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SESQUITERPENOIDS OF *CINNAMOSMA FRAGRANS* BAILLON

STRUCTURE OF BEMARIVOLIDE, BEMADIENOLIDE AND FRAGROLIDE*

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Abstract—Structures I, IX and XII have been assigned respectively to bemarivolide, bemadienolide and fragrolide, three new sesquiterpenoid lactones with the drimane skeleton. Some aspects of the reactivity of this class of compounds are discussed.

THE bark of *Cinnamosma fragrans* contains a number of sesquiterpenes possessing the drimane skeleton.[1] Evidence for the structure and absolute stereochemistry of the three major constituents, cinnamolide, cinnamosmolide and cinnamodial has been elucidated.[1] The structure of the minor components of *C. fragrans*, bemarivolide, bemadienolide and fragrolide and their correlation with compounds of known structure and absolute stereochemistry is the subject of this paper.

Bemarivolide (I). Elementary analysis and mass spectral data indicate a formula $C_{17}H_{24}O_4$ The NMR spectrum of I shows resonances for three tertiary methyls and for one acetate group (3H, s at 2·3 δ); the spectrum also shows the AB part of an ABX system at 4·32 δ (2H, octet at C-11), 5·82 δ (1H, qu at C-6; $J_1 = 3{\cdot}5$, $J_2 = 7$ c/s) is assigned to a proton on a carbon carrying an acetoxyl group and 6·76 δ (1H, tr at C-7) is attributed to a vinylic proton showing equal coupling ($J = 3{\cdot}5$ c/s) with the protons at C-6 and C-9. The presence of an α,β-unsaturated-γ-lactone in the structure of bemarivolide (I) is indicated by an UV absorption max at 217 mμ and absorption bands in its IR spectrum at 1762 and 1697 cm^{-1}; the latter also shows an absorption at 1735 cm^{-1} confirming the presence of an acetoxyl group in I.

Catalytic hydrogenation of bemarivolide (I) with Adams catalyst yielded, besides the normal hydrogenation product (II), a quantity of *cis*-dihydroconfertifolin (III) which must arise by the hydrogenolysis of the allylic acetate. These two products were also obtained when 6β-acetoxyconfertifolin (IV), prepared from cinnamosmolide,[1] was hydrogenated over Adams catalyst in acetic acid. These results, together with spectroscopic data, clearly indicate the structure and absolute stereochemistry shown in I

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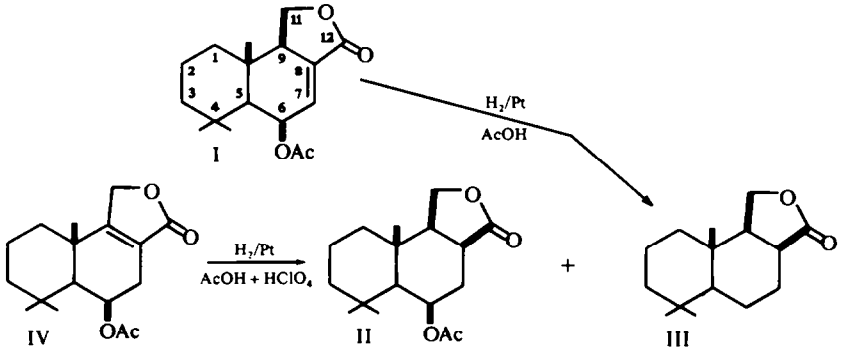
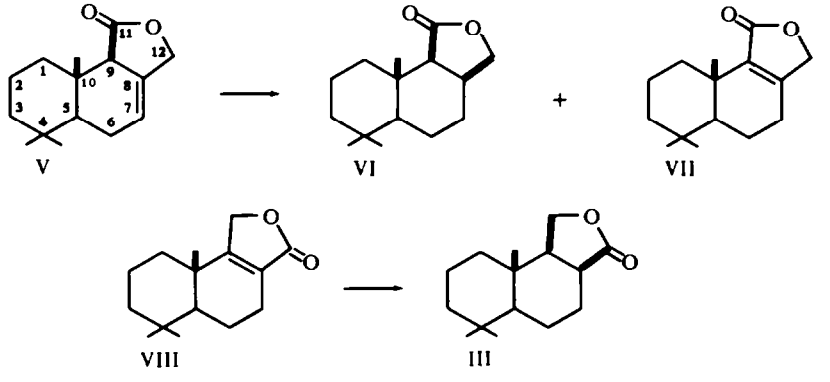
for bemarivolide; furthermore, they provide evidence that 6β-acetoxyconfertifolin (IV) on hydrogenation must be converted, at least in part, to bemarivolide (I), thus accounting for the observed hydrogenolysis of the acetate group.

The migration of a double bond from a di- or tri- to a tetra-substituted position on catalytic hydrogenation is not exceptional,[2] and proof that such a rearrangement



occurs is obtained by the isolation of the compound with the tetrasubstituted double bond together with the normal hydrogenation product. The reverse migration is more difficult to ascertain since the less substituted double bond is, normally, more readily hydrogenated and the intermediate escapes detection.

Overton *et al.*[3] observed that drimenin (V) on hydrogenation yields the dihydro derivative (VI) and isodrimenin (VII) and that the latter is inert to hydrogenation under the conditions in which confertifolin (VIII) was hydrogenated to *cis*-dihydroconfertifolin (III). To explain this, they postulated that the hydrogenation of the double bond in VIII proceeds *via* its migration from C-8 to C-7. Such a migration is not possible for isodrimenin (VII) because of the high energy required to break the conjugated system and therefore the tetrasubstituted double bond cannot be hydrogenated easily. This hypothesis finds confirmation not only in the observation that

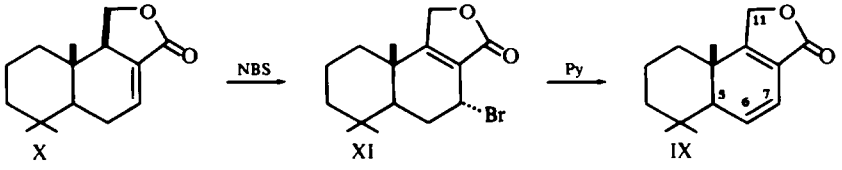


hydrogenation of IV partially occurs with hydrogenolysis, but also in the fact that treatment of IV in acetic acid with Adams catalyst and traces of hydrogen, results in an isomerization of IV to I; the equilibrium mixture so far obtained is, however,

largely in favour of the tetrasubstituted double bond as shown by gas chromatography.

Bemadienolide (IX). A formula $C_{15}H_{20}O_2$ for bemadienolide is supported by elementary analysis and mass spectral data. The NMR spectrum of IX includes resonances for three tertiary methyls, a methylenoxy group (2H broad singlet at 4·89 δ) and two vinylic hydrogens (2H, m at 6·34 δ). Its UV spectrum shows the typical absorption max for an α,β-unsaturated-γ-lactone and a max at 273 mμ attributed to a conjugated homoannular diene system. The IR spectrum of IX shows absorption bands at 1753 and 1641 cm^{-1} confirming the presence of an unsaturated-γ-lactone group.

At this stage the structure IX was assumed for bemadienolide and proof was obtained by its correlation with cinnamolide (X). Treatment of cinnamolide with N-bromosuccinimide (NBS) results in the migration of the double bond from C-7 to C-8 and introduction of a Br atom in 7α. In fact the NMR spectrum of XI shows that

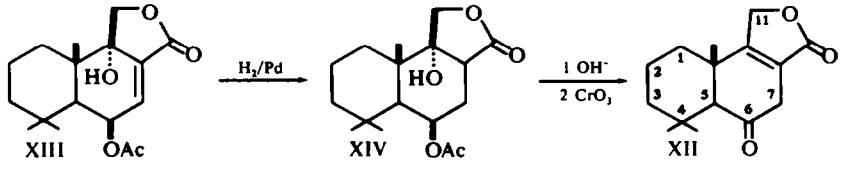


X XI IX

the signal for the vinylic proton present in the NMR spectrum of X has been replaced by a multiplet at 5·12 δ; the NMR spectrum also includes signals for the methylenoxy protons (2H at 4·8 δ) which, although lacking major coupling, shows homoallylic coupling (J = 1 c/s). The spectroscopic data are consistent with the presence (XI; 7α-bromoconfertifolin) of an α,β-unsaturated-γ-lactone. The behaviour of cinnamolide with NBS, which is analogous to that of cinnamosmolide with thionyl chloride described below, is not unexpected when one considers the tendency of the C-7 double bond in these compounds to isomerize to the tetrasubstituted position.

Treatment of the bromoderivative (XI) with hot pyridine results in dehydroalogenation and affords a product identical in all respects with bemadienolide (IX).

Fragrolide (XII). Elementary analysis and mass spectral data indicate the formula $C_{15}H_{20}O_3$. Its NMR spectrum shows singlets of three tertiary methyls and a one-proton singlet at 2·66 δ assigned to the proton at C-5. Multiplets at 3·37 δ (2H) and at 4·99 δ (2H) are assigned to the C-7 and C-11 protons. The presence of an α,β-unsaturated-γ-lactone and a non-conjugated ketone in fragrolide (XII) is indicated by its UV and IR spectra. The resulting structure deduced for fragrolide was confirmed by identity of XII with a compound previously obtained from cinnamosmolide (XIII) by alkaline treatment of its dihydroderivative (XIV) and oxidation of the unsaturated alcohol obtained.

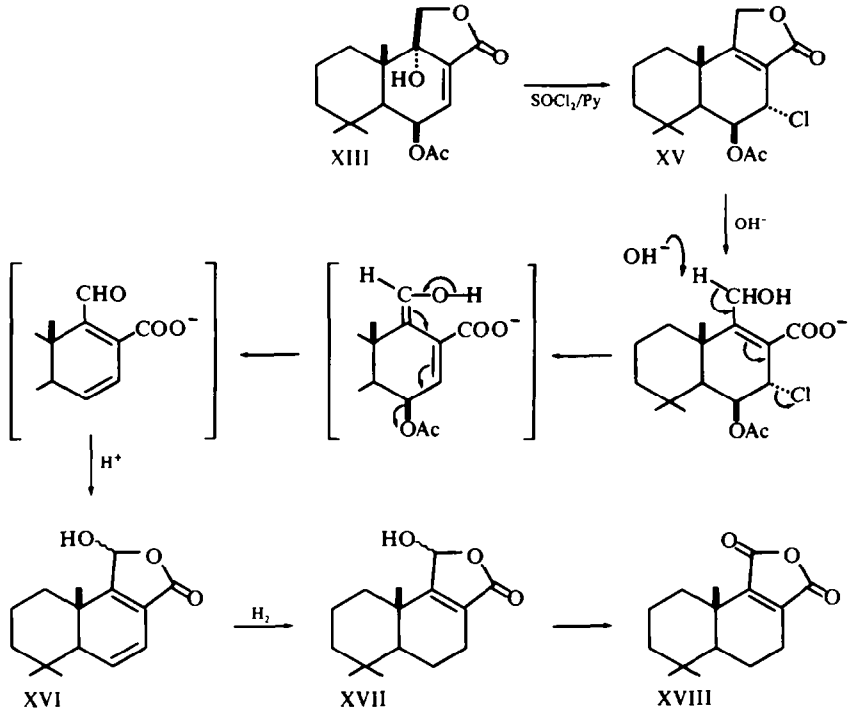


XIII XIV XII

The ease of migration of the double bond from C-7 to C-8 in these compounds indicates the correlation of cinnamosmolide (XIII) to valdiviolide (XVII) and winterin (XVIII).[4]

Treatment of cinnamosmolide (XIII) with thionyl chloride and pyridine yields a compound the spectroscopic characteristics of which are consistent with structure XV. Thus its NMR spectrum shows a multiplet at 4·55 δ assigned to the C-7 proton which is coupled with the vicinal proton at C-6 and homoallylically with the C-11 protons.

Treatment of the chloroderivative (XV) with alkali and subsequent acidification gives the hydroxybutenolide (XVI) which formally arises from elimination of the chloro and acetoxy group presumably occurring *via* the sequence shown. Structure XVI for the product is evident from its spectroscopic data; its UV spectrum shows a max at 285 mμ assigned, in analogy with IX, to a homoannular conjugated diene.

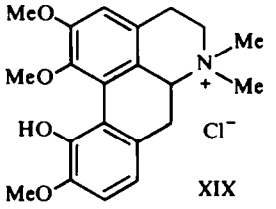


Absorption bands in the IR spectrum at 3546, 3311, 1761, 1648 cm^{-1} are consistent with the presence in XVI of a hydroxyl and a α,β-unsaturated-γ-lactone group. The NMR spectrum of XVI shows, besides resonances for three tertiary methyls and one hydroxylic proton, a multiplet at 6·3 δ (3H) assigned to two vinylic protons at C-6 and C-7 and the hemiacetal proton at C-11.

Confirmation for the structure (XVI) was obtained by catalytic hydrogenation which gives a compound identical in all respects to valdiviolide (XVII). Whereas the usual hydrogenation catalysts give mixtures of products which could not be separated.

Wilkinson's soluble catalyst[7] selectively hydrogenates the less substituted double bond.

The crude extract of the bark of *Cinnamosma madagascariensis*, another species of the Canellaceae family, does not contain any sesquiterpenoid compound; on the contrary, large quantities of anethole and related compounds were isolated. An alkaloid is also present: its chemical and physical properties are identical with those reported for chakranine[6] (XIX) previously isolated by Bhatnagar *et al.* from the roots of *Bragantia wallichii*.



XIX

EXPERIMENTAL

The general procedures are described in the accompanying paper.[1]

Isolation of bemarivolide (I). The fractions 31–34 combined with the mother liquor of the fractions 35–38 of the chromatography of *C. fragrans* crude extract,[1] on crystallization from ethyl ether gave a mixture of bemarivolide, cinnamosmolide and cinnamodial (500 mg). The mixture was chromatographed on Al_2O_3 (15 g; activity III) using benzene as eluent. The crude product obtained from the first fractions, on crystallization from isopropyl ether gave *bemarivolide* (I; 70 mg), m.p. 137–138°; $[\alpha]_D$ −258°; λ_{max} (isooctane) 217 mμ (log ε 3·96). (Found: C, 69·75; H, 8·20. Calc. for $C_{17}H_{24}O_4$: C, 69·83; H, 8·27%).

Isolation of fragrolide (XII). Fractions 12–19 combined with the mother liquor of the fractions 6–11 of the chromatography of *C. fragrans* crude extract[1] on crystallization from light petroleum–ethyl ether gave impure cinnamolide. The residue obtained after evaporation of the mother liquor (3·5 g) was chromatographed on Al_2O_3 (140 g; activity III) and fractions of 30 ml were collected using the following solvents as eluents: light petroleum (fr 1–8), light petroleum–benzene (9:1; fr 9–26), light petroleum–benzene (8:2; fr 27–38), light petroleum–benzene (1:1; fr 39–55), benzene (fr 56–75), benzene–$CHCl_3$ (9:1; fr 76–82). The crude product from fractions 62–67 (250 mg), twice rechromatographed on Al_2O_3 (10 g; activity III) and crystallized from isopropyl ether yielded *fragrolide* (XII; 25 mg), m.p. 165–166°; $[\alpha]_D$ +149°; λ_{max} (isooctane) 211 mμ (log ε 3·96); ν_{max} 1755, 1723, 1675 cm^{-1}. (Found: C, 72·50; H, 8·25. Calc. for $C_{15}H_{20}O_3$: C, 72·55; H, 8·20%).

Isolation of bemadienolide (IX). Fractions 1–8 (80 mg) of the chromatography of fragrolide were absorbed on Al_2O_3 (5 g; activity III) and chromatographed: with light petroleum–benzene (8:2) some 40 mg of bemadienolide largely contaminated by cinnamolide were obtained. Preparative VPC yielded pure *bemadienolide* (IX; 25 mg), m.p. 124–125°; $[\alpha]_D$ +22°; λ_{max} 273 mμ (log ε 3·42). (Found: C, 77·58; H, 8·55. Calc. for $C_{15}H_{20}O_2$: C, 77·55; H, 8·69%).

Hydrogenation of bemarivolide (I). Bemarivolide (120 mg) in AcOEt (10 ml) was hydrogenated over PtO_2 (140 mg) until the absorption of H_2 ceased (30 min). The soln filtered, evaporated to dryness and the residue chromatographed on Al_2O_3 (5 g; activity II) with light petroleum, light petroleum–benzene, benzene, benzene–AcOEt as eluents yielded *cis*-dihydroconfertifolin (III; 45 mg from light petroleum–benzene; m.p. 134°; $[\alpha]_D$ −5°), and 6β-acetoxy-*cis*-dihydroconfertifolin (II; 50 mg from benzene–AcOEt 9:1; m.p. 135–136°; $[\alpha]_D$ −25·1°).

Treatment of cinnamolide (X) *with NBS*. Cinnamolide (1 g) and NBS (0·76 g) in CCl_4 (10 ml) were refluxed for 5 hr. The soln was filtered, evaporated *in vacuo* and the residue was chromatographed with light petroleum and light petroleum–AcOEt as eluents. Light petroleum–AcOEt (8:2) fractions, on crystallization from isopropyl ether gave *7α-bromoconfertifolin* (XI; 1 g), m.p. 128–129°; $[\alpha]_D$ +47·4°; λ_{max} (isooctane) 217 mμ; ν_{max} 1752, 1662 cm^{-1}. (Found: C, 57·50; H, 6·65. Calc. for $C_{15}H_{21}BrO_2$: C, 57·56; H, 6·76%).

Dehydrobromination of 7α-bromoconfertifolin (XI). 7α-bromoconfertifolin (100 mg) in pyridine (3 ml) was left at 90° for 15 hr. Conventional work-up gave a crude residue (70 mg) which, after chromatography with CH_2Cl_2 as eluent and crystallization from hexane, yielded a product identical in all respects with bemadienolide (IX).

Treatment of cinnamosmolide (XIII) *with thionyl chloride*. Cinnamosmolide (950 mg) in pyridine (10 ml) was treated with $SOCl_2$ (1·4 ml) at 0° and left at room temp overnight. Usual work-up gave a crude residue which, after chromatography with CH_2Cl_2 as eluent and crystallization from AcOEt–light petroleum yielded the *chloroderivative* (XV; 600 mg), m.p. 178°; $[\alpha]_D$ +46·7°; λ_{max} 216 mμ (log ε 4·12); ν_{max} 1762, 1670 cm^{-1}; NMR: 2·1 δ (3H, s, $C\underline{H}_3$—COO—); 4·55 δ (1H, m, C-7), 4·91 δ (2H, m, C-11) and 5·62 δ (1H, m, C-6). (Found: C, 62·56; H, 7·07. Calc. for $C_{17}H_{23}ClO_4$: C, 62·48; H, 7·05%).

Alkaline treatment of chloroderivative (XV). The chloroderivative (300 mg) in 5% KOH aq (6 ml) was stirred for 18 hr at room temp. The soln was acidified with 1N HCl, stirred for 1 hr and extracted with CH_2Cl_2. Evaporation of the solvent gave a crude product (180 mg) which after chromatography and crystallization from isopropyl ether yielded *hydroxybutenolide* (XVI; 100 mg), m.p. 171–172°; $[\alpha]_D$ +40·5; λ_{max} 284 mμ (log ε 3·55). (Found: C, 72·75; H, 8·20. Calc. for $C_{15}H_{20}O_3$: C, 72·55; H, 8·12%).

Hydrogenation of hydroxybutenolide (XVI). Hydroxybutenolide (100 mg) in benzene (6 ml) was hydrogenated over $RhCl(PPh_3)_3$ (Wilkinson's catalyst; 25 mg) for 24 hr. The soln evaporated *in vacuo* and the residue dissolved in ethyl ether, chromatographed on Florisil with the same solvent, and crystallized from AcOEt–light petroleum and then from benzene yielded valdiviolide (XVI; 35 mg), m.p. 177–178°; $[\alpha]_D$ +103°; λ_{max} 221 mμ (log ε 4·01).

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