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BIOSYNTHESIS OF THE ALKALOIDS OF HALOXYLON SALICORNICUM I

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The biosynthesis of piperidine and pyridine alkaloids has been studied extensively. The piperidine ring of the majority of these alkaloids, e.g. anabasine,[2] N-methyl isopelleteriene[2] and sedamine[3], has been shown to arise from lysine via an unsymmetrical intermediate, 6-amino-2-ketohexanoic acid, and Δ'-piperideine. The 2-alkylpiperidine alkaloids e.g. N-methyl-isopelleteriene[2,4] and anaferine[2], are formed by reaction between Δ'-piperideine and the appropriate β-keto acid derived from acetate. In this step the terminal carboxylic acid group of the keto acid is lost as carbon dioxide. A second pathway from acetate to alkyl substituted piperidine alkaloids, coniine[4] and pinidine[5] has also been established.

The pyridine ring of anabasine (III), and the related alkaloid nicotine has been shown to effectively arise from glyceraldehyde[6] and aspartic acid.[7]

Piperidine and pyridine alkaloids occur widely in the Chenopodiaceae. Recently a number of new piperidine alkaloids, aldotripiperideine (IV), halosaline (V) and haloxine (VIII) as well as anabasine (III) have been isolated from Haloxylon Salicornicum (Mag. Tand.) Boiss.[8] The co-occurance of these alkaloids in this species is of interest from a biosynthetic viewpoint.

An alternative biosynthetic route to anabasine has not so far been discovered in higher plants. An attractive hypothesis for the biosynthesis of this alkaloid in H. Salicornicum envisages the dimerization of Δ'-piperideine (I) to tetrahydroanabasine (II), a reaction which occurs at physiological pH.[9] Oxidation of tetrahydroanabasine would then yield anabasine (III). This view is supported by the ability of a cell-free extract of Medicago sativa plants to bring about this oxidation.[10] From a phytochemical aspect the hypothesis is also attractive in that the Chenopodiaceae are only distantly related to the Solanaceae, in which the biosynthesis of anabasine and nicotine has heretofore been studied.

This hypothesis concurs with that we propose for the biosynthesis of the piperidine alkaloids of H. Salicornicum. Aldotripiperideine (IV) is

visualised as being found by trimerization of Δ'-piperideine (I), a process which occurs in acid solution.[11] Halosaline (V) may be formed by reaction of Δ'-piperideine (I) with 3-ketohexanoic acid (VI), derived from acetate. The tricyclic haloxine (VIII) is presumed to be formed from tetrahydroanabasine (II) and 3-ketohexanoic acid (VI). Loss of the carboxylic acid group in this instance is prevented by amide formation between it and the β-nitrogen of tetrahydroanabasine.

The plants used in this investigation were grown from seed kindly supplied by Professor Vivi Täckholm, Botany Dept., University of Cairo. The freshly collected seeds germinated reasonably well but if kept for more than a few months they failed to germinate. The plants were difficult to cultivate and appeared to benefit from a periodic application of a weak saline solution.

In separate experiments 0.1 mc each of Dl {6-^{14}C} lysine and 2-^{14}C sodium acetate were administered to six, one-year old H. Salicornicum plants growing hydroponically. The plants were grown on for twelve days and halosaline isolated by established methods. The halosaline from the acetate was inactive. This result was unexpected but it may be that the enzyme necessary for the formation of acetyl coenzyme A may not be present in this plant. The halosaline from the lysine feed was active (percentage incorporation 0.02).

The active halosaline from the lysine feed was converted to 1-(2-piperidyl) pentane. This was subjected to a Hofmann degradation. The mixture of products was oxidized with osmium tetroxide / periodate and formaldehyde isolated as its dimedone derivative. The formaldehyde dimedone had essentially the same activity as the halosaline indicating that lysine was incorporated into the alkaloid unsymmetrically. Halosaline is efficiently formed by reduction of 1-(2-piperidyl)-2-pentanone[12] and separation on a dry column chromatogram.

The anabasine isolated from the lysine feed had very low activity and no conclusions as regards its biosynthesis in H. Salicornicum can as yet be drawn. However the fact that halosaline is biosynthesised in the expected manner leaves the question of an alternative biosynthetic pathway to this alkaloid still open.

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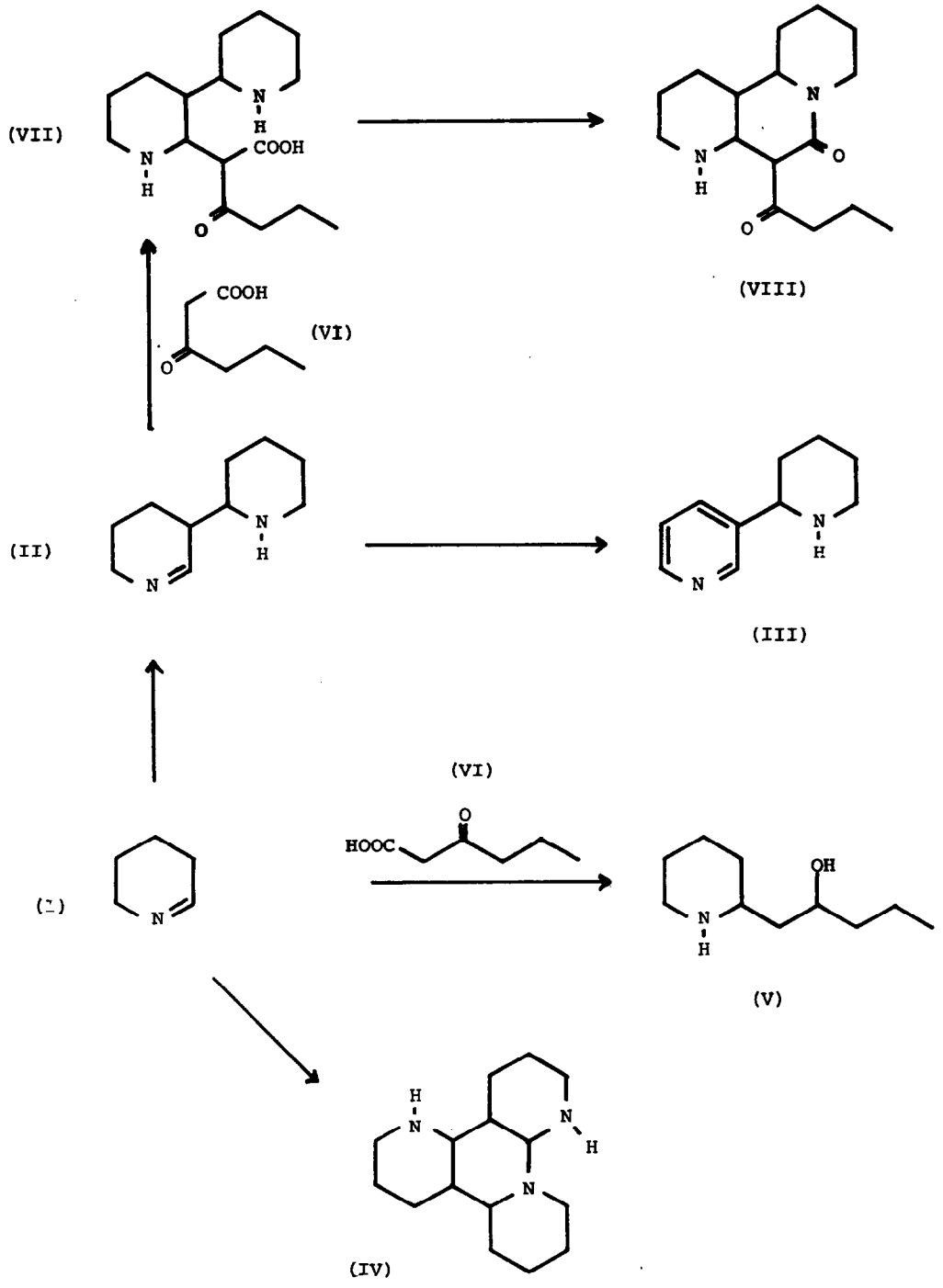
(VII)
COOH
(VI)
(VIII)
(II)
(III)
(VI)
HOOC
OH
(V)
(IV)

References

1 E. Leete, E.G. Gros and T.J. Gilbertson, *J. Amer. Chem. Soc.*, 1964, 86, 3907; E. Leete, *J. Amer. Chem. Soc.*, 1969, 91, 1679.

2 M.F. Keogh and D.G. O'Donovan, *J. Chem. Soc. (C)*, 1970, 1792; R.N. Gupta and I.D. Spenser, *Phytochemistry*, 1969, 8, 1937.

3 R.N. Gupta and I.D. Spenser, *Canad. J. Chem.*, 1967, 45, 1275.

4 H.W. Liebisch, N. Marchov and H.R. Schütte, *Z. Naturforsch*, 1968, 23B, 1116.

5 E. Leete, *J. Amer. Chem. Soc.*, 1964, 86, 2509; E. Leete and K.N. Juneau, *J. Amer. Chem. Soc.*, 1969, 91, 5614.

6 D. R. Christman and R.F. Dawson, *Biochemistry*, 1963, 2, 182; J. Fleeker and R.U. Byerrum, *J. Biol. Chem.* 1965, 240, 4099; E. Leete and A.R. Friedman, *J. Amer. Chem. Soc.*, 1964, 86, 1224.

7 A.R. Friedman and E. Leete, *J. Amer. Chem. Soc.*, 1963, 85, 2141; T. Griffith and R.U. Byerrum, *Biochem. Biophys. Res. Comm.*, 1963, 10, 293; T.M. Jackamiez and R.U. Byerrum, *J. Biol. Chem.*, 1966, 241, 1296; J. Fleeker and R.U. Byerrum, *J. Biol. Chem.*, 1967, 242, 3042.

8 F. Sandberg, L. Svanquist, M. Ödherg and L. Sonmark, *Svensk Farm. Tidskr.*, 64, 541, (1960); K.H. Michel, F. Sandberg, F. Haglid and T. Norin, *Acta Pharm. Suecia*, 4, 97 (1967).

9 C. Schöpf, F. Braun and A. Komazak, *Chem. Ber.*, 1956, 89, 1821.

10 K. Hasse and P. Berg, *Biochem. Z.*, 1959, 331, 349.

11 C. Schöpf, H. Arm, G. Benz and H. Krimm, *Naturwissenschaften*, (1951) 38, 186.

12 J. Van Noordwijk, J.J. Millink, B.J. Visser and J.H. Wisse, *Recueil*, 1963, 82, 763.