The Structure of Axillarin, a Novel Pyrrolizidine Alkaloid from *Crotalaria axillaris* Ait

By D. H. G. CROUT

(*Department of Chemistry, University of Exeter, Exeter*)

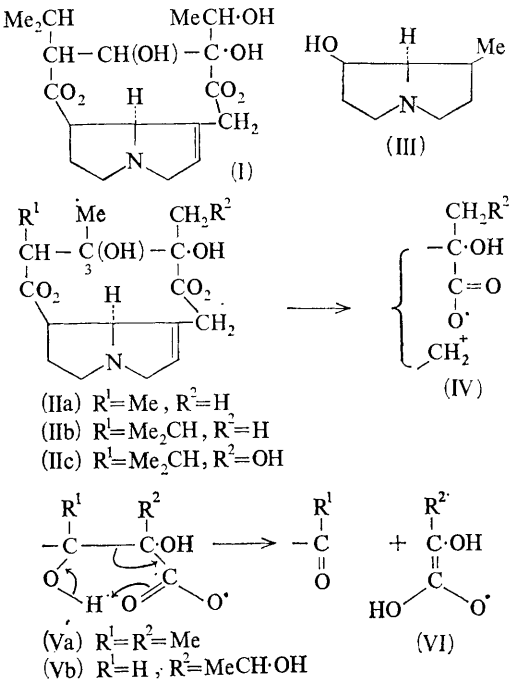
SEED of *Crotalaria axillaris* Ait (Leguminosae) yielded 2·5% of an alkaloid mixture consisting of three components. The major alkaloid, for which the name axillarin is suggested, has the composition $C_{18}H_{27}NO_7$, m.p. 205° (decomp.), $[\alpha]_D$ + 65·1° (pyridine), hydrochloride m.p. 228°, picrate m.p. 214—216° (decomp.). Structure (I) is proposed for axillarin on the following evidence.

The mass spectrum confirmed the molecular formula and showed major fragments with *m/e* 136, 120, 119, 93, and 80. This ion series has been observed in the mass spectra of monocrotaline[1] (IIa) and senecionine.[2] The mass spectra of the related alkaloids fulvine, crispatine, trichodesmine (IIb), seneciphylline, retrorsine, sceleratine,[3] and chlorodeoxysceleratine,[4] which like monocrotaline and senecionine are all macrocyclic diesters of the pyrrolizidine base retronecine, have also been examined and in each case the same characteristic ion series was observed.[5] The cyclic diester structure was confirmed by hydrogenation (2 moles uptake) followed by alkaline hydrolysis to give retronecanol (III) and a non-crystalline acidic component. Hydrogenolysis of the allylic ester function under these conditions is characteristic of retronecine esters.[6]

The n.m.r. spectrum of axillarin (pyridine) showed doublets at τ 9·01, 8·77 (J 7 c./sec.) and τ 8·42 (J 6 c./sec.) indicating the presence of three CHMe groups. The two upfield doublets were shown to be due to an isopropyl substituent by spin-decoupling experiments and by the characteristically low results of *C*-methyl determinations [1·5 C–Me per molecule, parallel determinations on monocrotaline (IIa) and junceine (IIc) giving 2·5—2·8 and 1·3 C–Me per molecule respectively].

Hydroxyl and hydrogen-bonded ester groups were indicated by the i.r. spectrum, ν_{max} (KBr) 3490, 3420 and 1730 cm.$^{-1}$. The presence of a 1,2,3-triol system was demonstrated by the rapid consumption of two moles of periodate per mole of axillarin, giving acetaldehyde as the only volatile carbonyl compound. Reduction of axillarin with $LiAlH_4$ gave a neutral product derived from the necic acid which on treatment with HIO_4 followed by hot 2,4-dinitrophenylhydrazine gave the corresponding derivative of 2-isopropylprop-2-enal.

The proposed structure [as in (I)] for the necic acid component of axillarin is the only one which accommodates all of these results and is supported by the mass spectrum. It has been shown[1,2] that fragmentation of retronecine diesters starts by fission of the labile allylic ester bond [(II) → (IV)] followed by stepwise fragmentation of the necic acid



component until only the necine remains. This then undergoes fragmentation to give the ion series mentioned above. The major ion produced by fragmentation of the necic acid component of monocrotaline (IIa) has been attributed to the product of a McLafferty rearrangement (Va) → (VI).[1] The mass spectra of trichodesmine (IIb), junceine (IIc),[7] fulvine, and crispatine, all retronecine diester alkaloids with a hydroxyl group at C(3) of the necic acid component [as in (II)], give analogous rearrangement ions. In each case, except for crispatine, this ion is the most abundant in the region of the spectrum corresponding to fragmentation of the acid component. The most abundant ion in the corresponding portion of the

spectrum of axillarin has *m/e* 250. Accurate mass-determination confirmed the composition of this ion as $C_{14}H_{20}NO_3$, corresponding to loss of a fragment $C_4H_7O_4$ from the molecular ion. The production of this ion can be accounted for by the analogous McLafferty rearrangement (Vb) → (VI). This evidence also establishes the mode of esterification of the necic acid as that shown in (I) and rules out the alternative possibility with the ester groups interchanged.

Four types of C_{10} necic acid have been reported;[3] their structures can be dissected into two C_5 units with isoprene skeletons. The available evidence[8] indicates that the biosynthesis of these acids does not occur *via* the acetate–mevalonate pathway but involves common branched-chain amino-acids. The structure for the necic acid component of axillarin [as in (I)] represents a new, fifth member of this class and by extrapolation from previous work and suggestions is probably derived *in vivo* from valine and isoleucine, with loss of the carboxyl group of the latter.

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