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BIOSYNTHESIS OF THE TROPOLONE RING OF COLCHICINE

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It has been established that ring A and carbons 5, 6, and 7 of colchicine (V) are derived from phenylalanine (1,2,3) or closely related metabolites such as cinnamic acid (3). Until recently the origin of the tropolone ring has remained a mystery. No radioactivity was detected in this ring when acetic acid-1-C^{14} was administered to Colchicum plants (4,5), although it has been established that the tropolone ring of the mold metabolite puberulic acid is derived from acetate (6). Battersby (3) and I (7) showed that the administration of tyrosine-3'-C^{14} to Colchicum plants yielded radioactive colchicine in which the activity was mainly confined to the tropolone ring. Very recently Battersby (8) has established that this activity was located at C-12 . This labelling pattern is in agreement with the biogenetic scheme illustrated in Fig. 1 which is an elaboration of the one suggested by Battersby (3). Oxidation of a diphenol such as II, which could be plausibly derived from phenylalanine and a C_6-C_1 unit (indicated with heavy lines in structure II) derived from tyrosine. Coupling of the resultant diradical III

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yields the intermediate IV in which X is a suitable leaving group such as phosphate. Ring expansion of the dienone as illustrated in Fig. 1. then affords the tropolone ring with the correct oxygenation pattern , colchicine being finally obtained by unexceptional methylation and acetylation. The placement of the amino group in intermediate II is arbitrary and it could be just as well introduced at a later stage in the biosynthesis.

We have now independently confirmed this hypothesis by feeding DL-tyrosine-4-C^{14} (I) (9) (101.3 mg., 5.73 x 10^7 d.p.m.) to twenty sprouting Colchicum byzantinum corms by previously described methods (1). Three weeks after feeding the tracer the plants (wet weight 2490 g.) were harvested and colchicine (0.74 g., 2.49 x 10^5 d.p.m./mM. = 0.8 % incorporation) isolated (2). Treatment of the radioactive colchicine with sodium methoxide caused ring contraction of the tropolone ring affording colchinoic acid (VI) (10), which was decarboxylated by refluxing in quinoline in the presence of copper chromite. The evolved carbon dioxide was collected as barium carbonate and had an activity of 2.44 x 10^5 d.p.m./mM., indicating that essentially all the radioactivity of the colchicine was located at C-9 in agreement with the biosynthetic scheme illustrated in Fig. 1.

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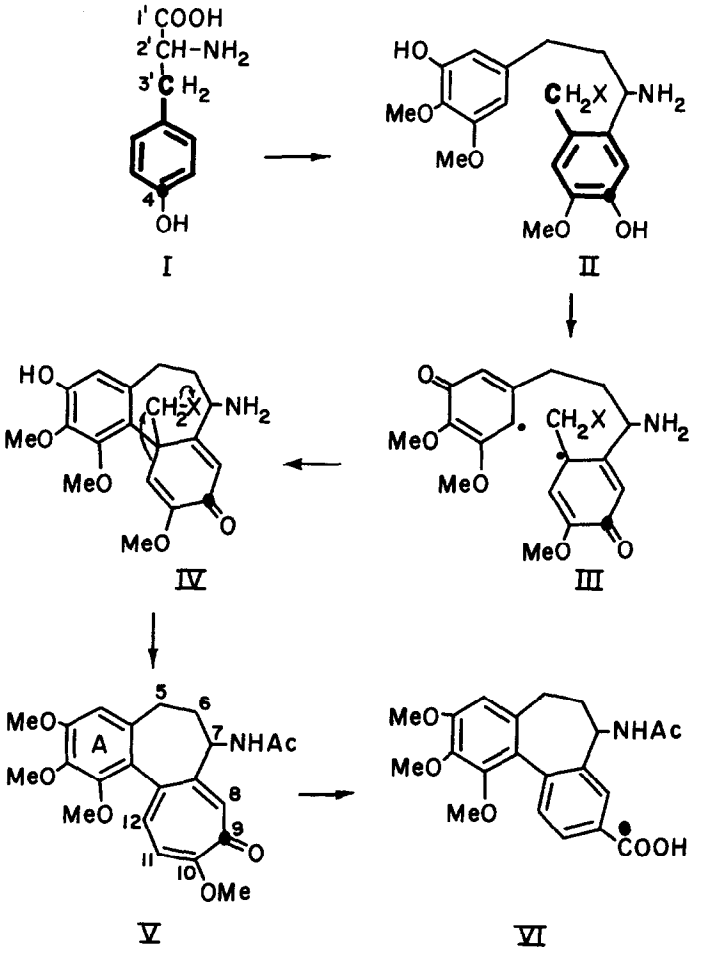

Figure 1. Biogenetic Scheme for Colchicine

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