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EPOXIDATION EXPERIMENTS *IN VIVO* WITH DEHYDROHYOSCYAMINE AND RELATED COMPOUNDS

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A PREVIOUS paper of one of us[1] reported on the ability of overground organs of *Datura ferox L.* to convert hyoscyamine (I) into (-)scopolamine, i.e. hyoscine (IV). From the results of the synthesis of scopolamine[2,3] involving epoxidation of tropenyl acetate[2] and (-)tropenyl tropoylate[3] (6,7-dehydrohyoscyamine), one of us (G.F.) suggested[4,5] that the conversion of hyoscyamine into hyoscine takes the same pathway.

In order to check the correctness of this assumption feeding experiments with (-) 6,7-dehydrohyoscyamine (III) have been carried out essentially by the same technique as used for hyoscyamine.[1] *Datura ferox L.*

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[1] A. Romeike, *Flora* **143**, 67 (1956).

[2] G. Fodor, J. Tóth, I. Koczor, P. Dobó and I. Vincze, *Chem. & Ind.* 764 (1956); *J. Chem. Soc.* In press (1959).

[3] G. Fodor, J. Tóth, A. Romeike, I. Vincze, P. Dobó and G. Janzsó, *Angew. Chem.* **69**, 678 (1957).

[4] G. Fodor, *Abhandl. Dtsch. Akad. Wiss. Kl. Chem.* 93 (1957).

[5] G. Fodor, *Tetrahedron* **1**, 86 (1956).

grafted[1] on Cyphomandra betacea (CAV) SENDTN. is practically void of alkaloids. Branches of half a year old Datura scions were cut (green weight 15.5 g) and placed into a $1.5.10^{-3}$ molar solution of (-) 6.7-dehydrohyoscyamine acetate of pH 6.7.

After a week, the alkaloids were extracted and separated by paper chromatography. The fraction which showed the R_f value characteristic for hyoscine (IV) was converted into the picrate, m.p. 175°, $[\alpha]_D^{20} = -6.5^\circ$ (c = 2; dimethyl formamide). (Found: C, 52.2; H, 5.0; N, 10.5. $C_{23}H_{24}O_{11}N_4$ requires C, 51.9; H, 4.5; N, 10.5%) identical in every respect with an authentic sample and with the compound obtained from feeding experiments with (-)hyoscyamine (Found: C, 52.0; H, 4.5; N, 10.7%).

Decisive evidence for the intermediate role of tropenyl (-)tropoylate (III) in the epoxidation of hyoscyamine was expected to be furnished by isolating 6.7-dehydrohyoscyamine after feeding of Datura ferox with hyoscyamine in the presence of oxidation inhibitors, e.g. calcium nitrate or cysteine (cf. Romeike[6]).

In this case, however, no definite ring of tropenyl tropoylate could be found with certainty on paper chromatograms, the main product being a hitherto unknown tropanol ester[6] which is also formed to a slighter extent along with hyoscine in normal epoxidations. The alkamine of this alkaloid U[6]

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[6] A. Romeike and L. Zimmerman, Naturwissenschaften 45, 187 (1958).

[7] The absolute configuration of valerine has been determined by G. Fodor, I. Vincze and J. Tóth, Experientia 13, 183 (1957).

is not identical either with tropine or with pseudotropine, teloidine, scopine or oscine. First, the structure of 3R:6R (-)dihydroxytropane 3-tropic acid ester((-)tropoyl valerine, II) had been assumed,[8] and this compound was synthesized hydrobromide m.p. 174°, $[\alpha]_D^{23} = -69°$ (c = 2; in water); (Found: C, 53.6; H, 6.3; N, 3.8; Br, 20.9. $C_{17}H_{24}O_4NBr$ requires C, 52,5; H, 6.3; N, 3.6; Br, 20.7%), and compared with alkaloid U. These compounds were not identical.

Feeding experiments with S(-) tropoyl valerine (II) under the same conditions as with dehydrohyoscyamine led again to the formation of hyoscine, while in the presence of cysteine it was converted into the alkaloid U.

In contrast to intact branches of Datura ferox on Cyphomandra, homogenized scions thereof proved to be unable to carry out epoxidation either of hyoscyamine (I) or of dehydrohyoscyamine (III). On the other hand, scions of Datura stramonium L., Datura innoxia MILL., Datura metel L., Atropa belladonna L. grafted on Cyphomandra and fed with hyoscyamine and dehydrohyoscyamine leave these compounds unaffected.

No epoxidation took place when Datura ferox on Cyphomandra was fed either with unesterified tropanols e.g. tropine, tropenol, teloidine, or with apoatropine;[8] accordingly, the action of the oxidizing enzyme in play appears to be strongly stereospecific and limited to the esters of S tropic

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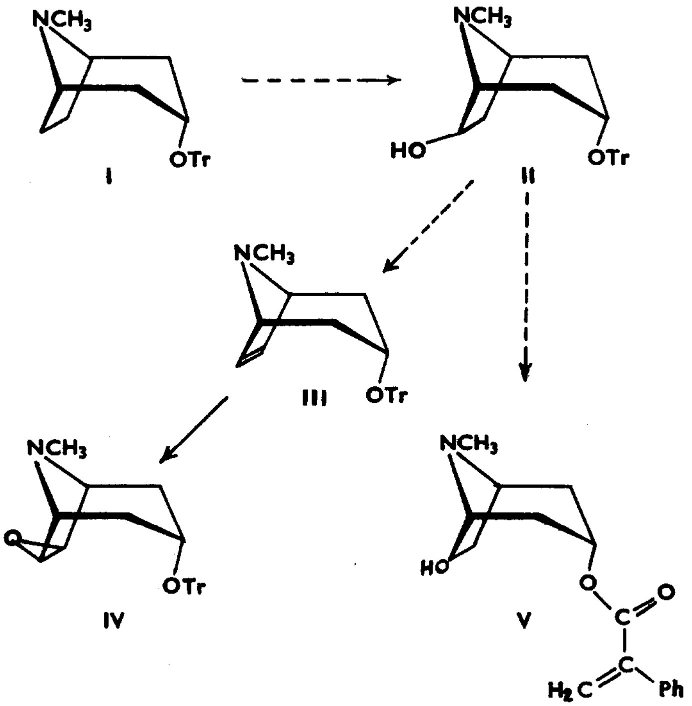
[8] G. Fodor, Lecture, Congress, 50th Anniversary of the Society of Hungarian Chemists, Budapest, May 16, 1958; G. Fodor, P. Dobó, G. Janzsó, I. Koczor, A. Romeike, J. Tőth and I. Vincze, Magy. Kém. Folyóirat 64, 296 (1958).

acid[9] with tropine, tropenol and 3R:6R -tropandiol. However, mandelyl tropine "homatropine" is epoxidized in vivo; the optical activity of the new epoxy-tropanium ester salt still awaits investigation to show whether the D or the L mandelyl ester (or both) is attacked.

Our present working hypothesis for the interconversion of natural tropane alkaloids in vivo may be depicted by the following scheme I→II→III→IV



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[9] S configuration of (-) tropic acid has been determined recently by correlating with D (-) alanine by G. Fodor and Gy. Csepreghy, Tetrahedron Letters No. 7, 16 (1959).

Dr. Romeike suggests for alkaloid U the structure of atropoyl-3R:6R (-) dihydroxy tropane (V), regarding it as a by-product of hyoscine formation in the plant, unable to undergo epoxidation. Further investigations are in progress.