separated as reported previously [6]. Known compounds were identified by comparing the 400 MHz ^{1}H NMR spectra with those of authentic material.

(+)-*Copaen*-8-*one* (**5**). Colourless oil (TLC: Et_2O–petrol, 1:4, R_f 0.69); IR $\nu_{max}^{CCl_4}$, cm^{-1}: 1715 (C=O); MS *m/z* (rel. int.): 218.167 $[M]^+$ (22) (calc. for $C_{15}H_{22}O$: 218.167), 203 $[M - Me]^+$ (9), 175 $[M - C_3H_7]^+$ (21), 134 $[M - C_5H_8O]^+$ (54), 119 $[134 - Me]^+$ (100); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.06 (*m*, H-1), 2.33 and 2.25 (*m*, H-2), 5.32 (*dddq*, H-3), 1.85 (*dd*, H-5), 1.99 (*d*, H-6), 2.33 (*m*, H-7), 2.49 and 2.44 (*d*, H-9), 2.28 (*m*, H-11), 0.81 (*d*, H-12), 0.97 (*d*, H-13), 0.85 (*s*, H-14), 1.71 (*dt*, H-15); *J* [Hz]: 1,5 = 6.5; 2,3 = 2',3 = 3,5 = 3, 15 ~ 1.5; 6,7 = 2; 11,12 = 6.5; 11,13 = 6; ^{13}C NMR ($CDCl_3$, C-1–C-15): δ 41.7, 30.0, 116.7, 142.0, 50.9, 40.7, 59.3, 213.1, 52.5, 38.5, 28.0, 19.3, 18.5, 21.3, 22.9; $[\alpha]_D^{24} = +14$ ($CHCl_3$; *c* 0.53); CD (MeCN): $\Delta\varepsilon_{305} + 0.12$.

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REVISED STRUCTURES FOR GUAIANOLIDE α-METHYLENEBUTYROLACTONES FROM FEVERFEW

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Key Word Index—*Tanacetum parthenium*; Compositae; feverfew; sesquiterpene lactones; parthenolide; guaianolides; migraine.

Abstract—The structures of two series of guaianolides present in feverfew, *Tanacetum parthenium*, are established as tanaparthin-α-peroxide, canin and *seco*-tanapartholide-A [major group] and the corresponding '*β*'-series [*β*-peroxide, artecanin and the *seco*-B derivative] using a combination of spectroscopic and X-ray crystallographic analyses and chemical transformations.

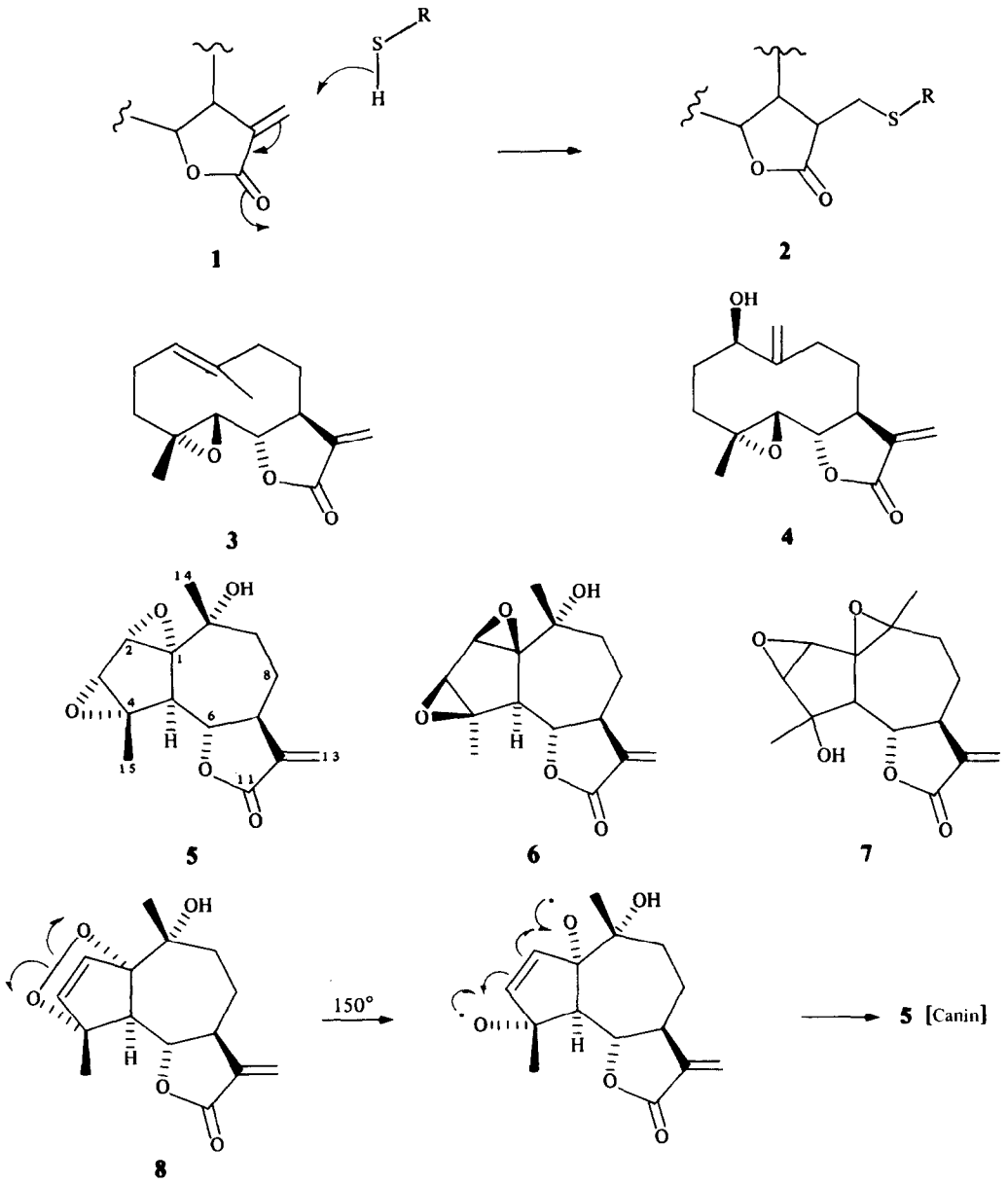
Feverfew, *Tanacetum parthenium*, has been used since ancient times for a variety of medicinal purposes, and has gained considerable prominence recently due to its ability to alleviate the symptoms of migraine [1–3], arthritis and psoriasis [4], and to inhibit blood platelet aggregation [5]. During the latter studies [5], a clear link was established between the anti-aggregatory properties of feverfew extracts and the presence therein of a series of sesquiterpene lactones containing α-methylenebutyrolactone units (**1**). This function is known to be a potent Michael acceptor of sulphydryl groups [(**1**)→(**2**)] [5, 6], and it appears [5] that such reactions are a key feature of the ability of feverfew extracts to suppress blood platelet aggregation *in vitro*, and are also possibly linked with the anti-inflammatory and migraine prophylactic properties of the plant. During our studies of feverfew extracts [5], some spectroscopic inconsistencies taken with the considerable confusion existing in the literature over the structures of two bis-epoxides, canin and artecanin, found in the plant led us to re-investigate the nature of these and related sesquiterpene lactones.

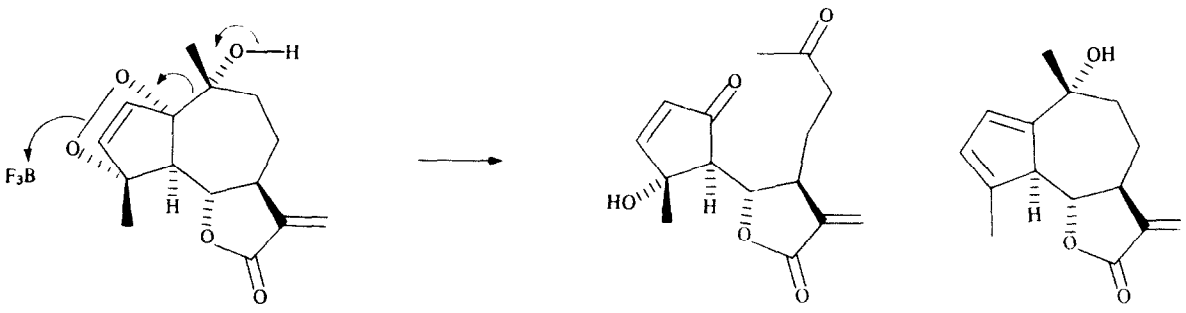
The major sesquiterpene lactone present in feverfew is parthenolide (**3**) [7], a germacranolide found in a variety of other plants [8]. Our extraction of feverfew also gave parthenolide (**3**) as the major component, accompanied by six other α-methylenebutyrolactones: epoxy-artemorin (**4**) [7], and a closely related series consisting of two bis-epoxides, an endoperoxide and two cyclopentenones [7]. Our starting point was the major bis-epoxide which appeared to be identical with canin, a material which has been the subject of a highly confusing series of structural assignments during the past two decades [9]. Originally designated as the bis-α-epoxide (**5**) [10], the compound was later given the bis-*β*-stereochemistry (**6**) and also confused with isomeric chrysartemin structures (**7**). X-Ray analysis [9] has established that canin (identical with chrysartemin A) from various *Artemisia* species is indeed the bis-α-epoxide (**5**) or its enantiomer. However, Bohlmann and Zdero [7] have used the bis-*β*-epoxide structure (**6**) for 'canin', the major bis-epoxide of feverfew. A divergence of spectroscopic data [7, 9] together with closely similar physical properties led us to carry out our own X-ray analysis of feverfew canin, which was shown to be identical with *Artemisia* canin [9], and to have the bis-

α-epoxide structure (**5**). In view of this finding, the structures proposed for the related endoperoxides in feverfew must also be revised as their stereochemistries were determined [7] by correlation with 'canin'. (The stereochemistries of the cyclopentenone lactones have not yet been determined).

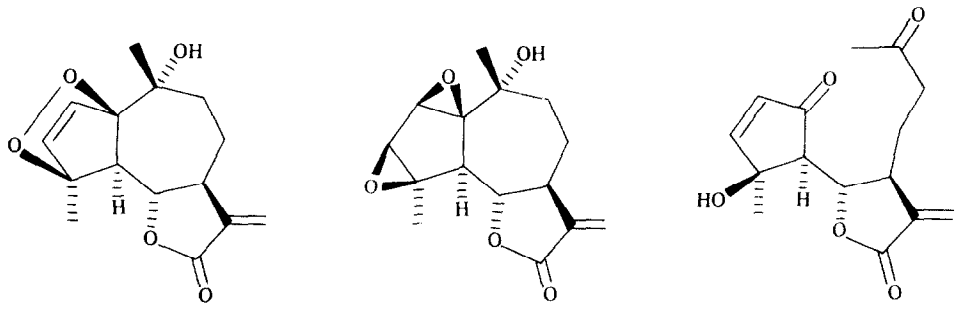
The crystalline endoperoxide isolated from our feverfew sample is a remarkably stable compound, which does however undergo a smooth, stereospecific, thermal rearrangement [11] [C_6D_6, sealed tube, 150° (oil bath); *ca* 1.5 hr] to give only canin (**5**); this endoperoxide must therefore be the α-isomer (**8**), and not the β-isomer as originally proposed [7], and should therefore be called tanaparthin-α-peroxide. The two cyclopentenone-containing lactones are though [7] to be derived from an endoperoxide precursor by acid-catalysed rearrangement. When tanaparthin-α-peroxide (**8**) was treated with $BF_3 \cdot OEt_2$ ($CHCl_3$, 20°, 15 hr), a single cyclopentenone was isolated (30%) after chromatography. This proved to be identical to the minor of the two previously unseparated natural cyclopentenone-lactones, which therefore has structure (**9**) and which should be called *seco*-tanapartholide A [7].

In the light of these findings, it seems likely that the precursor to the major α-series [(**5**), (**8**) and (**9**)] is the as yet unknown cyclopentadiene (**10**) [7] which undergoes addition of singlet oxygen mainly to the more exposed α-face, possibly assisted by the α-hydroxyl group. The minor series of metabolites therefore could arise from oxygen addition to the β-face of the diene (**10**) and is thus composed of tanaparthin-β-peroxide (**11**) [7] (not isolated in this work), the bis-β-epoxide artecanin (**6**) [12] and *seco*-tanapartholide B (**12**). Slightly more of the *seco*-B isomer (**12**) was isolated relative to the *seco*-A isomer (**9**) [*seco*-A (**9**), < 20 mg/kg; *seco*-B (**12**), *ca* 30 mg/kg] despite belonging to the 'minor' β-series. This, coupled with our





8 **9** **10**



11 **6** **12**

failure to isolate the β-endoperoxide (**11**), could indicate that the latter is less stable than the α-isomer (**8**) with respect to rearrangement [cf (**8**) to (**9**)]; this could be due to the *anti* disposition of the alcohol and peroxide groups.

A final point concerns the quantities of α-methylenebutyrolactones present in feverfew. With the exception of parthenolide (**3**), Bohlmann and Zdero [7] found less than 5 mg/kg of all the other lactones. Our plant samples, by contrast, provided *ca* 330 mg/kg of endoperoxide (**8**) and *ca* 56 mg/kg of canin (**5**). While variations within plant sources and the age of the plant material make comparisons difficult, we note that migraine sufferers and others who regularly take feverfew could be ingesting much larger quantities of these latter compounds than previously thought.

EXPERIMENTAL

Fresh leaves (3.6 kg) taken from flowering plants, grown at Sutton Bonington and Castle Donington, Leicestershire, were covered with $CHCl_3$ and the mixture agitated for *ca* 0.5 hr at ambient temp. The $CHCl_3$ was separated, the extraction repeated with fresh $CHCl_3$ and the combined extracts evapd to leave a viscous green oil (*ca* 43 g). A portion (10 g) was roughly fractionated by CC (Kieselgel HF 254; loading 100:1) using gradient elution from $CHCl_3$–petrol (1:1) up to $CHCl_3$–MeOH (9:1). Subsequent column chromatography, mainly using $CHCl_3$ and $CHCl_3$–MeOH as eluants gave the pure lactones. Crude fractions were most conveniently assayed for the presence of α-methylenebutyrolactones by IR ($\nu_{C=O}$ 1770–1790 cm^{-1}) and ^1H NMR spectra [in $CDCl_3$, the α-methylene protons occur as sharp doublets between δ5.4–5.8 (*J ca* 3 Hz) and between δ6.2–6.4 (*J ca* 3.5 Hz)], as well as by TLC analysis.

Canin (**5**). X-ray parameters as ref. [9]; mp 240°–242° [lit. [10] mp 246°]; $[\alpha]_D^{20}$ −13.4° ($CHCl_3$; *c* 0.35) [lit. [10] $[\alpha]_D^{20}$ −30.5° (EtOH; *c* 0.67)]; δ_H ($CDCl_3$) as ref. [7]; δ_C ($CDCl_3$), 19.5 (15-Me), 23.8 (8-CH_2), 27.3 (14-Me), 34.2 (9-CH_2), 44.8 (7-CH), 50.4 (5-CH), 58.4 (3-CH), 58.8 (2-CH), 72.5, 73.8, 79.9 (1-, 4-, and 10-C), 78.4 (6-CH), 120.3 (13-CH_2), 139.7 (12-C), and 169.5 (11-C) ppm. Assignments were made by ^1H–^{13}C correlation spectra.

Tanaparthin-α-peroxide (**8**). Mp 95–96° dec. [lit. [7] mp 117°]; $[\alpha]_D^{20}$ −32.1° ($CHCl_3$; *c* 0.11) [lit. [7] $[\alpha]_D^{24}$ −24° ($CHCl_3$; *c* 0.22)]; δ_H ($CDCl_3$) as ref. [7]; δ_C ($CDCl_3$) 13.7 (15-Me), 22.9 (8-CH_2), 27.7 (14-Me), 33.1 (9-CH_2), 42.9 (7-CH), 69.6 (5-CH), 71.1 (10-C), 79.5 (6-CH), 93.5, 99.8 (1- and 4-C), 119.6 (13-CH_2), 133.9, 137.3 (2- and 3-CH), 139.9 (12-C), and 170.0 (11-C) ppm.

seco-*Tanapartholide A* (**9**). Oil, $[\alpha]_D^{20}$ −11.2° (EtOH; *c* 1.05), δ_H ($CDCl_3$, 400 MHz) 1.58 (*s*, 15-Me), 1.89–1.99 (*m*, 8-CH_2), 2.21 (*s*, 14-Me·CO), 2.55–2.68 (*m*, 9-CH_2), 2.71 (*d*, *J* = 10.4 Hz, 5-CH), 3.47 (*dddt*, *J* = *ca* 7, 2.1, 2.0, and 1.7 Hz, 7-CH), 4.47 (*dd*, *J* = 10.4 and 2.1 Hz, 6-CH), 5.78 (*d*, *J* = 1.7 Hz, 13-CH_a), 6.07 (*d*, *J* = 5.8 Hz, 2-CH), 6.35 (*d*, *J* = 2.0 Hz, 13-CH_b), and 7.49 (*d*, *J* = 5.8 Hz, 3-CH); δ_C ($CDCl_3$) 25.2 (15-Me), 28.7 (8-CH_2), 30.0 (14-Me), 39.7 (9-CH_2), 42.1 (7-CH), 62.7 (5-CH), 78.7 (4-C), 80.3 (6-CH), 124.8 (13-CH_2), 131.0 (2-CH), 137.6 (12-C), 166.8 (3-CH), 169.8 (11-C), 202.6 (C=O), and 207.7 (C=O) ppm. (Numbering system as for (**5**)). (cf ref. [7]).

seco-*Tanapartholide B* (**12**). Oil, δ_H ($CDCl_3$, 400 MHz) 1.60 (*s*, 15-Me), 1.89 (*ca dq*, *J* = *ca* 7 and 1.6 Hz, 8-CH_2), 2.19 (*s*, 14-Me·CO), 2.33 (*d*, *J* = 9.0 Hz, 5-CH), 2.45–2.62 (*m*, 9-CH_2), 3.54 (*dddt*, *J* = *ca* 7, 2.7, 2.2, and 1.9 Hz, 7-CH), 4.58 (*dd*, *J* = 9.0 and 2.7 Hz, 6-CH), 5.75 (*d*, *J* = 1.9 Hz, 13-CH_a), 6.17 (*d*, *J* = 5.7 Hz, 2-CH), 6.35 (*d*, *J* = 2.2 Hz, 13-CH_b), and 7.47 (*d*, *J* = 5.7 Hz, 3-CH); δ_C ($CDCl_3$) 28.4 (8-CH_2), 28.9 (15-Me), 30.0 (14-Me), 39.5 (9-CH_2), 40.9 (7-CH), 58.2 (5-CH), 78.1 (4-C), 80.6 (6-CH), 124.3 (13-CH_2), 133.1 (2-CH), 137.9 (12-C), 165.8 (3-CH), 169.5 (11-C), 204.7 (C=O), and 207.7 (C=O) ppm.

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A TRITERPENE ALCOHOL, LANSIOL, FROM *CLAUSENA LANSIUM*

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Key Word Index—*Clausena lansium*; Rutaceae; aerial portion; triterpene; 3β-hydroxy-23,24,24-trimethyllanosta-9(11)-25-diene; structural analysis.

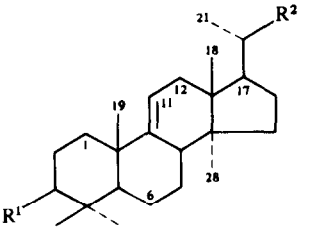
Abstract—A new tetracyclic triterpene alcohol characterized as 3β-hydroxy-23,24,24-trimethyllanosta-9(11)-25-diene has been isolated from the aerial parts of *Clausena lansium*.

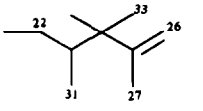
INTRODUCTION

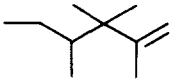
Our continued interest in the chemistry of new constituents from *Clausena* species [1–7] prompted us to study the chemical constituents of *Clausena lansium* (Lour.) Skeels (Syn *C.wampi* Olive) (Rutaceae). The ethanolic extract of the leaves of this plant on fractionation by a combination of column chromatography and PLC on silica gel of the hexane fraction afforded a new tetracyclic triterpene alcohol designated as lansiol. The structural analysis of lansiol is the subject of the present communication.

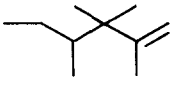
RESULTS AND DISCUSSION

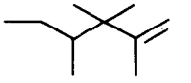
Lansiol (1), mp. 197–198° ($CHCl_3$–MeOH) $[\alpha]_D^{25}+83°$ ($CHCl_3$; *c* 1), ν_{max}^{KBr} 3350 cm^{-1} (OH) confirmed by the formation of the mono acetate and Collin's oxidation to give a ketone (lansione-3). The presence of a vinylidene group was indicated at 1648 and 890 cm^{-1}. It showed a molecular ion peak at *m/z* 468 in its mass spectrum corresponding to the molecular formula $C_{33}H_{56}O$. This, coupled with the presence of nine methyl signals between δ 0.68 and 1.03 and one vinylic methyl singlet at δ 1.55, confirmed its terpenoid nature. There was one proton

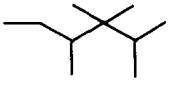


1 R^1 = R^2 = 

2 R^1 = R^2 = 

3 R^1 = O R^2 = 

4 R^1 = R^2 = 

5 R^1 = R^2 = 

Part 2 in the series 'Chemical Constituents of *Clausena lansium*'.

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