Tetrahedron Letters No. 36, pp 3477 - 3480, 1973. Pergamon Press. Printed in Great Britain.

THE BIOSYNTHESIS OF CHRYSANTHEMUM DICARBOXYLIC ACID, AND THE ORIGIN OF THE 'PYRETHRIN II's'

S. A. Abou Donia, Christine F. Doherty and Gerald Pattenden[1]

Department of Chemistry, University College, Cathays Park, Cardiff, CF1 1XL

(Received in UK 3 July 1973; accepted for publication 23 July 1973)

Chrysanthemum monocarboxylic acid (CMA) (3a), and the related acid (2a) occur as insecticidal esters [where (1b-d) constitute the alcohol moieties] in Chrysanthemum cinerariaefolium.[2] The two acids represent the only examples of naturally occurring monocyclic monoterpenes containing cyclopropane ring structures. The carbon frameworks in these monoterpenes[3] are derived biogenetically by an unusual 'tail-to-middle' combination of iso-pentane units[4], and certain stereochemical and other features of this combination were discussed in the preceding communication. CMA is structurally analogous to 'presqualene', and several groups have suggested biogenetic pathways which link chrysanthemyl to the acyclic artemisyl and santolinyl monoterpenes.[3] We now report some results of feeding experiments with ^{14}C-CMA in C. cinerariaefolium which link (3a) and (2a) biogenetically, and show that (2a) (and the natural esters from 2a)* can be derived from (3a) (and the natural esters from 3a)*, in Nature by an oxidative-esterification sequence at the vinyl methyl group of (2a).

Dissected achenes from C. cinerariaefolium were incubated with the potassium salt of 1(R),3(R)-(+)-trans-^{14}C-CMA (3a, labelled as indicated; 5μCi., 13.5 mg per 10 g. achenes)[5] employing the vacuum infiltration technique. Separation and saponification of the radioactive 'pyrethrin I's' and 'pyrethrin II's' from several feeding experiments (a total of 35μCi was fed) produced

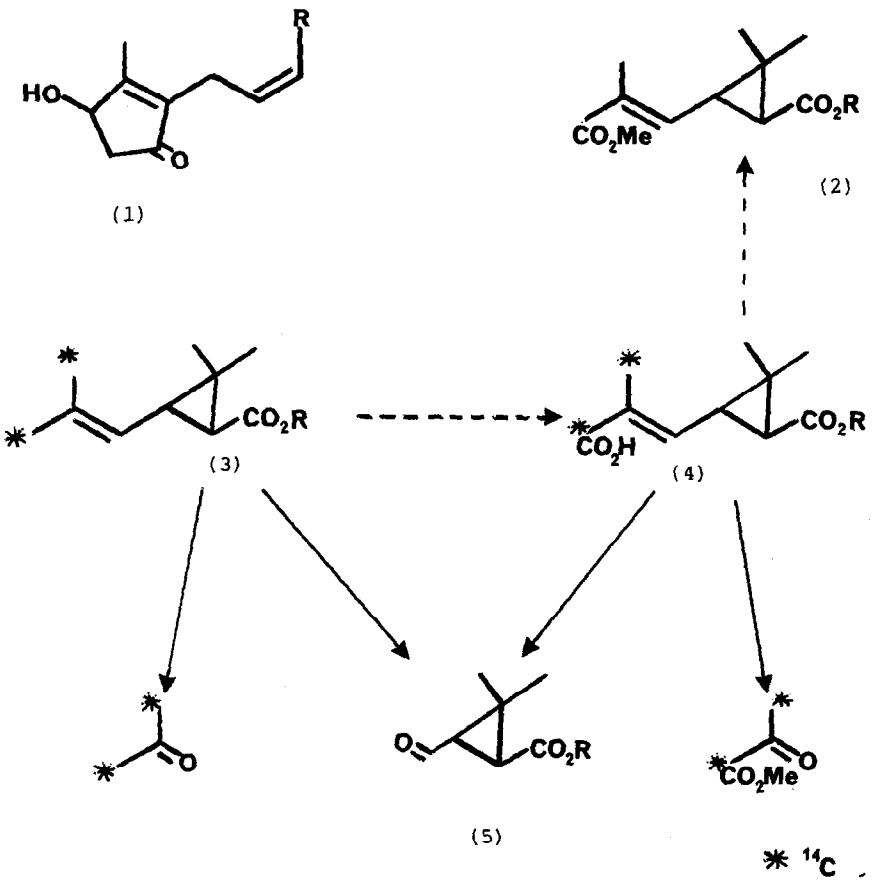
*The naturally occurring esters from (2a) and (1a-c) are known collectively as the 'pyrethrin II's' whereas those from (3a) and (1a-c) are known collectively as the 'pyrethrin I's.'

^{14}C-CMA (3a) (activity 1.6 x 10^7 d.p.m. mmole.,$^{-1}$ incorporation yield 18.5%) and ^{14}C-di-acid (4a) (activity 0.93 x 10^4 d.p.m. mmole.,$^{-1}$ incorporation yield 0.08%) respectively, which were rigorously purified to constant activity by chromatography and crystallisation (the CMA as the corresponding amide).

Cleavage of the side chain in ^{14}C-CMA (total activity 46.3 x 10^3 d.p.m.) using OsO_4-$NaIO_4$, and separation and purification of the 2,4-dinitrophenyl hydrazones (2,4-DNP) of the carbonyl products, gave acetone 2,4-DNP, activity 41.4 x 10^3 d.p.m. and inactive 2,4-DNP of cyclopropane aldehyde (5b). Similarly, degradation of the ^{14}C-di-acid (4a; total activity 3.29 x 10^3 d.p.m.) produced methyl pyruvate 2,4-DNP, activity 3.4 x 10^3 d.p.m. and inactive 2,4-DNP of (5b). These degradation data thus showed that no skeletal modifications had occurred in (3a) either prior to or during its incorporation into the pyrethrin I's and pyrethrin II's.

The side chain ester methyl group in the pyrethrin II's (2a; R = 1) has been shown from previous studies to be derived from L-methionine.[4] Together with this information, the present data indicate that the 'pyrethrin II's' can be derived from the 'pyrethrin I's' in Nature by an oxidative process at the vinyl methyl group of the CMA part of the esters leading to (4; R = 1b-d) (presumably via the step-wise sequence $CH_3 \rightarrow CH_2OH \rightarrow CHO \rightarrow CO_2H$), followed by 'esterification' of the latter with the S-methyl group from L-methionine. The relatively low incorporation of ^{14}C-CMA into the 'pyrethrin II's', when compared with that incorporated into the 'pyrethrin I's', is possibly due to the absence of the appropriate oxidative enzymes (to effect the conversion $CH_3 \rightarrow CO_2H$) during the early flowering season when the present feeding experiments were carried out. Feeding later in the season could possibly result in increased incorporations into the 'pyrethrin II's.'

Recent investigations on the metabolism of pyrethrins[6] have shown that the rethrin esters from (3a) and (1a,d) are metabolised in insects and mammals principally by oxidation at the vinyl methyl group of the CMA part of the ester, forming in succession the corresponding hydroxymethyl, aldehyde and carboxylic acid (4, R = 1a,d) compounds. It seems likely, therefore,



a R = H; b R = Me; c R = Et; d R = $CH{:}CH_2$

that the manner in which Nature converts the 'pyrethrin I's' to the 'pyrethrin II's' in the plant, closely parallels the detoxifying route of the 'pyrethrin I's' in insect and mammalian bodies.

One of us (S.A.A.) is indebted to the Arabian Republic of Egypt, and another (C.F.D.) to the Science Research Council, for maintenance awards.

References

1. Address correspondence to this author at - Chemistry Department, The University, Nottingham, NG7 2RD.

2. M. Matsui and I. Yamamoto, 'Pyrethroids', in Naturally Occurring Insecticides, Edit. M. M. Jacobson and D. G. Crosby, Dekker, New York, 1971

3. See preceding paper, and references cited therein.

4. M. P. Crowley, P. J. Godin, H. S. Inglis, M. Snarey, and E. M. Thain, Biochim. Biophys. Acta, 60, 312 (1962); P. J. Godin, H. S. Inglis, M. Snarey and E. M. Thain, J. Chem. Soc., 5878 (1963).

5. L. Crombie, C. F. Doherty and G. Pattenden, J. Chem. Soc. (c) 1076 (1970).

6. I. Yamamoto, E. C. Kimmel, and J. S. Casida, and E. C. Kimmel, Pyrethrum Post, 11, 94 (1972); A. Kobayashi, K. Yamashita, K. Oshima, and I. Yamamoto, Agric. Biol. Chem., 35, 1961 (1971).