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FURTHER STUDIES ON THE BIOSYNTHESIS OF THE NON-TRYPTOPHAN DERIVED PORTION OF AJMALINE AND RELATED ALKALOIDS

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IN a recent communication[1] we reported that the administration of sodium acetate-1-C^{14} to Rauwolfia serpentina plants led to the formation of radioactive ajmaline (III) which had one half of its total activity located at C_3 and C_{19}. This result is consistent with the biogenetic scheme illustrated in Fig. 1. The poly-β-keto ester (I) is formed from three molecules of acetylcoenzyme A. A one carbon side chain derived from formaldehyde, or its biological equivalent, is introduced at C_3. Feeding experiments with sodium formate-C^{14} substantiate this idea[2]. At C_4 condensation occurs with malonylcoenzyme A, which may be also derived from acetylcoenzyme A by a carboxylation reaction[3]. The resulting intermediate II is numbered to indicate its biogenetic relationship to the indole alkaloids. The carboxyl group at C_{16} is lost in the formation of ajmaline. It is of interest to note that Wenkert, starting with prephenic acid and formaldehyde, has arrived at a very similar intermediate (V) by a series of hypothetic transformations[4].

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[1] E. Leete, S. Ghosal and P. N. Edwards, J. Amer. Chem. Soc. 84, 1068 (1962).

[2] P. N. Edwards and E. Leete, Chem. and Ind. 1666 (1961).

[3] S. J. Wakil and J. Ganguly, J. Amer. Chem. Soc. 81, 2597 (1959).

[4] E. Wenkert, J. Amer. Chem. Soc. 84, 98 (1962).

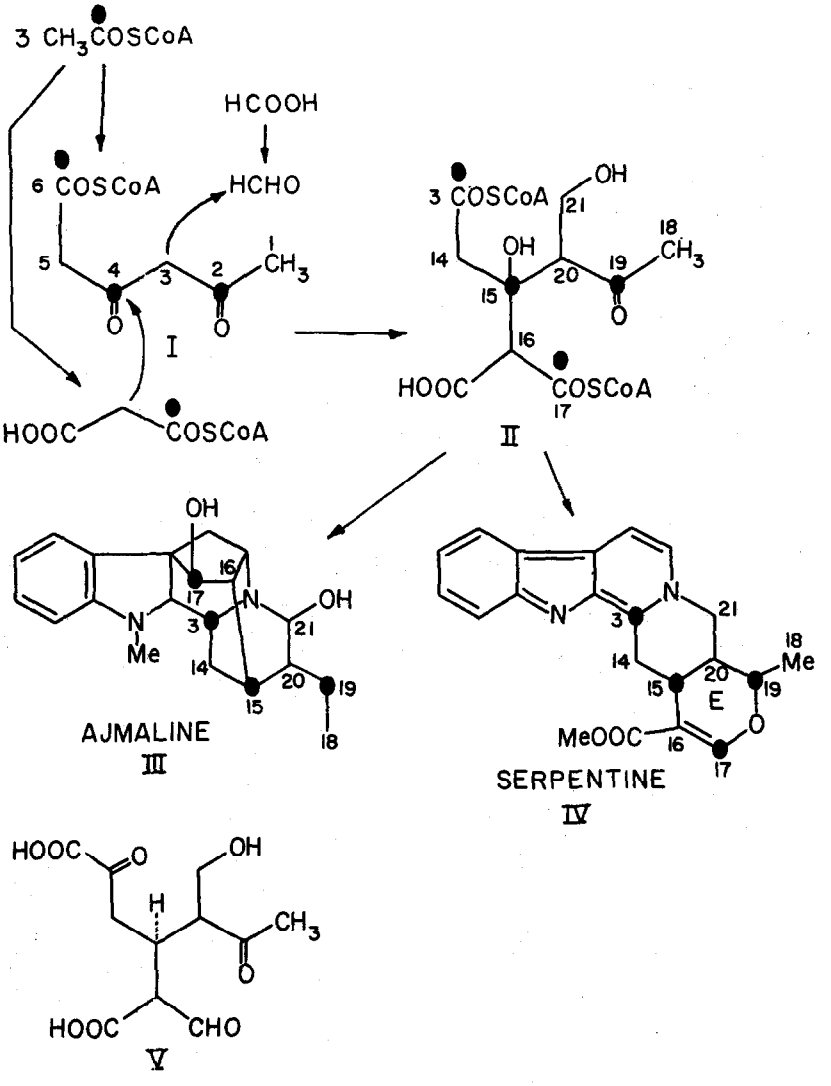

Fig. 1. Hypothetical biogenesis of the non-tryptophan derived portions of ajmaline and serpentine

Since our previous report we have carried out an additional degradation on the radioactive ajmaline derived from acetate-1-C^{14}. On heating with Raney nickel in wet xylene decarbonoajmaline was obtained[5] and was found to have the same specific activity as the ajmaline, indicating that position C_{21} was inactive.

Radioactive serpentine (6.0×10^5 d.p.m./mM.) was also isolated from the plants which had been fed sodium acetate-1-C^{14} (0.2mc.). Activity at C_{18} and C_{19} was determined by carrying out a Kuhn-Roth oxidation which yielded acetic acid (1.4×10^5 d.p.m./mM.). A Schmidt reaction on this acetic acid afforded carbon dioxide assayed as barium carbonate (1.4×10^5 d.p.m./mM.) and inactive methylamine. Thus approximately one quarter of the total activity of the serpentine was located at C_{19}, a result which is consistent with our biogenetic hypothesis. Hydrolysis of the serpentine yielded serpentinic acid which gave inactive carbon dioxide when subjected to the Schmidt reaction, indicating that there was no activity in the carbomethoxy group of serpentine. This result may be rationalized by postulating that there is no randomisation of activity between the two carbonyl groups of the hypothetical intermediate, malonylcoenzyme A, and that the carbonyl attached to the coenzyme A is the one which is involved in the formation of the heterocyclic ring E of serpentine.

When malonic acid-1,3-C^{14} (0.1mc., 5.04 mg.) was administered to a one-year old R. serpentina plant, radioactive serpentine (3.7×10^5 d.p.m./mM.), ajmaline (2.2×10^5 d.p.m./mM.), and reserpine (2.8×10^5 d.p.m./mM.) were isolated four weeks later. Kuhn-Roth oxidation on the serpentine yielded essentially inactive acetic acid. A Schmidt reaction on serpentinic acid yielded carbon dioxide, assayed as barium carbonate, having 48% of the

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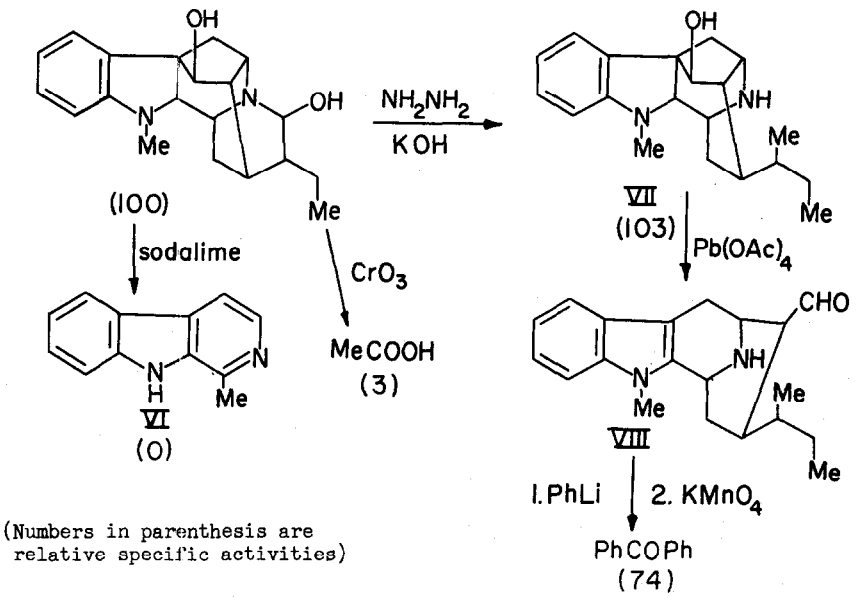
[5] R. Robinson, Chem. and Ind. 285 (1955).

specific activity of the serpentine. The radioactive ajmaline was subjected to the degradation illustrated in Fig. 2. Sodalime fusion yielded inactive



(Numbers in parenthesis are relative specific activities)

Fig. 2. Degradation of the ajmaline-C^{14} derived from malonic acid-1,3-C^{14}

harman (VI). Kuhn-Roth oxidation gave acetic acid which contained only a small amount of radioactivity (3%). Wolff-Kischner reduction of the ajmaline[6] afforded deoxydihydroajmaline (VII), which was oxidized to deoxydihydroajmalal (VIII) with lead tetraacetate in benzene, using the procedure which Bartlett et al.[7] used on deoxyajmaline. This aldehyde

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[6] F.A.L. Anet, I. Chakravarti, R. Robinson and E. Schlittler, J. Chem. Soc. 1242 (1954).

[7] M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R.L.S. Amai, P. Beak, N. V. Bringi, and E. Wenkert, J. Amer. Chem. Soc. 84, 622 (1962).

was allowed to react with phenyl-lithium in ether and the phenylated product was oxidized without purification to yield benzophenone which had 74% of the specific activity of the ajmaline. The formation of benzophenone rather than benzoic acid was unexpected and may indicate that the aldehyde VIII underwent a Tishchenko reaction yielding an ester which then reacted with phenyl-lithium affording a gem-diphenyl derivative. This reaction is being investigated in more detail. These results indicate that malonic acid was incorporated into serpentine and ajmaline as a single unit with very little randomisation, and support our biogenetic hypothesis. The small amount of activity found at C_{18} and C_{19} in ajmaline and serpentine also implies that decarboxylation of malonic acid to acetic acid does not occur to any appreciable extent in R. serpentina.

Work is proceeding on further degradation of the radioactive serpentine and reserpine derived from malonic acid-1,3-C^{14}.

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