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THE CARDIAC GLYCOSIDES OF CALOTROPIS PROCERA

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THE plant Calotropis procera produces the cardiac "glycosides" uscharidin ($C_{29}H_{38}O_9$), calotropin ($C_{29}H_{40}O_9$) and calotoxin ($C_{29}H_{40}O_{10}$)[1] which have unusual "glycosidic" functions in the place of the hexose and deoxyhexose sugars normally found in this class of compound. In addition there are the constituents uscharin[2] ($C_{31}H_{41}NO_8S$) and voruscharin[3] ($C_{31}H_{43}NO_8S$) that incorporate a thiazoline and a thiazolidine function, respectively in the glycosidic fragment and give rise to uscharidin on hydrolysis in the presence of mercuric chloride.

Although there have been a number of interesting studies on the chemistry of these compounds it cannot be said that the structures proposed by Hesse and co-workers[4] [e.g., uscharidin (I) and calotropin (II)] account for their behaviour in a satisfactory way. Thus it has been suggested that uscharidin is converted to calactinic acid (Hesse's "Boraxsäure") by action of aqueous borax[4] or chromatography on alumina[5]. The structure (III) for calactinic acid was proposed on the assumption that 1-hydroxypent-3-en-2-one (IV) was formed by hydrolysis and the ketol (V) that was isolated was derived from (IV) by hydration.

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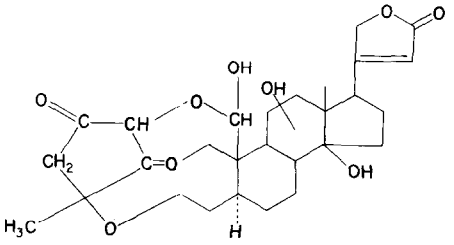
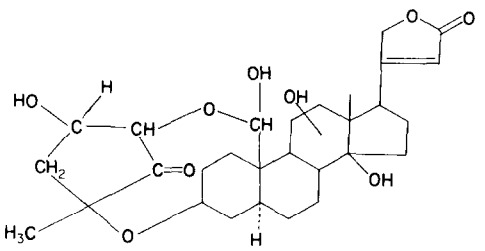
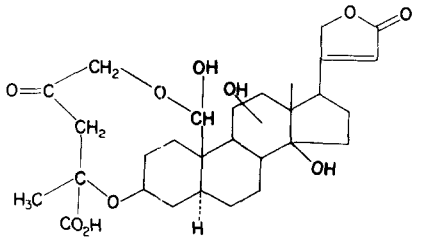
[1] G. Hesse, L.J. Heuser, E. Hütz and F. Reicheneder, Liebigs Annalen 566, 130 (1950).
[2] G. Hesse and H.W. Gampp, Ber.dtsch.Chem.Ges. 85, 933 (1952);
[3] G. Hesse and K. Mix, Liebigs Annalen 625, 146 (1959).
[4] G. Hesse and G. Ludwig, Liebigs Annalen 632, 158 (1960).
[4] G. Hesse and G. Lettenbauer, Liebigs Annalen 623, 142 (1959).
[5] C.H. Hassall and K. Reyle, J.Chem.Soc. 85 (1959).



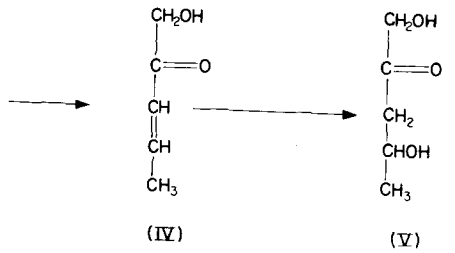
(I)



(II)



(III)

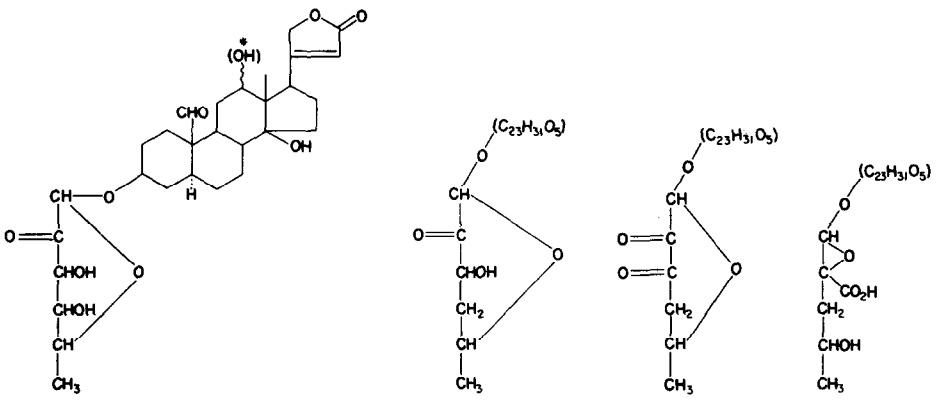


(IV) (V)

However, this assumption is untenable since we have found that the ketol (V) is optically active. Moreover, evidence of periodate oxidation of calactinic acid derivatives excludes the structure (III). In particular, dihydrocalactinic acid, formed by the action of sodium borohydride yields dihydrocalotropagenin[5] on hydrolysis; there is, then, no formyl group at position 10 in the steroid nucleus of dihydrocalactinic acid. It follows that dihydrocalactinic acid derived from (III) should react with periodic acid. However, as in the case of calactinic acid itself, there is no uptake during 21 hours. Similarly, the observation that β-hydroxybutyric acid is formed by periodate cleavage of the polyol, $C_{29}H_{52}O_9$, formed by the reduction of tetrahydrocalactinic acid with lithium aluminium hydride, cannot be accommodated by the structure (III).

We propose the structures (VI)→(IX) for calotoxin, calotropin,

uscharidin and calactinic acid respectively.



[Where $C_{23}H_{31}O_5$ represents calotopagenin moiety as in (VI)]

The structure (IX) for calactinic acid accounts for its reactions[8,9] and its formation from uscharidin by a process that, like saccharinic acid formation, is catalysed by calcium ions[10]. The reactions of uscharidin lead to the structure (VIII); they include cleavage with hydrogen peroxide at room temperature and pH 8.7 to release a dicarboxylic acid that, on hydrolysis, liberated β-hydroxybutyric acid. In addition, periodic acid cleavage of the "glycosidic" function produced by acid-catalysed hydrolysis of hexahydrouscharidin, gave crotonaldehyde and formic acid[4]. Similarly, the nature of the periodic acid oxidation products, the absorption spectra

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* The assignment of the hydroxyl group to the 12-position in calotropagenin is tentative. It is based on evidence which favours the 11 or 12-position,[5,6] and on unpublished evidence[7] which excludes the 11-position.

6 O.P. Mittall, Ch. Tamm, Ek. Weiss and T. Reichstein, Helv.Chim.Acta 45, 924 (1962).

7 C.H. Hassall and H.R. Roderick, unpublished results.

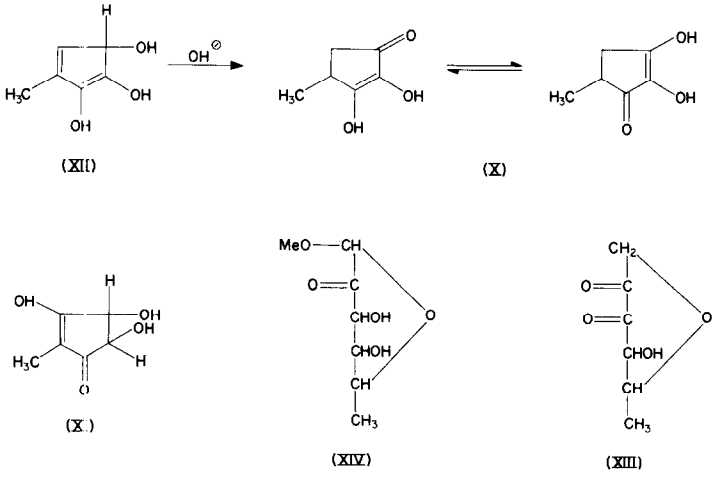
8 R.F. Curtis, C.H. Hassall and J. Weatherston, J.Chem.Soc., in the press.

9 D.H.G. Crout, R.F. Curtis and C.H. Hassall, J.Chem.Soc., in the press.

10 G. Machell and G.N. Richards, J. Chem.Soc. 1924 (1960).

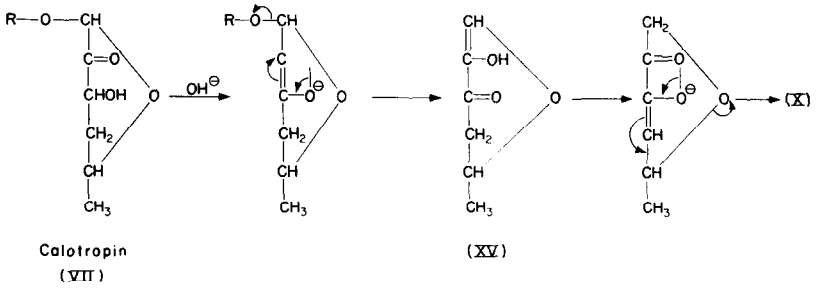
and the evidence of functional groupings in calotoxin and calotropin indicate the molecular structures (VI) and (VII) respectively.

The constitutions proposed by Hesse and co-workers for the "glycosides" include methyl reductic acid functions. These were introduced largely to account for the production of an optically-active compound $C_6H_8O_4$, with acidic and reducing properties similar to reductic acids, when calotoxin was pyrolysed. In the case of calotropin, pyrolysis gave a similar optically-active compound, $C_6H_6O_3$, which was converted readily by mild alkali to optically-inactive methyl reductic acid (X) identical with synthetic material; this compound was also obtained by the hydrolysis of calotropin with mild alkali. Hesse et. al. suggested that the optically active compound produced by pyrolysis of calotoxin and calotropin had the structures (XI) and (XII) respectively. However, we have identified the pyrolysis product from calotoxin as 1,5-anhydro-2,3-dioxorhamnitol (XIII) by showing that, after racemisation, it is identical with this compound, prepared by pyrolysis or the action of mild alkali on methyl-α- and methyl-β-2-oxorhamnopyranoside (XIV) (cf. the action of alkali on methyl β-2-oxo-glucopyranoside[11].)



[11] O. Theander, Acta. Chem. Scand., 12, 1887 (1958).

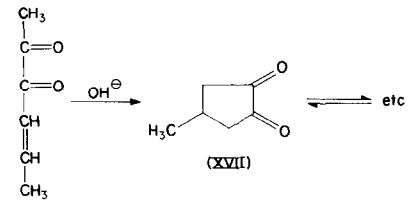
We assign a similar structure (XV) to the pyrolysis product from calotropin and attribute the formation of methyl reductic acid by the action of alkali to an intramolecular Michael-type condensation. The model compound hex-4-en-2,3-dione (XVI) gives 1-methylcyclopentan-3,4-dione (XVII) under similar conditions.



Calotropin
(VII)

(XV)

(X)



(XVI)

(XVII)