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CALLIMORPHINE: IDENTIFICATION AND SYNTHESIS OF THE CINNABAR MOTH "METABOLITE".

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Summary - Callimorphine, a putative pyrrolizidine alkaloid metabolite found in some Arctiid moths which feed as larvae on plants containing pyrrolizidine alkaloids, has been identified and synthesised.

A number of Arctiid moths with warning colouration feed as larvae on plants containing pyrrolizidine alkaloids[1]. They store the alkaloids in their bodies apparently for defensive purposes and, in some cases, the males also metabolise them to dihydropyrrolizines which they secrete on coremata[2]. These metabolites are believed to act as sex pheromones[2].

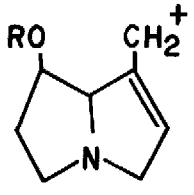
When reared on Senecio vulgaris L. or Senecio jacobeae L. the pupae and imagines of the Cinnabar moth (Tyria jacobeaea L.) were found to contain, as well as the food plant alkaloids, a significant amount (15-25% of total alkaloid) of a substance with elemental composition $C_{15}H_{23}NO_5$ which was not detected in either larval food plant[3]. The Garden Tiger moth (Arctia caja L.) also contains this substance when reared on the same Senecio species[4] and recently it has been found in the Scarlet Tiger (Callimorpha dominula L.) reared on Symphytum caucasicum[5].

The present investigation was undertaken to ascertain the structure of this substance in the hope that its identification might indicate its role, which remains unknown, or allow it to be synthesised for further investigation.

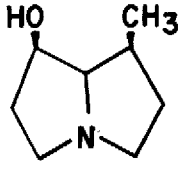
The isolation of alkaloid mixtures containing this substance and high resolution mass spectral data establishing its elemental composition have been reported elsewhere[4]. A partial purification of the "metabolite" was achieved on the basis of its expected pK_a (c.8.5) by extraction from chloroform into aqueous buffer pH7.0. This gave material (>1 mg) sufficiently pure (approx 70%) for study by gc-ms. The mass spectrum [M^+297(4), 253(3), 226(4), 155(20), 154(24), 138(90), 137(60), 136(50), 120(50), 119(60), 118(72), 117(90), 94(94), 93(100), 80(90), 73(66), 55(74), 43(98)] is typical of 1,2-dehydropyrrolizidine alkaloids esterified at C_9 and with a free hydroxyl at C_7. The presence of a prominent fragment ion at m/e 138,(1), resulting from fission of the C_9-O bond, is a characteristic feature of the spectra of such molecules. D_2O exchange resulted in the replacement of the C_7 hydroxyl hydrogen, as indicated by a change in the M^+ ion from m/e 297 to 298 and the fragment ion at m/e 138 to 139. Acetylation and trimethylsilylation resulted in formation of monoacetyl [M^+339(2), 297(1), 280(1), 279(2), 197(8), 196(12), 180(36), 136(25), 120(36), 119(36), 118(36), 117(57), 94(21), 93(61), 90(25), 89(21), 73(21), 60(32), 55(32), 43(100)] and monotrimethylsilyl [M^+369(3), 298(2), 253(5), 227(10), 226(9), 210(24), 208(22), 136(7), 134(7), 120(36), 119(14), 118(20), 117(20), 94(96), 93(100), 43(92)]

derivatives involving reaction at the C_7 hydroxyl group as indicated by a shift of the fragment ion at m/e 138 in the mass spectrum of the parent compound to m/e 180, (2) and m/e 210, (3) respectively.

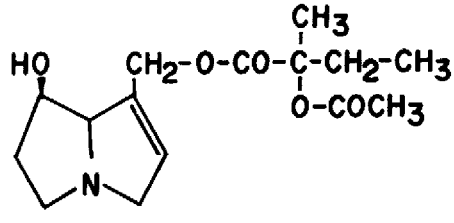
Hydrogenolysis (Pt/H_2 in methanol) which selectively cleaves the C_9-O bond, followed by methylation with CH_2N_2 yielded an aminoalcohol having the gc retention time (co-chromatography) and mass spectrum [M^+ 141(20), 122(7), 121(9), 120(6), 97(90), 83(30), 82(100), 55(56), 43(94)] of retronecanol (4) and a methylester [M^+ 174(1), 145(6), 143(3), 125(5), 115(100), 144(34), 99(20), 84(14), 83(60), 82(34), 73(100), 59(68), 55(98), 43(100)] representing the unknown esterifying acid moiety of the "metabolite". The identification of retronecanol confirms that the amino-alcohol present in the "metabolite" is retronecine, the necine of the larval food plant alkaloids. The mass spectrum of the methyl ester suggested methyl-α-acetoxy-α-methylbutyrate as its structure. This was prepared[6] and found to be identical in retention time and mass spectrum with the ester from the "metabolite". Thus the "metabolite", named callimorphine, has the structure (5).



(1) R=H
(2) R=COCH3
(3) R=Si(CH3)3



(4)



(5)

Mattocks[6] had previously made an unsuccessful attempt to synthesis (5) in the course of work on the toxicity of pyrrolizidine alkaloids. We have synthesised it using the method of Culvenor et al[7]. The mixture of two diastereoisomers obtained from reaction of 9-chlororetronecine hydrochloride with the sodium salt of (racemic)α-acetoxy-α-methylbutyric acid in aqueous alcohol, was an oil which co-chromatographed, underivatised and as the trimethylsilyl derivative, with callimorphine and gave the same mass spectra.

The amount of material available has so far prevented determination of the stereochemistry of the acid of callimorphine.

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