyl radical yielding (l) (m/e 194). Thus, energetically plausible fragmentations can be suggested for most of the characteristic ions in the spectrum of uleine.
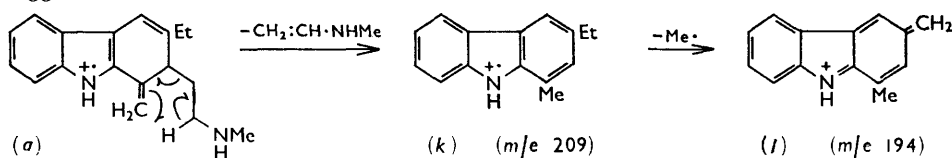
The spectrum (Fig. 3) of the *N*-acetylcarbazole (IId) shows three important peaks. The ion (*m*) (*m/e* 235) almost certainly involves the conventional [10] loss of *N*-methylacetamide [arrows in (IId)], whilst the *m/e* 222 species is identical with that in the spectrum (Fig. 2) of (IIe). The latter's intense *m/e* 223 peak is now absent, presumably because of the unavailability of a hydrogen atom on the aliphatic nitrogen, which was invoked earlier in the formation of (*c*) (*m/e* 223). The fragment (*e*) (*m/e* 207) is presumably due to loss of a methyl radical from *m/e* 222, although no metastable ion could be found to substantiate this proposal.

It is interesting that the ketone (Ie) * has a fragmentation pattern (Fig. 4) very similar to that (Fig. 1) of uleine (Ia). Major peaks, two mass units higher than those in the uleine spectrum, appear at *m/e* 268, 239, 225, 211, 196, and 183. The structures corresponding to these ions are presumably analogous to those suggested for the corresponding uleine fragments. Peaks corresponding to *m/e* 222, 208 to 204, and 180 are much less important in the spectrum (Fig. 4) of (Ie). A peak at *m/e* 198 represents a cleavage specific to the keto-compound; we cannot offer a reasonable formulation for it at present.

The mass spectra of the tetrahydro-4-methoxycarbazoles (IIIa) and (IIIe) do not show a molecular ion. The first recorded peak is at M − (R¹ + H), and since the rest of their
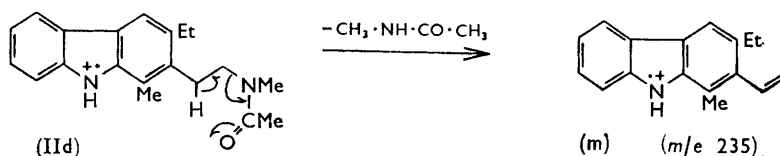
spectra are almost superimposable on those of (IIa) and (IId) (Fig. 3), respectively, it seems reasonable to assume that the first change overtaking (IIIa) and (IIIe) in a mass spectrometer is the loss of a hydrogen atom and R^1, with isomerization to a carbazole. It is to be noted that elimination of the substituent R^1 at C-4 is the same first step as that postulated to occur [(Ia) ⟶ (*a*)] in the fragmentation of uleine (Ia).
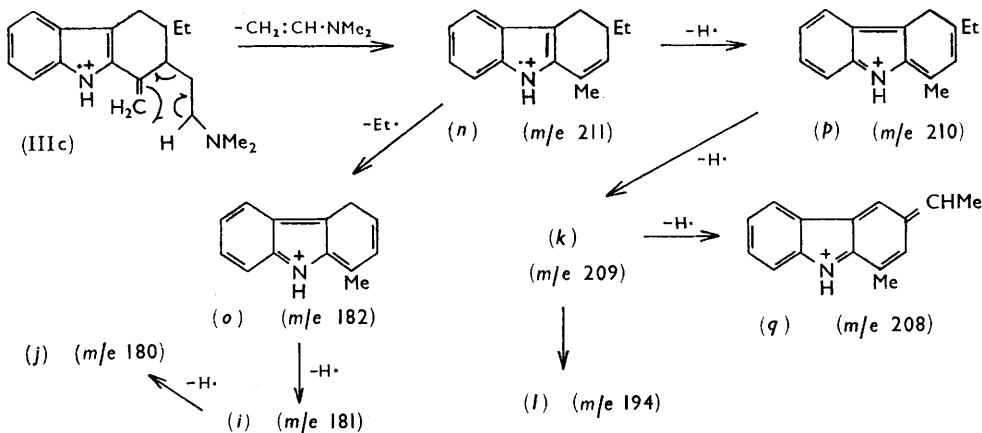
The C-4 unsubstituted tetrahydrocarbazole (IIIc) does give a molecular-ion peak (*m/e* 282 in Fig. 5) and appears to fragment similarly. Thus, if one invokes a six-membered intermediate [arrows in molecular ion (IIIc)], identical with that employed in (*a*) ⟶ (*k*), and ion (*n*) (*m/e* 211) is generated. Homolysis of the allylic bond with expulsion of an ethyl radical would yield (*o*) (*m/e* 182), which represents the second most abundant ion.

* The ketone (Ie) was isolated (ref. 4) from *A. dasycarpon*, and its structure established by interconversion with uleine (Ia).

Alternatively, (*n*) could lose a hydrogen atom or a hydrogen molecule, giving rise to the *m/e* 210 (*p*) or 209 (*k*) species, from which loss of a benzylic hydrogen atom would explain the peak at *m/e* 208 (*q*) and loss of a methyl radical the *m/e* 194 fragment (*l*). The ions at *m/e* 181 and 180 are again assigned structures (*i*) and (*j*), easily derived from (*o*) by a dehydrogenative process. A small peak at *m/e* 280 indicates dehydrogenation of the molecular ion, presumably to the carbazole (IIa), the spectrum of which then contributes to the overall spectrum.

In agreement with these assignments is the spectrum of the 4-deuterio-analogue (IIIf), in which peaks at *m/e* 209, 194, 180, and 167 are only partially moved to one higher mass number.

The nitrile function of (IIIb) does not influence in any major way the mass-spectrometric fragmentation of the molecule. The spectrum corresponds largely to that (Fig. 5) of (IIIc) with each peak moved by twenty-five units owing to the extra substituent, save only *m/e* 167 and 180, which are, as expected, only partly shifted. The reluctance to lose the elements of hydrogen cyanide [11] is to be contrasted with the facile loss of methanol from (IIIa) and (IIIe).

An interpretation of the mass-spectrometric fragmentation of dihydrouleine (Va) (Fig. 6) was made possible by the availability of dideuteriouleine (Vb), the spectrum which showed the masses of all fragments [save only the molecular ion, $M - CH_3$, $M - C_2H_5$, and *m/e* 222 (partially)] species to be shifted by only one unit. The three peaks were two mass units higher than in the spectrum (Fig. 6) of dihydrouleine (Va). Thus, one deuterium atom is lost in the formation of all the major fragments from (Va). The rationalization of this finding is implicit in the fragmentation scheme proposed below.
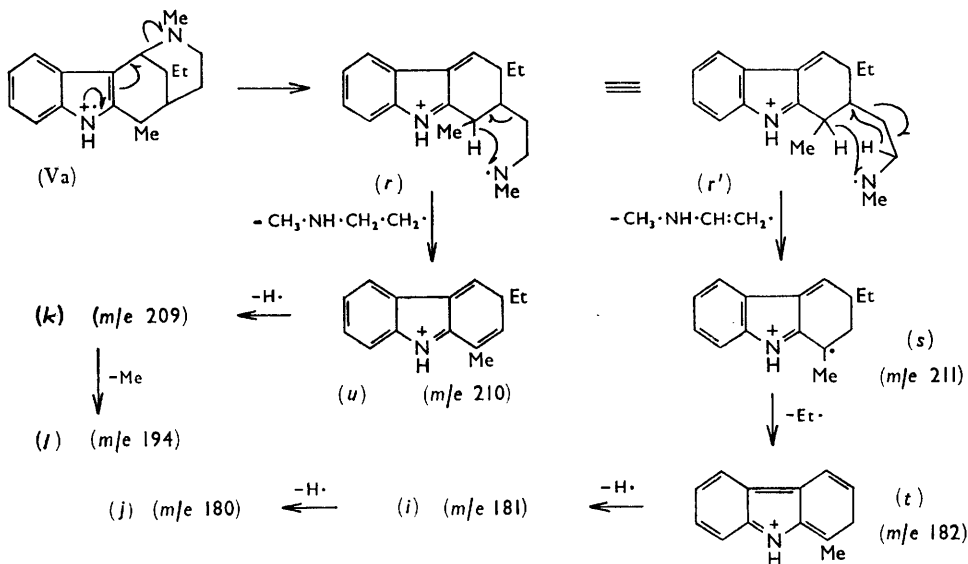
Initial cleavage of the $C-4-N_b$ bond would produce (*r*). This has an allylic ethyl group, loss of which would explain the $M - C_2H_5$ peak (*m/e* 239). Further break-up of (*r*) through abstraction in a six-membered intermediate of the C-1 hydrogen atom by N_b [arrows in (*r*)], and cleavage of the then allylically activated 2–10 bond, would lead to (*u*) (*m/e* 210), which could then lose a hydrogen radical, yielding (*k*) (*m/e* 209), the latter being the progenitor of (*l*) (*m/e* 194).

An alternative mode of further fragmentation of (*r*) [arrows in (*r'*)] could involve transfer of a C-11 hydrogen atom, and would lead to the *m/e* 211 species (*s*), allylic loss

[11] See McLafferty, *Analyt. Chem.*, 1962, **34**, 26.

of the ethyl radical then yielding the most abundant ion in the spectrum, (*t*) (*m/e* 182).
Successive loss of two hydrogen atoms from (*t*) would give ions at *m/e* 181 and 180
[(*i*) and (*j*)].

A peak at *m/e* 157 [shifted to *m/e* 159 in the 2-deuterio-analogue (Vb)], which also
appears in the spectra of the tetrahydrocarbazoles (VIb) and (VIc), appears to correspond
to fragment (*v*) (the site of positive charge and radical being unspecified).

Analogously to the methylene derivatives (IIIa) and (IIIe), the spectra of the dihydro-
products (VIa) (Fig. 7) and (VId) do not show a molecular ion, but only (M — MeOH)
fragments [(*w*) = *m/e* 282 in Fig. 7]. In each case, this ion loses hydrogen to a small
extent to give the corresponding carbazoles (IIa) and (IId) (*m/e* 280) which then con-
tribute to the overall fragmentation. More important, the initial (M — MeOH) ion (*w*)
(*m/e* 282) can undergo allylic fission of the amino-side-chain, producing the ion (*x*) (*m/e*
210) from which could be formed (*k*) (*m/e* 209) (by loss of hydrogen) and thence (*l*) (*m/e*
194) by loss of a methyl radical from (*k*).

A comparison of the spectrum (Fig. 8) of the C-4 unsubstituted tetrahydrocarbazole
(VIc) with that (Fig. 5) of its exocyclic methylene analogue (IIIc) is instructive. In
addition to the molecular ion (*m/e* 284) and peaks at *m/e* 157 (*v*) and 167, major peaks
exist in the spectrum of (VIc) at *m/e* 182 and 211. All these are increased (partially in
the cases of *m/e* 157 and 167) by one unit in the spectrum of the 4-deuterio-analogue and by
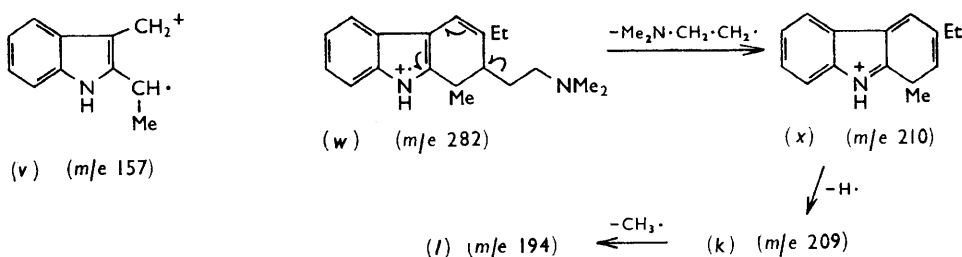
twenty-five units in the spectrum of the cyano-derivative (VIb). This illustrates again
the negligible influence of a nitrile group on the fragmentation in this series [compare
(IIIb) and (IIIc)].

Elimination of the amino-side-chain [arrows in molecular ion (VIc)] leads to (*y*) (*m/e*
211), from which loss of a hydrogen atom would give (*p*) (*m/e* 210) and expulsion of an
ethyl radical the base peak, *m/e* 182 (*o*). This ion could seccessively lose two hydrogens,
giving first (*i*) and then (*j*).
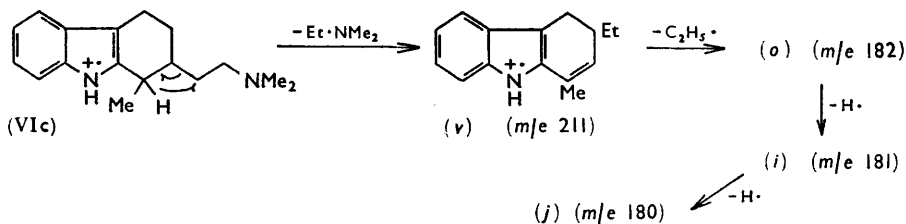
EXPERIMENTAL

Melting points were determined on a Kofler block, and all rotations were measured in chloro-
form. Thin-layer chromatography was done on silica gel " G," using ethyl acetate–benzene–
methanol–water (40:40:20:1). Methiodides and ethiodides were prepared in benzene
solution at room temperature. ·Aqueous acidic solutions were made alkaline with solid
potassium carbonate, and solutions in organic solvents were dried over anhydrous magnesium

sulphate. Mass spectra were measured in the usual fashion [10] by Drs. H. Budzikiewicz and M. Ohashi, and the n.m.r. spectra (CDCl$_3$ solution with tetramethylsilane as internal standard) by Dr. Lois J. Durham.

Reaction of Uleine (Ia) *Methiodide with Sodium Methoxide.*—Uleine methiodide [6] (200 mg.) in methanol (10 ml.) was treated with sodium methoxide [from sodium metal (250 mg.) in methanol (15 ml.)] at room temperature for 1 hr. Ether (100 ml.), then water (100 ml.), were added and the mixture was shaken. The upper layer was separated, washed twice with water, dried, and evaporated. The pure *methoxy-derivative* (IIIa) (95 mg.) was obtained as a gum by preparative thin-layer chromatography (elution of band at R_F 0·2 located by its violet fluorescence under ultraviolet light); ceric sulphate reaction: immediate green, grey-green after heating; $[\alpha]_D^{28}$ +56° (c 1·36), $\lambda_{max.}$ (CHCl$_3$) 2·88m μ, $\lambda_{max.}$ (EtOH) 298 mμ (log ε 4·29), $\lambda_{min.}$ 265 mμ (log ε 3·59), $\lambda_{infl.}$ 239 and 310 mμ (log ε 4·24, 4·27). Mass spectrum: no molecular ion but characteristic peaks at m/e 280 (56%), 266 (13), 263 (12), 249 (5), 235 (17), 222 (62), 221 (40), 220 (48), 218 (32), 208 (53), 207 (98), 206 (100), 205 (72), 204 (86), 194 (34), 191 (33), 180 (28), 167 (19), and 165 (15).

The *ethiodide* of (IIIa) had m. p. 190—195° (from acetone) (Found: C, 55·95; H, 6·7. C$_{22}$H$_{33}$IN$_2$O requires C, 56·4; H, 7·0%).

Aromatization of (IIIa) *to 2-(2-Dimethylaminoethyl)-3-ethyl-1-methylcarbazole* (IIa).—The 4-methoxy-derivative (IIIa) (223 mg.) was dissolved in methanol (5 ml.) and treated with concentrated hydrochloric acid (3 drops) at room temperature for 2 hr. The solution was poured into water (30 ml.), made alkaline, and extracted with ether. The dried organic phase was evaporated, and the residue (200 mg.) crystallized from ether–hexane, to give the carbazole (IIa), m. p. 117—119° undepressed on admixture with (IIa) obtained by Hofmann degradation [6] of uleine methiodide. Identity was confirmed by infrared and ultraviolet spectra, and thin-layer chromatographic comparison.

Reaction of Uleine (Ia) *Methiodide with Potassium Cyanide.*—Uleine methiodide (300 mg.) in methanol (20 ml.) was stirred with potassium cyanide (300 mg.) at room temperature for 48 hr. The mixture was poured into water (100 ml.) and extracted with ether. The dried ethereal layer gave the *cyanide* (IIIb) as a glass (105 mg.), which was purified by preparative thin-layer chromatography (elution of band at R_F 0·1, located by its violet fluorescence under ultraviolet light); ceric sulphate reaction: dirty pink, pale brown after heating; $[\alpha]_D^{27}$ +44° (c 1·77), $\lambda_{max.}$ (CHCl$_3$) 2·86m, 4·47w, 6·10w, 6·18w μ, $\lambda_{max.}$ (EtOH) 220, 303 mμ (log ε 4·22, 4·18), $\lambda_{min.}$ 263 mμ (log ε 3·65), $\lambda_{infl.}$ 238 mμ (log ε 4·10). Mass spectrum: m/e 307 (7%) (molecular ion), as well as typical peaks at m/e 278 (3), 261 (2), 247 (4), 236 (87), 234 (69), 219 (48), 207 (100), 205 (39), 192 (26), 182 (19), 180 (26), and 167 (16).

Lithium Aluminium Hydride Reduction of Uleine (Ia) *Methiodide.*—Uleine methiodide (180 mg.) was reduced with excess lithium aluminium hydride in refluxing tetrahydrofuran for 15 min. The solution was cooled, and remaining hydride was decomposed with the minimum amount of water. The slurry was filtered, the precipitate washed with ether, and the filtrate dried and evaporated. The residue (140 mg.) was chromatographed on neutral alumina (activity II). Elution with benzene–ether (19 : 1) gave *2-(2-dimethylaminoethyl)-3-ethyl-1,2,3,4-tetrahydro-1-methylenecarbazole* (IIIc) as a colourless gum with the following properties; ceric sulphate reaction: immediate green, dark blue after heating; $[\alpha]_D^{26}$ +38° (c 0·99), $\lambda_{max.}$ (CHCl$_3$) 2·88m, 6·12m, and 6·19m μ, $\lambda_{max.}$ (EtOH) 303, 312 mμ (log ε 4·21, 4·20), $\lambda_{min.}$ 268 mμ (log ε 3·59), $\lambda_{infl.}$ 243 mμ (log ε 4·07). The n.m.r. spectrum showed signals at 0·88 (3-proton triplet, J = 6 c./sec., CH_3·CH$_2$), 2·03 [6-proton singlet, $(CH_3)_2$N], 4·90 and 5·18 (two 1-proton singlets, CH_2:), 6·90—7·60 (4 protons, HAr), and 8·17—8·41 p.p.m. (1 proton, HN). The mass spectrum is Fig. 5.

The corresponding 4-deuterio-derivative (IIIf) was prepared and purified exactly as above except that lithium aluminium deuteride instead of lithium aluminium hydride was employed. Mass spectrum: m/e 283 (15%) (molecular ion), as well as m/e 237 (7), 225 (9), 210 (36), 209 (63), 195 (42), 194 (69), 183 (100), 182 (35), 181 (44), 168 (29), and 167 (17).

Reaction of Uleine with Acetic Anhydride–Pyridine.—Uleine (200 mg.) was dissolved in pyridine (3 ml.), and a mixture (5 ml.) of acetic anhydride and pyridine (1 : 1) was added. The solution was left at room temperature for 24 hr. and the solvents were removed under reduced pressure. The residue, on addition of acetone, crystallized, to give the pyridinium *amide* (IIId), m. p. 155—160°, which gave a dirty green ceric sulphate reaction, turning to brownish-green after heating, $\lambda_{max.}$ (Nujol) 3·03m and 6·10vs μ, $\lambda_{max.}$ (EtOH) 305 mμ (log ε 4·22), $\lambda_{min.}$ 263 mμ

(log ε 3·16), $\lambda_{infl.}$ 240 mμ (log ε 4·14) (Found: C, 72·7; H, 8·0; N, 9·4. $C_{27}H_{33}N_3O_3$ requires C, 72·45; H, 7·4; N 9·4%).

When (IIId) was heated in methanol for 15 min., or treated with excess of sodium methoxide in methanol at room temperature for 0·5 hr., it was quantitatively converted into the 4-*methoxy-derivative* (IIIe), m. p. 173—175° (from ether). This substance gave the same ceric sulphate reaction as (IIId), and had $[\alpha]_D^{28}$ +49° (c 1·02), $\lambda_{max.}$ (CHCl₃) 2·88w, 3·06w, and 6·15vs μ, $\lambda_{max.}$ (EtOH) 303 mμ (log ε 4·23), $\lambda_{min.}$ 262 mμ (log ε 3·41), $\lambda_{infl.}$ 240 mμ (log ε 4·19). The mass spectrum did not exhibit a molecular ion, but showed typical peaks at m/e 308 (17%), 265 (2), 235 (38), 222 (100), 220 (9), 207 (19), 194 (4), and 180 (3) (Found: C, 73·7; H, 8·0; N, 8·3. $C_{21}H_{28}N_2O_2$ requires C, 74·1; H, 8·3; N, 8·2%).

Reaction of Uleine (Ia) *with Acetyl Chloride.*—Uleine (50 mg.) in benzene (20 ml.) was treated with acetyl chloride (50 mg.) in benzene (10 ml.) in the presence of anhydrous potassium carbonate (1 g.) with stirring for 1 hr. Water (50 ml.) was added while stirring was continued. The two phases were separated, the aqueous layer was extracted with ether, and the combined organic layers were dried and evaporated. The residue (41 mg.) gave the *amide* (IId), m. p. 208—209° (from ether), $\lambda_{max.}$ (CHCl₃) 2·88w and 6·12vs μ, $\lambda_{max.}$ (EtOH) 217, 241, 250, 261, 298, 328, and 341 mμ (log ε 4·47, 4·66, 4·49, 4·27, 4·31, 3·14, and 3·08), $\lambda_{min.}$ 223, 257, and 272 mμ (log ε 4·46, 4·21, and 3·55), $\lambda_{infl.}$ 234 and 288 mμ (log ε 4·59 and 4·06). The n.m.r. spectrum exhibited signals at 1·35 (3-proton triplet, $J = 7$ c./sec. $CH_3 \cdot CH_2$), 2·02, 2·12, 2·15 (three singlets corresponding in all to 3 protons, $CH_3 \cdot CO$), 2·52, 2·62 (two singlets corresponding in all to 3 protons, $CH_3 \cdot N$), 3·02 (3-proton singlet, $CH_3 \cdot Ar$), 7·00—8·30 (5 protons, HAr and 1 proton HN). The mass spectrum is Fig. 3 (Found: C, 77·75; H, 7·7; N, 9·0. $C_{20}H_{24}N_2O$ requires C, 77·9; H, 7·8; N, 9·1%).

The identical carbazole (IId) was obtained when the tetrahydro-4-methoxy-1-methylene derivative (IIIe) (30 mg.) was dissolved in methanol (5 ml.) containing concentrated acid (3 drops) and left for 1 hr. at room temperature. The solution was then poured into water (20 ml.), made alkaline, and extracted with ether. The ether layer, on evaporation, gave a semi-crystalline residue (25 mg.) which was recrystallized from ether to give (IId), m. p. 207—208°, identical in all respects with the specimen described above.

3-*Ethyl-1-methyl-2-(2-methylaminoethyl)carbazole* (IIe).—The amide (IId) (55 mg.) was heated on a steam-bath with methanol (3 ml.) and concentrated hydrochloric acid (5 ml.) for 4 days. The solvent was removed under reduced pressure, and the residue dissolved in water. The aqueous solution was washed with ether, made alkaline, and extracted with ether. The dried ethereal extract gave a gum (40 mg.) which was purified by preparative thin-layer chromatography (elution of band at R_F 0·05) and crystallized from ether, m. p. 136—137°, $\lambda_{max.}$ (CHCl₃) 2·88m μ, $\lambda_{max.}$ (EtOH) 240, 250, 261, 298, 331, 346 mμ (log ε 4·39, 4·23, 4·03, 4·05, 3·34, 3·27), $\lambda_{min.}$ 247, 257, 272, 342 mμ (log ε 4·22, 3·57, 3·51, 3·23), $\lambda_{infl.}$ 234, 286 mμ (log ε 4·32, 3·84). The mass spectrum is Fig. 2.

2-(2-*Dimethylaminoethyl*)-3-*ethyl-1-methylcarbazole* (IIa).—The N-methyl hydriodide of (IIe) was prepared in the usual manner, by treatment with methyl iodide, dissolved in water, and extracted with ether after being made alkaline. The dried ether extract was evaporated, and the residue crystallized from ether–hexane, to give the carbazole (IIa), m. p. 117—119°, identical (mixed m. p. and infrared spectra) with the Hofmann degradation product [6] of uleine methiodide which was prepared by the following modified procedure. Uleine methiodide was heated in methanol with aqueous potassium hydroxide in a current of nitrogen on a steam-bath over-night. The methanol was boiled off and the aqueous suspension extracted with ether, to give the carbazole (IIa) (95%), identical (m. p., mixed m. p., infrared, and ultraviolet spectra) with a sample prepared by Schmutz's procedure.[6] The mass spectrum exhibited a molecular ion peak at m/e 280 (62%), as well as typical peaks at m/e 236 (15), 222 (66), 221 (32), 220 (26), 218 (24), 217 (23), 208 (34), 207 (100), 206 (99), 205 (65), 204 (87), 194 (23), 192 (30), 191 (45), 180 (27), and 167 (21).

Lithium Aluminium Hydride Reduction of Uleine (Ia) *to Dihydrouleine* (Va).—Uleine (200 mg. vacuum-dried at 100° for 3 hr.) was stirred in ether (30 ml.) with excess of lithium aluminium hydride for 48 hr. Remaining hydride was destroyed by addition of the minimum of water, and the slurry was filtered. The filtrate and ether washings of the precipitate were dried and evaporated. The residue (185 mg.) was crystallized from methanol, to give dihydrouleine (Va), m. p. 84—99°, undepressed on admixture with dihydrouleine [6] prepared by catalytic reduction of uleine. The substance gave a grey colour with ceric sulphate which turned dirty green after

heating. The mass spectrum is Fig. 6. The dideuterio-analogue (Vb) was prepared exactly as above except that lithium aluminium deuteride was used in place of lithium aluminium hydride. The mass spectrum exhibited peaks at m/e 270 (52%) (molecular ion), 255 (17), 241 (17), 239 (17), 223 (25), 222 (23), 213 (48), 212 (94), 211 (33), 210 (38), 197 (32), 196 (32), 195 (39), 184 (74), 183 (100), 182 (50), 181 (43), 168 (50), 167 (32), 159 (50), 158 (37), and 157 (34).

Reaction of Dihydrouleine (Va) *Methiodide with Sodium Methoxide.*—Dihydrouleine methiodide (150 mg.) was treated with sodium methoxide (from 200 mg. of sodium) in methanol (5 ml.) at room temperature for 0·5 hr. Ether (100 ml.) and water (100 ml.) were added, and the ether layer was separated, washed with water, dried, and evaporated. The residual (VIa) (95 mg.) was homogeneous on thin-layer chromatography, and was employed as such for physical measurements, $[\alpha]_D^{28}$ −18° (c 0·17), $\lambda_{max.}$ (EtOH) 227, 282, 289 mμ (log ε 4·56, 3·95, 3·92), $\lambda_{min.}$ 252, 286 mμ (log ε 3·74, 3·91). The n.m.r. spectrum contained signals at 1·00 ($CH_3 \cdot CH_2$), 1·40 (3-proton doublet, $J = 7$ c./sec., $CH_3 \cdot CH$), 2·25 [6-proton singlet, $(CH_3)_2N$], 3·35 and 3·45 (two singlets, 3 protons, CH_3O), 4·50—4·70 (a proton, β-indole-$CH \cdot O$), 6·80—7·30 p.p.m. (4 protons, HAr). The mass spectrum is Fig. 7. The substance was easily converted into the fully aromatic carbazole (IIa) by exposure to air.

Reaction of Dihydrouleine (Va) *Methiodide with Potassium Cyanide.*—Dihydrouleine methiodide (200 mg.) was heated under reflux with potassium cyanide (200 mg.) in methanol (20 ml.) for 24 hr. The methanol was boiled off and the residue partitioned between ether and water. The dried ether layer was evaporated to give the *cyanide* (VIb) as a glass (88 mg.) which was obtained pure by preparative thin-layer chromatography (elution of band at R_F 0·1). The substance gave a yellow ceric sulphate reaction, turning pinkish-brown after heating, and had $[\alpha]_D^{28}$ −4° (c 0·96), $\lambda_{max.}$ (CHCl$_3$) 2·99m, 4·48w μ, $\lambda_{max.}$ (EtOH) 223, 281, 288 mμ (log ε 4·39, 3·80, 3·74), $\lambda_{min.}$ 246, 286 mμ (log ε 3·50, 3·70). The n.m.r. spectrum contained signals at 1·00 (ill-defined 3-proton triplet, $CH_3 \cdot CH_2$), 1·35 (3-proton doublet, $J = 7$ c./sec., $CH_3 \cdot CH$), 2·27 [6-proton singlet, $(CH_3)_2N$], 4·15 (1 proton, β-indole-$CH \cdot CN$), 6·95—7·80 (4 protons, HAr), and 8·10—8·25 (1 proton, HN) p.p.m. The mass spectrum showed a molecular ion peak at m/e 309 (100%), as well as characteristic peaks at m/e 280(22), 264 (15), 253 (17), 236 (71), 235 (60), 222 (17), 219 (18), 211 (31), 209 (44), 208 (47), 207 (95), 194 (38), 192 (31), 182 (67), 181 (33), 180 (31), and 167 (32).

Lithium Aluminium Hydride Reduction of Dihydrouleine (Va) *Methiodide.*—Dihydrouleine methiodide (100 mg.) was reduced with excess of lithium aluminium hydride in refluxing tetrahydrofuran (10 ml.) for 15 min. The cooled solution was treated with water, filtered, and the filtrate and ether washings of the precipitate were dried and evaporated. The residue (60 mg.) was purified by preparative thin-layer chromatography (elution of band at R_F 0·2), to give the pure *tetrahydrocarbazole* (VIc), m. p. 118—120° (from ether–hexane) (grey ceric sulphate reaction, pale brown after heating), $[\alpha]_D^{28}$ −52° (c 5·66), $\lambda_{max.}$ (CHCl$_3$) 2·89m μ, $\lambda_{max.}$ (EtOH) 228, 285, 291 mμ (log ε 4·52, 3·98, 3·95), $\lambda_{min.}$ 249, 288 mμ (log ε 3·68, 3·94). The n.m.r. spectrum showed signals at 0·97 (ill-defined 3-proton triplet, $CH_3 \cdot CH_2$), 1·33 (3-proton doublet, $J = 7$ c./sec., $CH_3 \cdot CH$), 2·23 and 2·27 [two 3-proton singlets, $(CH_3)_2N$], 6·90—7·60 (4 protons, HAr), and 7·65—7·85 p.p.m. (1 proton, HN). The mass spectrum is Fig. 8.

The 4-deuterio-derivative (VIe) was prepared exactly as above by employing lithium aluminium deuteride. Its mass spectrum showed a molecular ion peak at m/e 285 (74%), as well as characteristic peaks at m/e 256 (4), 240 (8), 239 (8), 225 (4), 212 (37), 211 (20), 197 (8), 195 (7), 184 (25), 183 (100), 182 (23), 181 (15), 169 (18), 168 (25), 158 (28), and 157 (26).

Reaction of Dihydrouleine (Va) *with Acetic Anhydride–Pyridine.*—Dihydrouleine (110 mg.) was kept at room temperature overnight with 1 : 1 acetic anhydride–pyridine (5 ml.). The solvent was removed under a vacuum at room temperature, and the residue was exposed to excess sodium methoxide in methanol (5 ml.) at room temperature for 0·5 hr. The solution was partitioned between ether (100 ml.) and water (100 ml.), and the ether layer was separated, washed with water, dried, and evaporated. The residue (90 mg.) was purified by preparative thin-layer chromatography (elution of band at R_F 0·5), to give the pure 4-*methoxy-amide* (VId) as a gum, $[\alpha]_D^{27}$ +25° (c 0·74), $\lambda_{max.}$ (CHCl$_3$) 2·99m and 6·16vs μ. Its mass spectrum exhibited no molecular ion but contained characteristic peaks at m/e 310 (69%), 281 (41), 274 (6), 263 (7), 251 (8), 236 (23), 234 (24), 222 (53), 210 (61), 209 (53), 208 (43), 194 (100), 182 (51), 181 (57), 180 (63), and 167 (36).

Exposure to air converted (VId) into the fully aromatic carbazole (IId), identified by ultra-violet and infrared spectra and mixed m. p.

Catalytic Hydrogenations of the Tetrahydro-1-methylenecarbazoles (III).—Samples (10 mg.) of (IIIa), (IIIb), (IIIc), and (IIIe) were hydrogenated in ethanol over pre-reduced Adams catalyst at room temperature for 3 hr. The products obtained by filtration and evaporation were identified as (VIa), (VIb), (VIc), and (VId), respectively, by comparison of their ultraviolet and infrared spectra and thin-layer chromatographic behaviour, and in the case of (VId), also by mixed m. p.

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