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OBSERVATIONS ON THE NON-ENZYMATIC TRANSFORMATION OF PHENYLALANINE TO TROPIC ACID

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We (1) and others (2-4) have shown that tropic acid (II), the acid moiety of the ester alkaloids hyoscyamine and hyoscine, is formed from phenylalanine in Datura species. By the use of doubly labelled phenylalanine it was established that this biosynthetic sequence involves migration of the carboxyl group of phenylalanine from C-2 to C-3 . The migration is probably intramolecular, although the mechanism is still obscure (5,6). Recently Yamada, Kitagawa and Achiwa (7) reported the interesting chemical transformation of phenylalanine to tropic acid . Phenylalanine ethyl ester (III), dissolved in acetic acid, was treated with sodium nitrite affording ethyl 3-acetoxy-2-phenylpropionate (V) in 24% yield . Hydrolysis with 10% hydrobromic acid yielded tropic acid. The mechanism which these authors suggested is illustrated in Figure 1 .

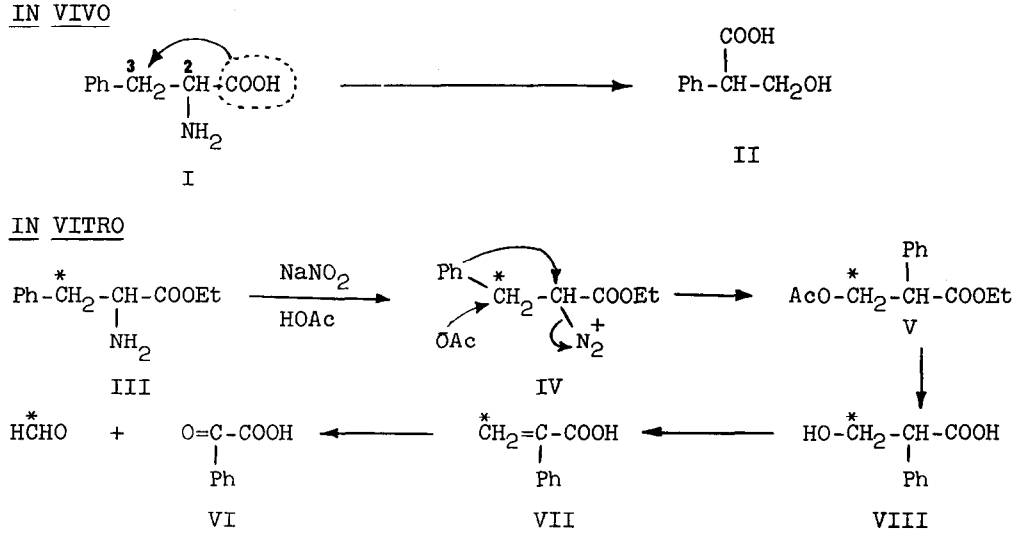

FIGURE 1 . The formation of tropic acid *in vivo* and *in vitro* (^{14}C = *)

The initial product formed is the diazonium ion IV, which undergoes a concerted migration of the phenyl group from C-3 to C-2 with loss of nitrogen from the diazonium ion and solvolytic reaction at C-3 with an acetate ion.

We have now investigated the *in vitro* formation of tropic acid starting with L-phenylalanine-3-^{14}C . The reaction was carried out as described (7) and resulted in the formation of radioactive tropic acid (VIII) (3.7 x 10^5 dpm/mM.), which was degraded as previously described (1). Refluxing with 40 % potassium hydroxide yielded atropic acid (VII) (3.7 x 10^5 dpm/mM.) which was cleaved with osmium tetroxide and sodium metaperiodate affording formaldehyde, isolated as its dimedone derivative (3.6 x 10^5 dpm/mM.), and phenylglyoxylic acid (VI), isolated as its oxime ($<$0.01 x 10^5 dpm/mM.). Our results thus substantiate the mechanism suggested by Yamada *et al.* for the *in vitro* formation of tropic acid from phenylalanine. This *in vitro* mechanism for the formation of tropic acid must be unrelated to the *in vivo* mechanism. The observations (7) that L-phenylalanine was converted to R(+)-tropic acid *in vitro* , whereas S(-)-tropic acid is formed from L-phenylalanine *in vivo* , therefore are not particularly pertinent to the problem of tropic acid biosynthesis.

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