Application of the Claisen Rearrangement to the Synthesis of Heterocyclic Bicyclo[2,2,2]octenones: an Approach to the Morellins Based on New Biogenetic Suggestions

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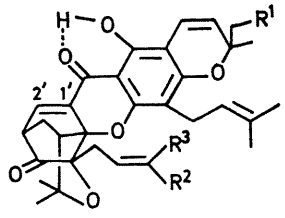
Summary The Claisen rearrangement followed by an intramolecular Diels–Alder reaction on the intermediate cyclohexane dienone leads to the novel heterocyclic bicyclo[2,2,2]octenone structure found in the morellins and gambogic acid, and it is suggested that this synthetic pathway may be involved in the biogenesis of these natural products.

THE carbon skeleton found in gambogic acid (1)[1,2] and the morellins (2—7)[3–5] (metabolites from *Garcinia* species of the Guttiferae family) have been the subject of study for more than 150 years,[1] and in 1963 the full structure of morellin[3,5] was published by Venkataraman *et al.* on the basis of an *X*-ray crystallography study[3] of isomorellin *p*-bromosulphonate.[5] This revealed that morellin (2) has the novel heterocyclic bicyclo[2,2,2]octenone and subsequently the structures of the other members of this class were derived largely by spectral methods and by comparison with the

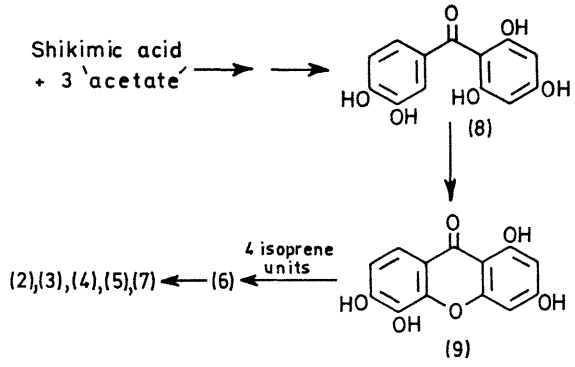


	R^1	R^2	R^3	
(1)	$Me_2CH{=}CH\,CH_2$	Me	CO_2H	gambogic acid
(2)	H	Me	CHO	morellin
(3)	H	CHO	Me	isomorellin
(4)	H	Me	CO_2H	morellic acid
(5)	H	CO_2H	H	isomorellic acid
(6)	H	Me	Me	deoxymorellin
(7)	H	CHO	Me	dihydroiosmorellin

(single bond at C-1′ and C-2′)

n.m.r. spectrum of morellin. More recent work has shown that this ring system exists in bronianone (isolated from *Garcinia* hombroniana Pierre) which is a polyisoprenylated benzophenone derivative.[6] We now report a synthesis of the heterocyclic bicyclo[2,2,2]octenone system found in the morellins and gambogic acid, and which is based on new biogenetic suggestions for the formation of these natural products.

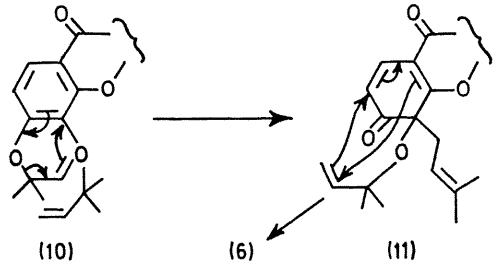
In contrast to previous biogenetic suggestions,[5,7] we regard the morellins and gambogic acid to be derived directly from 1,3,5,6-tetrahydroxyxanthone (9) formed by oxidative coupling of a benzophenone such as maclurin (8).[8,9] This is supported by the presence of both 5,6- and 6,7-oxygenated xanthones in *Garcinia* species.[8,10] Isoprenylation of 1,3,5,6-tetrahydroxyxanthone with four isoprene units can lead to deoxymorellin (6) and related metabolites (Scheme 1). The postulate[1,3,5] that isoprenylation occurs at C-7 in the shikimate derived ring is unattractive since 7-isoprenylxanthones are as yet unknown.[8] An alternative route to the heterocyclic bicyclo[2,2,2]octenone system involves a Claisen rearrangement on the 5,6-diallyl ether (10) followed



SCHEME 1

by a Diels–Alder reaction on the intermediate dienone (11) (Scheme 2). This pathway is favoured because migration of the allyl group in 6-allyloxyxanthones[11] occurs exclusively to the 5-position and although *intramolecular* Diels–Alder adducts have not been previously *isolated* from rearrangements of allyl aryl ethers, adducts have been obtained from rearrangement of aryl propargyl ethers.[12] Furthermore, while elevated temperatures are required for the Claisen rearrangement *in vitro*, allyl migration is involved in the biosynthesis of some quinoline alkaloids[13] and in the transformation of chlorismic acid to prephenic acid.[14]

To develop a new synthetic route to the morellins based on these suggestions (Scheme 2), the Claisen rearrangement of

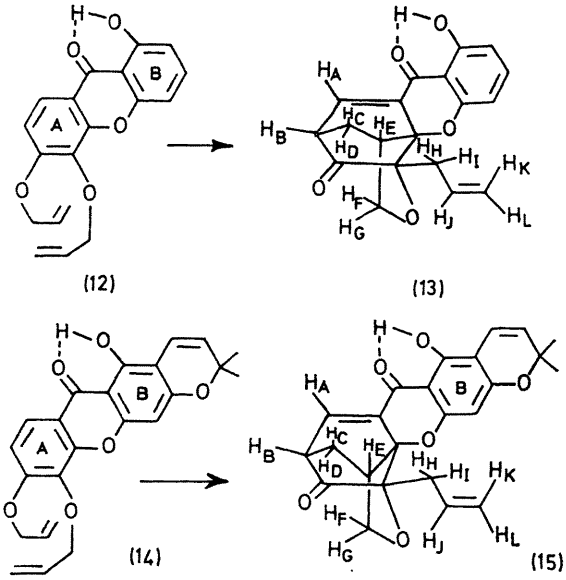


SCHEME 2

1-hydroxy-5,6-diallyloxyxanthone (12) and jacareubin 5,6-diallyl ether (14) was studied. In both cases by boiling in decalin for 14 h, rearrangement occurred to give the bicyclo-[2,2,2]octenones (13 and 15). The structures are supported by spectroscopic examinations and comparison of the data

with that recorded for the morellins. Thus comparison of the spectra of the starting materials (12 and 14) and products (13 and 15) in both cases shows that ring A has lost its aromatic character, and with the involvement of one allyl group has been transformed to an alicyclic ketone; ring B remains unchanged. The u.v. spectra of the products (13 and 15) confirm the loss of the xanthone chromophore and as expected, the absorption maxima of (15) [λ_{max} nm (ϵ) 233 (16,400), 240 (16,400), 275 (17,500), 287 (20,200), and 345 (14,400)] resembles that of morellin (2) [λ_{max} nm (ϵ) 234 (30,200) 279 (17,400), 291 (17,400), and 361 (14,300)].[1] The i.r. spectra of the bicyclo[2,2,2]octenones (13 and 15) show the aliphatic ketone group at 1733 and 1742 cm^{-1}, respectively, and the aryl ketone at 1645 and 1640 cm^{-1}, respectively. The chemical shifts for the protons in both bicyclo[2,2,2]octenones (13 and 15) are given: H_A, τ 2·73d and 2·71d (both J 7 Hz); H_B, τ 6·58c; (in both cases); H_C and H_D, τ 8·05—8·35c and 8·10—8·40c; H_E, H_H and H_I, τ 7·1—7·9c in both cases; H_F, τ 5·63q in both cases (J 7·5 and 4 Hz); H_G, τ 6·24d and 6·25d (both J 7·5 Hz); H_J, H_K and H_L, τ 4·5—5·15c (2H) and 5·38c (1H) in each case, and the assignments are supported by spin-decoupling experiments. Thus, double irradiation at H_A causes H_B to form a quartet, while double irradiation at H_B causes H_A to appear as a singlet and simplifies the signals due to H_C and H_D in the region of τ 8·2—8·4 (2H). Double resonance at τ 8·16 causes H_B to appear as a doublet (J 7 Hz). H_F is coupled to H_G and H_E, but H_G is not coupled to H_E because the dihedral angle approaches 90°. Thus double resonance at H_F causes H_G to appear as a singlet, whereas double irradiation at H_G causes H_F to appear as a doublet (J 4 Hz). Double irradiation at H_E (τ 7·42) shows the geminal coupling between H_F and H_G as J 7 Hz.

The mass spectral fragmentation of both (13 and 15) shows that the molecular ion loses 28 m.u. (CO) followed by 41 m.u. (C_3H_5) and again 28 m.u. (CO). In addition, due to the presence of the 2,2-dimethylpyran ring in (15) 15 m.u.



are lost and the most intense peak is at m/e 363 ($M-15-28$)

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