Tetrahedron Letters No. 22, pp 2199 - 2202, 1972. Pergamon Press. Printed in Great Britain.

Preskimmianine: The Biogenetic Precursor of Skimmianine from Dictamnus albus L

R. Storer and D.W. Young

School of Molecular Sciences, The University of Sussex, BRIGHTON BN1 9QJ, U.K.

(Received in UK 17 April 1972; accepted for publication 24 April 1972)

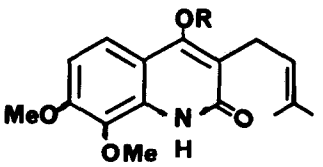
In connection with our work on the structure and biogenetic origins of fraxinellone,[1] we have examined the root of Dictamnus albus L for possible intermediates between limonin and fraxinellone. In the course of this study, we isolated by chromatography of the neutral fractions, a new alkaloid, $C_{17}H_{21}NO_4$ m.pt. = 151-2°C which we have named preskimmianine.

Preskimmianine exhibited NH and amide absorptions at 3100 and 1635 cm^{-1} respectively in the infra-red, and the ultra-violet spectrum with λ_{max}^{MeOH} = 218(4.67), 232 sh(4.43),249(4.22),257(4.32),287(3.91)297(3.95),309(4.00)321(4.09) and 334 nm (3.99) was typically that of a 2-quinolone.[2,3] No base shift was observed. The n.m.r. spectrum ($CDCl_3$) had an N-H absorption (which exchanged with D_2O) at 0.85τ, and three methoxyl absorptions at 6.03(6H) and 6.06τ(3H). The presence of a dimethylallyl group was indicated by two methyl singlets at 8.20 and 8.31τ and an olefinic triplet at 4.69τ which was coupled to a two-proton doublet at 6.63τ (J = 6.5 Hz). Two ortho coupled aromatic protons appeared at 2.52 and 3.15τ (J = 9 Hz).

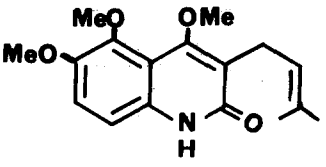
From the above evidence, preskimmianine must have the structure (I,R = CH_3) or II. The structure (I,R = CH_3) has the same methoxyl substitution pattern as the furanoquinoline alkaloid skimmianine (III) which has been shown[4] to be a constituent of the whole plant Dictamnus albus L. Since (I,R = CH_3) would be a likely biogenetic precursor of skimmianine, we felt that this was the more likely

structure. This has been verified by synthesis.

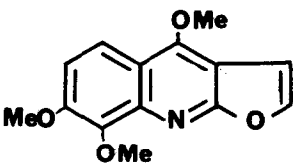
1-Chloro-3-methylbut-2-ene has been made from 3-methyl-but-2-enol by the method of Grundon[5] or, more conveniently, by adaptation of a method[6] involving addition of hydrochloric acid to isoprene. The chloride reacted with sodium diethylmalonate[5] to yield diethyl-(3-methylbut-2-enyl)-malonate(IV), and this was condensed with 2,3-dimethoxyaniline[7] to yield 3(3-methylbut-2-enyl)-4-hydroxy-7,8-dimethoxy-2-quinolone (I,R = H), m.pt. = 214-216°C. This was readily converted by diazomethane to preskimmianine (I,R = CH_3) identical in all respects to the natural product.



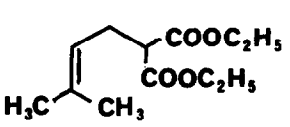
I



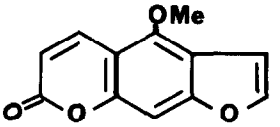
II



III



IV

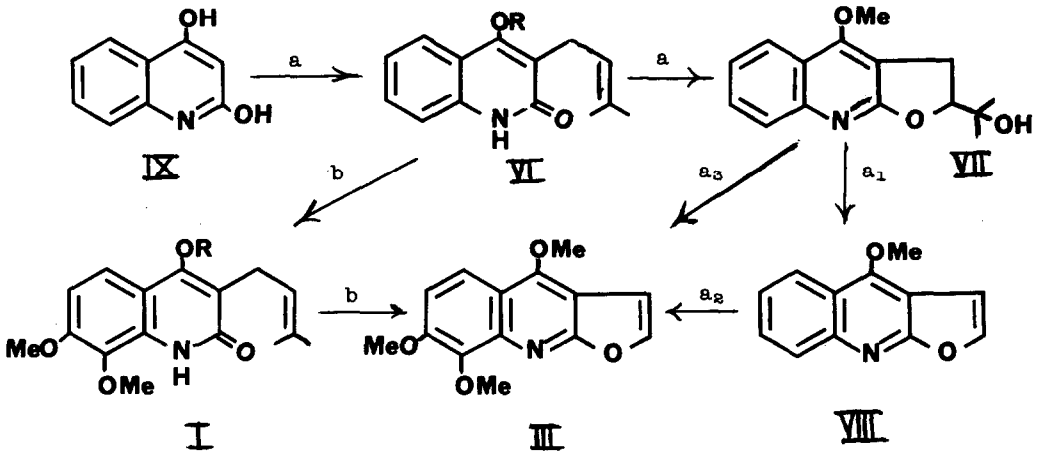


V

The fact that preskimmianine (I,R = CH_3) and skimmianine (III) co-occur in Dictamnus albus L suggests that preskimmianine is the biogenetic precursor of skimmianine. The biosynthesis of skimmianine is very similar to that of the parent furanoquinoline alkaloid dictamnine (VIII). The quinoline portion of skimmianine is known to be derived from anthranilic acid and acetate[8] and the furan portion of the alkaloid is derived from mevalonate.[9] The idea that the furan ring of natural products such as furanoquinoline alkaloids, benzofurans, and furocoumarins such as the Dictamnus albus product bergapten (V), are derived from isopentenyl precursors such as (VI) has long been held[10,11,12] and Grundon[13,14] has shown that the C^{14}-labelled dimethylallylquinolone (VI) and

C^{14}-labelled platydesmine (VII) are incorporated into dictamnine (VIII) in Skimmia japonica. 2.4-Dihydroxyquinoline (IX) is incorporated into both dictamnine and, to a lesser extent, skimmianine in this plant and so pathway a_1 in the following scheme is a likely route for dictamnine biosynthesis.

Grundon[14] found that platydesmine (VII, R = H) was incorporated into dictamnine to the extent of 18.9% and into skimmianine to the extent of 0.1% and suggested that the hydroxylation at positions 7 and 8 in skimmianine biosynthesis must occur subsequent to cyclisation of dimethylallyquinolone (VI) to platydesmine. Thus biosynthesis of skimmianine would involve one of the pathways a in the following scheme. Our finding of preskimmianine as an alkaloid in Dictamnus albus L would suggest that, at least in this plant, hydroxylation at positions 7 and 8 precedes cyclisation to a platydesmine-like structure, as indicated in pathway b in the scheme. It may be that the very low incorporation of platydesmine into skimmianine in Skimmia japonica[14] where incorporation into dictamnine is so efficient, indicates that platydesmine is not on the main pathway to skimmianine even in this plant.



SCHEME

Acknowledgments. One of us (R.S.) wishes to thank the S.R.C. for a maintenance award.

References

1. P. Coggon, A.T. McPhail, R. Storer and D.W. Young, Chem. Comm., 1969, 828.
2. G.W. Ewing and E.A. Steck, J. Amer. Chem. Soc., 1946, 68, 2181.
3. R. D. Brown and F.N. Lahey, Austral. J. Sci. Res., 1950, A3, 615.
4. (a) H. Gertig and H. Grabarczyk, Acta Polon. Pharm., 1961, 18, 97.
   (b) W. Renner, Naturwiss., 1961, 48, 53.
5. E.A. Clarke and M.F. Grundon, J. Chem. Soc., 1964, 438.
6. H.E. Ramsden and A.J. Gibbons, German patent, 1, 117, 107 (1961) cf Chem. Abs., 1964, 58, 2369d.
7. F. Mauthner, J. prakt. Chem., [2], 1937, 149, 328.
8. M. Matsuo, M. Yamazaki and Y. Kasida, Biochem. Biophys. Res. Comm., 1966, 23, 679.
9. A.O. Colonna and E.G. Gros, Chem. Comm., 1970, 674.
10. A.J. Birch and H. Smith, Chem. Soc. Special Publicn. No.12, 1958, 1.
11. R. Aneja, S.K. Mukerjee and T.R. Seshadri, Tetrahedron, 1958, 4, 256.
12. J.R. Price, Pure Appl. Chem., 1961, 2, 367.
13. J.F. Collins and M.F. Grundon, Chem. Comm., 1969, 621.
14. M.F. Grundon and K.J. James, Chem. Comm., 1971, 1311.