This study was supported in part by a Grant in Aid for Fundamental Scientific Research from the Ministry of Education, to which the authors are grateful.

Summary

Commercial DAHG J.P. was kept in various concentrations of aqueous ammonia and the following results were obtained.

1. When the sample was aged in aqueous ammonia, a temporary acceleration of the neutralizing rate was observed at an early stage of the aging process, as was similar to the results obtained in the previous paper.

2. The process of aging was composed of two steps: an increase of the diffraction around 36°-42° of 2θ value and an appearance and development of the peak at 18°-20° of 2θ. The former is considered to be related with the temporary acceleration of the neutralizing rate.

3. Depending on the concentration of aqueous ammonia, the aging product was different, and especially in the case of 28% aqueous ammonia, it resembled to nordstrandite.

4. The growth rate of crystal on the aging, in the case of 28% aqueous ammonia, was explained by the existing experimental equation, i.e., by equation (1).

5. The infrared absorption around 3400 cm⁻¹ was sharp compared with that of the aged sample in various atmosphere under relative humidity in the previous paper, and it was recognized to be shifted remarkably to 3700 cm⁻¹.

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The mass spectrum of 1-(2-hydroxybenzyl)-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (I, R=H), a member of benzylisoquinoline alkaloids, has been examined by Djerassi and his collaborators, who reported that the compound (I, R=H)
showed two characteristic peaks at m/e 178 and m/e 163. The base peak at m/e 178 is assigned to II (R=H) formed by fission of a bond which was doubly benzylic and ρ to the nitrogen atom and the peak at m/e 163 formed by loss of a methyl group from the peak at m/e 178. Also the similar behavior has been observed in the mass spectrum of its O-methyl ether (I, R=CH₃).

This paper deals with the fragmentation mechanism of some small but recognisable peaks in the mass spectra of several benzyltetrahydroisoquinoline alkaloids, using the deuterium exchange reaction of aromatic protons and the mass spectrometric shift technique on aromatic substituents.

A typical member of coclaurine type benzylisoquinoline alkaloids is N,O,O-trimethylcoclaurine (II), whose mass spectrum is shown in Fig. 1. The most abundant fragment in the spectrum occurs at m/e 206 (a), arising from the fission of a benzylic position. The peak at m/e 191 (b) is formed by the loss of a methyl radical from one of the methoxyl function in the fragment a, and consists of the two species, b (i) and b (ii). This is verified by the fragmentations of compounds (V) and (V) which exhibit two metastable peaks at m/e 180.0 (194²/209=180.0 : elimination of methyl radical from the fragment (m/e 209) corresponding to a) and at m/e 174.5 (191²/209=174.5 : elimination of trideuteromethyl radical). Since b is an odd-electron ion, it can further lose a hydrogen atom to produce a stable even-electron ion c (m/e 190), and the relative intensity of the peak m/e 190 (c) is greater than the fragment m/e 191 (b). This fragmentation sequence a→b→c is supported by the existence of metastable ions (see Table II).

Further decomposition of ion c is schematically illustrated by the sequence c→d→e; i.e. the loss of carbon monoxide from the dienone type ion c can furnish d (m/e 162), which in turn gives rise to the fragment e (m/e 132) by the elimination of a formaldehyde.

As shown in Table I, fragments a, b, c, d, and e occur at the same mass number in the spectra of all compounds having the partial structure of N-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. Those fragments are increased by one mass unit in the spectrum of compound (VII) which is the 8,3',5'-trideuterated analogue of N,O,O-trimethylcoclaurine (II).

The second class of coclaurine type alkaloids is represented by the compounds (X) and (XI), which carry no N-methyl group. The mass spectra of these compounds are characterized

![Fig. 1. Mass Spectrum of N,O-O-Trimethylcoclaurine (II)](image-url)
Chart 1. Fragmentation Mechanism of \(N,O,O\)-Trimethylcoclarine (III)

<table>
<thead>
<tr>
<th>Compound</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
<th>VIII</th>
<th>IX</th>
<th>X</th>
<th>XI</th>
<th>XII</th>
<th>XIII</th>
<th>XIV</th>
<th>XV</th>
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<td>297</td>
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<td>191</td>
<td>177</td>
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\(a\) The structure of fragments A, B, ..., and R correspond to those of ions a, b, ..., and r in Chart I, respectively.
by the displacement of the peaks at m/e 206, 191, 190, 162, 132 of N,O,O-trimethylcoclaurine (Ⅲ) to lower mass number by 14 mass units (m/e 192, 177, 176, 148, 118) (Table I). Moreover, the deuterium exchange of hydrogen atom attached to the secondary nitrogen causes the shift of these peaks by one mass unit.

These results provide the conclusive proof for the proposed fragmentation mechanism shown in Chart 1.

Similarly, compounds (XⅢ) and (XⅣ) which have one methoxyl group at the position of C(6) or C(7), exhibit an analogous fragmentation behavior. The fragments corresponding to a, b, and c occur at 30 mass units lower than those in Fig. 1, because of fewer methoxyl substituent. However, no practical difference due to the change of location of the substituent is observed. With the compound (XⅤ), further 14 mass units shift is observed, which is associated with the hydroxyl substituent instead of methoxyl group.

![Chemical structures](image)

Additional peaks in the mass spectrum (Fig. 1) of N,O,O-trimethylcoclaurine (Ⅲ) deserve comment. They occur at m/e 121, 91, and 65. These peaks are typical of compounds having the partial structure of β-methoxybenzyl group. The peak at m/e 121 is displaced by 30 mass units in the case of laudanosine (K) owing to an additional methoxyl group. In compound (Ⅶ), a deuterium-labeled derivative, the fragment at m/e 121 is also displaced by 2 mass units, and in compound (Ⅵ) having O-trideuteromethyl group at C(4') by 3 mass units. With compounds (Ⅻ) and (XⅡ), bearing no substituent in 1-benzyl grouping, 30 mass units shift towards lower mass number is observed. Therefore,
the m/e 121 ion in the mass spectrum of III (Fig. 1) can be represented by p. This affords the peaks at m/e 91 and m/e 65 by the successive elimination of formaldehyde and acetylene.

The mass spectrum of compound (XVI) which have ethoxyl group in stead of methoxyl group is shown in Fig. 2.

![Diagram of molecular structures and fragmentation pathways](chart_2.png)

The peaks at m/e 220, 121, and 91 must be associated with fragments a', p, and q, respectively. The fragments f and j (m/e 192) arise from the loss of ethylene with hydrogen rearrangement through a four or six-membered intermediate. The ion
m/e 191 is formed by elimination of an ethyl radical from fragment a'. The fragment f can lose a methyl radical, furnishing the ion g (m/e 177), which suffers the successive loss of a hydrogen and carbon monoxide (m/e 148, h). On the other hand, the ions i and j are decomposed to the more stabilized fragment k (m/e 190) by the loss of one or two hydrogen atoms. Subsequent elimination of carbon monoxide and formaldehyde from the fragment k furnishes the ion m/e 162 (l) and m/e 132 (m). Also with compound (XVII), analogous feature is observed.

**Experimental**

The mass spectra measured on a Hitachi Mass Spectrometer Model RMU 6 C and/or 6 D equipped with an all-glass inlet system: ion accel. voltage 1800 V; chamber voltage 70 eV; total emission 80 μA; target current 40 μA; evap. temp. 190°.

**Armepavine Trideutero-O-methyl Ether (VI)**—A diazomethane solution in dioxane (6 ml.)-D₂O (1 ml.) was prepared according to the description of Eggers, *et al.*² To this solution was added slowly a solution of armepavine (100 mg.) in a dioxane (2 ml.)-D₂O (1 ml.) with stirring and allowed to stand overnight. The solvent was evaporated *in vacuo* and the residue was dissolved in 5% HCl. The acid solution was washed with ether, made alkaline with NH₄OH and extracted with ether. The combined ether extract was washed successively with 5% NaOH aq. solution and with H₂O, dried over anhyd. K₂CO₃ and evaporated. An oily product was obtained in quantitative yield. NMR(CDCl₃) signals in methoxyl proton region: 6.18 τ (3H); 6.45 τ (3H). The compounds (V) and (V) were prepared from N-methylisococlaurine 4'-methyl ether and N-methylcoclaurine 4'-methyl ether in the same manner.

**N,O,O-Trimethylcoclaurine-d₃(VII)**—A solution of N-methylcoclaurine (150 mg.) in 5% NaOD-D₂O (1.5 ml.) were heated in a sealed tube at 140° for 20 hr. The alkaline solution was acidified with dil. HCl, washed with ether, made alkaline with NH₄OH and extracted with ether. The ether extract was washed with H₂O, dried over anhyd. K₂CO₃ and evaporated. The crystalline product (140 mg.) was dissolved in MeOH and was treated with diazomethane at room temperature for a day. Usual treatment of the product yielded a non-phenolic base as a colorless oil. NMR(CDCl₃) signals in aromatic proton region: 3.54 τ (1H); 2.99 τ (2H).

**Summary**

The mass spectra of several benzylisoquinoline alkaloids were examined and the fragmentation mechanism was discussed.

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