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DIHYDROPYRROLIZINE ANALOGUES OF PYRROLIZIDINE ALKALOIDS

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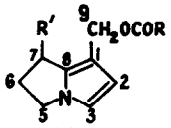
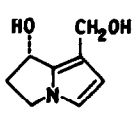
The dihydropyrrolizine analogues (I) of the hepatotoxic pyrrolizidine alkaloids have been suggested as possible toxic metabolites of the alkaloids (1,2,3). The formation of Ehrlich-positive metabolites has been demonstrated (2,4) and the major metabolite of this type formed in the rat from heliotrine and lasiocarpine has been identified as dehydroheliotridine (II) (4,5). We describe here the preparation and properties of the dehydro-alkaloids (I), the metabolite (II) and related derivatives. The numbering system proposed for these compounds is based on a 5H-pyrrolizine system (IV) rather than the usual 3H-pyrrolizine (III) (6) in order to correspond with the parent alkaloids.

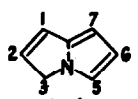
The oxidation of 1,2-dehydropyrrolizidine derivatives to pyrrolic products proceeds readily but mild conditions are needed to avoid subsequent polymerisation and other changes. One of the most useful reagents is manganese dioxide in chloroform suspension. Oxidation proceeds readily (6-24 hours at 25°) when hydroxyl functions are present at C7 and C9, the major products being dihydropyrrolizine derivatives of higher oxidation states involving 1-formyl and 7-keto groups. The crude product may be reduced with sodium borohydride in order to obtain the hydroxy derivatives such as (II). The oxidation products summarised in Table 1 and their relative rates of formation are best accounted for on the basis of the mechanism proposed for the manganese dioxide oxidation of alcohols by Hall and Story (7). Oxidation at the allylic hydroxyl of heliotridine, for example, is regarded as proceeding by formation of a manganic ester followed by fission of the O-Mn bond and loss of a proton to form the aldehyde (V). (V) is not isolable but is further oxidised to the dihydropyrrolizine (VI).



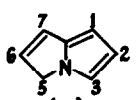
(I)



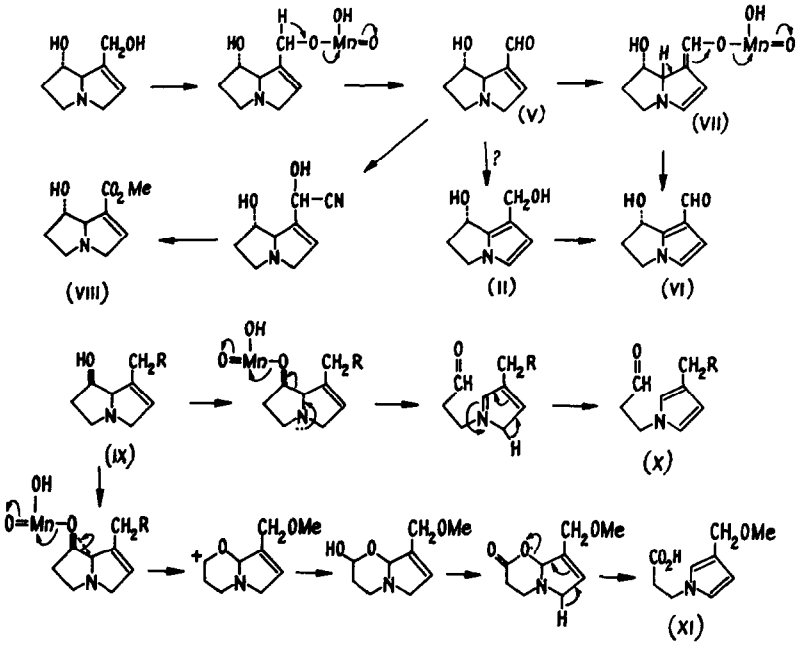
(II)



(III)



(IV)

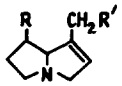
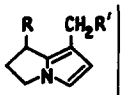
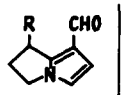
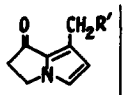
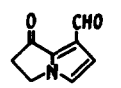
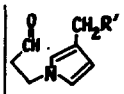


This apparently proceeds directly through the enol-manganate (VII) rather than *via* tautomerism to (II) since (VI) is formed more readily from heliotridine than from (II). The intermediate formation of (V) is demonstrated by the isolation of the methyl ester (VIII) when the oxidation is effected in the presence of hydrogen cyanide and methanol (c.f. (8)). Oxidation at the secondary, homoallylic hydroxyl may give the 7-keto derivative but in some instances, it also promotes fission of the C7-C8 bond. The formation of ring-opened aldehydes is favoured by 7β-OH configuration, e.g. (IX)→(X), R = H or OH, and is regarded as a fragmentation of the type discussed by Grob and Schiess (9). Formation of an acid, e.g. (IX)→(XI), R = OMe, is analogous to a reaction discussed by Hall and Story (7).

Similar ranges of products are obtained by oxidation of pyrrolizidine derivatives with permanganate in acetone and by catalytic dehydrogenation at room temperature in the presence of platinum or nickel catalysts. Some dehydro-alkaloids may be prepared with permanganate, e.g. dehydroheliotrine (XII) (70%) and dehydromonocrotaline (20%) but under catalytic conditions, the esterifying acids are lost. Chloranil is capable of giving high yields of the corresponding dihydropyrrolizines in some instances if exposure to quinonoid material is minimised during work-up. Products with a 7-OH group appear to be formed by these procedures with full retention of configuration at C7.

TABLE I

Products of Oxidation of Pyrrolizidine Derivatives with Manganese Dioxide[a]

Compound (R,R') 	Products[b] 				
Supinidine (H, OH)	trace	+++++			
Heliotridine[c] (α-OH, OH)	trace	+++		+	+
Retronecine[c] (β-OH, OH)	trace	+++			++
7-Angelylheliotridine (O-angelyl, OH)		++++			
Supinidine methyl ether[d] (H, OCH_3)	+	trace			
Retronecine methyl ether (β-OH, OCH_3)	trace		++		+[e]
Desoxyretronecine (β-OH, H)	trace		+		+++
Supinine (H, O-trachelanthyl)	(+)[f]	+++			
Heliotrine (α-OH, O-heliotryl)	trace		+++	trace	
7-Acetylheliotrine[d] (α-O-acetyl, O-heliotryl)		(traces of unidentified products)			
Echinatine (α-OH, O-trachelanthyl)				+++	

a In chloroform at 25° for 24 hr unless other period is indicated.

b The structures of all products are confirmed by n.m.r. and mass spectra. Each + represents c.20% in yield.

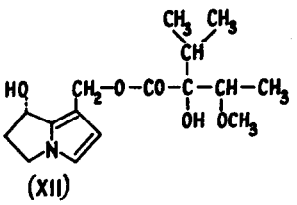
c Reaction time, 6 hr.

d Reaction very slow, compound mostly unchanged after 4 days.

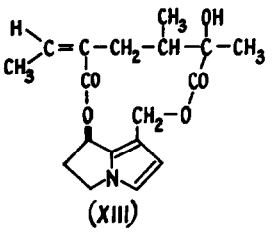
e The corresponding carboxylic acid is also formed.

f R' = OH in this product.

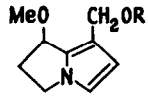
The dehydroalkaloids (1) are best prepared by the action of acetic anhydride on the alkaloid N-oxides, a reaction which Mattocks utilised for the spectrophotometric estimation of the alkaloids (10), but which he found unsuccessful in an attempted preparation of dehydroretrorsine (2). We find that short reaction times (2-5 min. at room temperature) and a different work-up procedure permit isolation of the unmodified dihydropyrrolizines in high yields. Dehydroheliotrine (XII) and dehydrolasiocarpine are non-crystalline and highly unstable at room temperature, whereas the macrocyclic compounds, dehydromonocrotaline and dehydrosenecionine (XIII) are crystalline and relatively stable at room temperature. In aqueous solution, these compounds undergo hydrolysis, polymerisation and other changes as yet undefined. Strong acids convert them immediately into insoluble red or red-black solids



(XII)



(XIII)



(XIV) R=Me
(XV) R=H

presumed to be polymeric. Strong bifunctional alkylating ability is evident in the complete conversion of dehydrosenecionine and dehydrolasiocarpine into a dimethyl ether (XIV) (configuration at C7 undefined) when left in methanol solution for 30 min. at room temperature. Reaction with ethanol occurs more slowly. The alcohols such as (II) are more stable than the esters and of lesser alkylating reactivity; (II) yields the mono-ether (XV) when refluxed in methanol for several hours. Dehydroheliotrine reacts readily with primary, secondary and tertiary amines at room temperature, giving the expected 1-aminomethyl derivatives. If both are present in solution together, reaction may thus occur between an alkaloid and its dihydropyrrolizine analogue, forming a stable dimeric quaternary compound. The compound from heliotrine and dehydroheliotrine has been found in extracts of *Heliotropium europaeum* (11).

The dihydropyrrolizine derivatives described have cytotoxic and nucleotoxic properties which have already been briefly described (4). It is hoped that more detailed studies now in progress will elucidate their role, particularly that of the known metabolite (II), in pyrrolizidine poisoning.

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