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SYNTHESES OF DIASTEREOISOMERIC RACEMATES OF MELANTHIOIDINE FOR DETERMINATION OF ITS STRUCTURE BY MASS SPECTROMETRY

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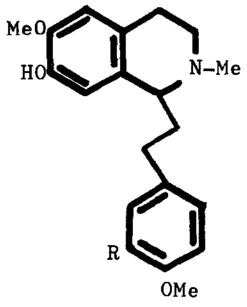
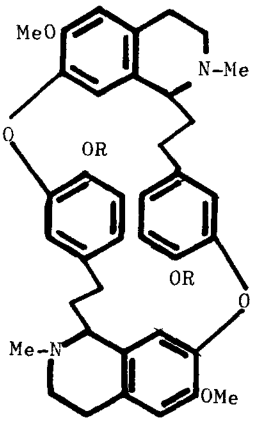
Melanthioidine (II), m.p. 142 - 144°, occurs in the leaves and corms of Androcymbium melanthioides which grows in Southern and Eastern Africa. In 1962, Santavy, et al.[1] proposed the molecular formula of $C_{42}H_{50}O_7N_2$ by molecular weight determination. Afterwards it has been reported by Battersby, et al.[2] that the structure of melanthioidine (II), $C_{38}H_{42}O_6N_2$, has a novel structure based upon the 1-phenethylisoquinoline (I) system by spectral elucidation. In a previous paper[3] a synthesis of diastereoisomeric racemates of OO-dibenzylmelanthioidine (III) by Ullmann reaction of 1-(3-bromo-4-methoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (Ia) has been reported.

The purpose of the present investigation was to study the hydrolysis of the diastereoisomeric racemates of OO-dibenzylmelanthioidine (III), eventually leading to the synthesis of diastereoisomeric racemates of melanthioidine, whose structure (II) was also elucidated by its mass spectrum.



I : R = H
Ia : R = Br



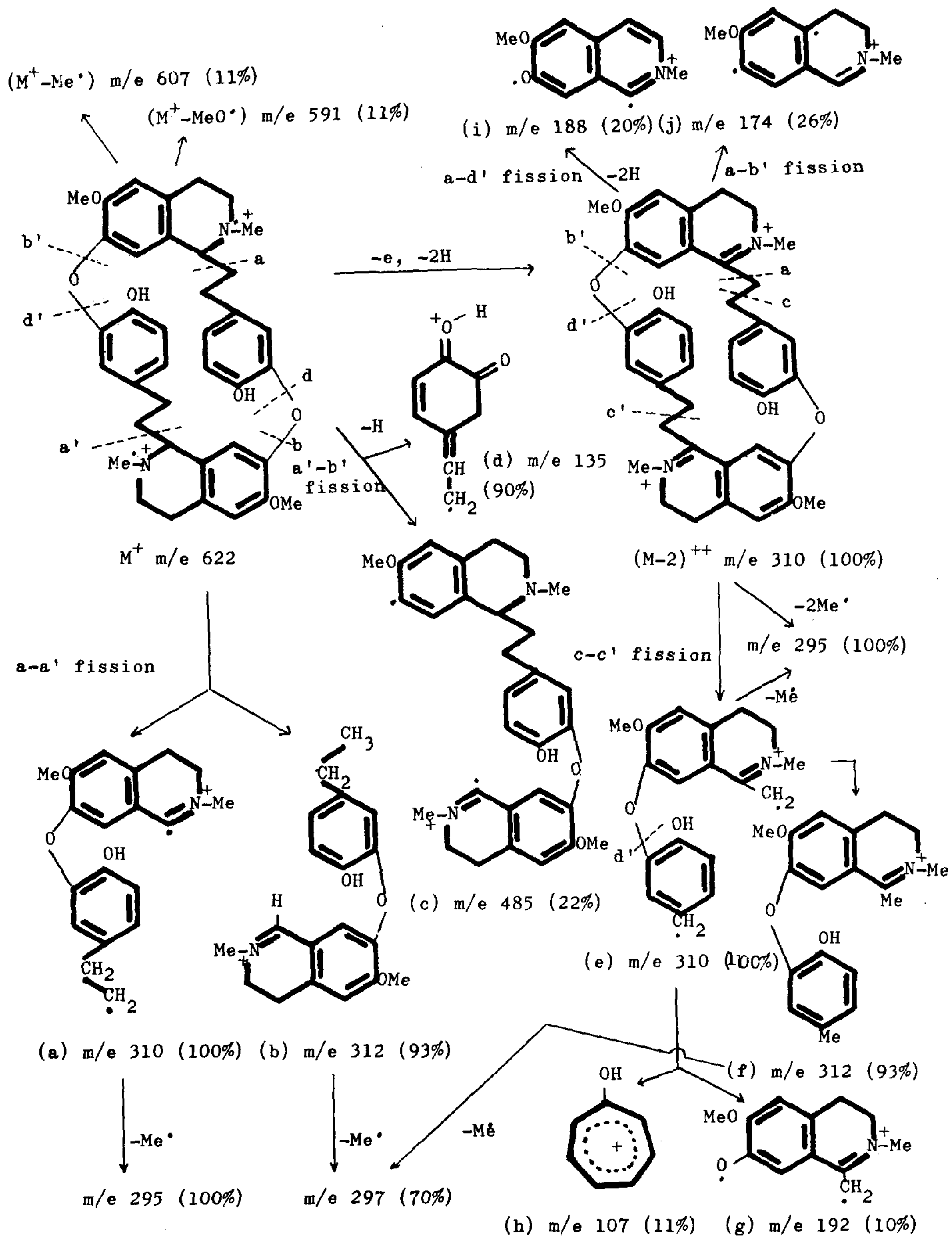
II : R = H
III : R = CH_2Ph

Debenzylation of (III) by refluxing with a mixture of ethanol and concentrated hydrochloric acid (1:1) for 5 hr. afforded the diastereoisomeric racemates of (II), whose recrystallisation from ethyl acetate gave a pale pink powder, m.p. 202 - 205° (Found: C, 70.69; H, 7.19. $C_{38}H_{42}O_6N_2$, $CH_3CO_2C_2H_5$ requires C, 70.96; H, 7.09%).

The infrared spectrum (in KBr) of (II) showed maxima at 1735 (ester C=O) $cm.^{-1}$ and the characteristic absorption bands at 696 and 733 $cm.^{-1}$ due to mono-substituted benzene in case of a starting material (III) have been disappeared. On the other hand the NMR spectrum (in $CDCl_3$) of (II) showed the protons (6H) of methoxyl groups at 6.17 and 6.21 τ, two N-methyl protons at 7.57 τ, and ten aromatic protons at 3.1 - 3.5 τ. Furthermore, the characteristic signals of ethyl acetate as crystallisation solvate was observed at 8.76 τ (3H, triplet, $C\underline{H}_3CH_2-$, J=9 c.p.s.), 7.90 τ (3H, singlet, $C\underline{H}_3CO-$), and 4.89 τ (2H, quartet, $CH_3C\underline{H}_2-$, J=9 c.p.s.). Thus, the signals in the NMR spectrum of our synthetic sample (II) were in accord with those of natural product reported by Battersby[4] except the signal of ethyl acetate.

The mass spectrum of (II) ($C_{38}H_{42}O_6N_2$: Calcd. M^+ 622) showed the molecular ion at m/e 622, most abandant peak at m/e 310 [ion a, $(M-2)^{++}$ and ion e] and m/e 312 (ion b and ion f) which would correspond to the favoured cleavage at a - a' with hydrogen transfer, and a characteristic fragment (ion c) at m/e 485, which would be derived by fission at a' - b' from the M^+ ion peak with loss of $C_8H_9O_2$ unit. Battersby[2] has already reported that the ion at m/e 310 is attributable only to the ion (a), but the cleavage at the highly activated allylbenzyl position of 1-phenethyl-3,4-dihydroisoquinoline moiety in the ion $(M-2)^{++}$ would also be feasible and give rise to the ion (e) at m/e 310.

The fragmentation process is well supported by the formation of the subsequent peaks at m/e 312 (ion f), at m/e 192 (ion g) and at m/e 107 (ion h). Furthermore, the radical ion at m/e 188 should be due to the loss of two hydrogen atom with the formation of the ion (i) through the fission at a - d' in which the possitive charge is stabilized by aromatization. On the other hand the cleavage at a - b' would afford the radical ion (j) at m/e 176.[5]


(M$^+$-Me·) m/e 607 (11%)
(M$^+$-MeO·) m/e 591 (11%)
MeO
N-Me
b'
a
O
OH
d'
d
OH
O
a'
b
Me-N
OMe
M$^+$ m/e 622
-e, -2H
a'-b' fission
-H
(d) m/e 135 (90%)
(i) m/e 188 (20%)
(j) m/e 174 (26%)
a-d' fission
-2H
a-b' fission
c
c'
(M-2)$^{++}$ m/e 310 (100%)
-2Me·
m/e 295 (100%)
c-c' fission
-Me·
a-a' fission
(c) m/e 485 (22%)
(e) m/e 310 (100%)
(f) m/e 312 (93%)
(a) m/e 310 (100%)
(b) m/e 312 (93%)
-Me·
-Me·
-Me·
m/e 295 (100%)
m/e 297 (70%)
(h) m/e 107 (11%)
(g) m/e 192 (10%)

Since the OO-dibenzylmelanthioidine (III) has already been proved to be diastereoisomeric racemates of (II) by Battersby, a total synthesis of diastereoisomeric racemates of melanthioidine has been accomplished, and it is of particular interest that the twenty-membered ring system as melanthioidine-type compound has been synthesized.

We thank Prof. A. R. Battersby, The Robert Robinson Laboratories, University of Liverpool for his kind comparison of our sample (III) with his specimen and for his sending the unpublished paper to us kindly. Further we are also grateful to Japan Electron Optics Laboratory Co. Ltd. for mass spectral measurement.

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2. A. R. Battersby, R. B. Herbert, and F. Santavy, Chem. Comm., 1965, 415.
3. T. Kametani, S. Takano, and K. Haga, Chem. Pharm. Bull. (Tokyo), in press.
4. A. R. Battersby, R. B. Herbert, Mrs. Lucy Mo, and F. Santavy, Unpublished paper.
5. The mass spectrum was determined with a JMS-01SG type mass spectrophotometer equipped with an all glass inlet system (130 - 140° C), ionizing potential, 75 eV.; accel. voltage, 6KV; and electron mult., 2KW.