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CIS-LONGIPINANE-2,7-DIONE, A SESQUITERPENE DIKETONE IN FLOWERS OF *TANACETUM VULGARE*

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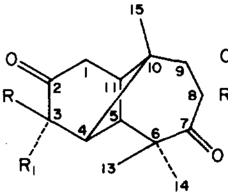
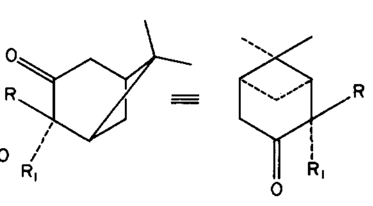
Key Word Index—*Tanacetum vulgare*; Compositae; *cis*-longipinane-2,7-dione; absolute stereochemistry; NMR; X-ray.

Abstract—The structure of a new *cis*-longipinane-2,7-dione, isolated from flowers of *T. vulgare*, was elucidated by a comparison of the NMR data with those of other terpenoids with a cyclobutane ring. The absolute stereochemistry was established by correlation of the CD spectrum of the new compound and its C-3 epimer with those of pinocamphone (*trans*), and isopinocamphone, (*cis*). X-ray analysis confirmed the proposed structure.

In an investigation on the sesquiterpene lactones in the flowers of *Tanacetum vulgare* L. collected in Bulgaria [1], a crystalline compound (**1**), mp 113.5–114.5°, $C_{15}H_{22}O_2$ (analysis), $[M]^+$ m/z 234, was isolated. The IR spectrum showed a strong doublet at 1705 and 1715 cm^{-1} for two non-conjugated ketone groups, one in a six- and the other in a seven-membered ring (no NMR evidence for aldehyde protons and no IR bands for hydroxyl groups). The UV spectrum (λ_{max} 212 and 290 nm) confirmed the presence of a non-conjugated ketone. Thus, according to these data **1** was a tricyclic carbon skeleton with two non-conjugated ketone groups, one of them in a six- and the other in a seven-membered ring.





1 R=Me (C-12), R_1=H
1a R=H, R_1=Me (C-12)

2 R=H R_1=Me
2a R=Me R_1=H

The ^{1}H NMR spectrum (300 MHz) showed signals for a total of 22 protons resonating only in the higher field (δ 0.8–2.8), five of them between 2.45 and 2.75, probably next to the carbonyls. Nine of the protons were in three tertiary methyls (singlets at δ 0.88, 1.08 and 1.10), while another three protons were in one deshielded secondary methyl group (doublet at δ 1.20, $W_{1/2}$ = 7 Hz). The signals of the remaining five protons were: one broad A_2X_2 multiplet of the protons at δ 1.77, a second sharp multiplet ($W_{1/2}$ = 7 Hz) of two protons at δ 2.20 and a broadened singlet ($W_{1/2}$ = 4 Hz) of one proton at δ 1.44. The last two relatively sharp signals were indicative of the presence of non-interacting protons. Within the tricyclic sesquiterpenes, this was possible in skeletons with a cyclobutane ring, where the dihedral angles between the protons were *ca* 90°. The most probable one was the tricyclic skeleton of longipinane with four-, six- and seven-membered carbon rings, the latter two rings in **1** being supported by its IR carbonyl frequencies.

Since two of the tertiary methyls and the secondary one were deshielded by the neighbouring carbonyls, structure **1** was the only possible one for a longipinane diketone. This was confirmed by extensive decoupling experiments. By intensive irradiation at δ 2.64 ± 0.1 (i.e. of four of the protons next to the carbonyls), without affecting the $\underline{CH}$Me quartet at 2.49, the multiplet at 1.77 collapsed to two AB doublets of one proton each (δ 1.77, 1.79, J_{gem} = 15 Hz, CH_2-9) and the multiplet at 2.20 into two AB doublets of one proton each (δ 2.19, 2.21, J_{gem} = 7 Hz). The latter coupling of 7 Hz was typical for long-range interaction through 4σ-bonds of the 1,3-*cis*-cyclobutane protons (H-4 and H-11 in **1**). The remaining protons were assigned (see Experimental) according to their coupling constants and the chemical shifts, after taking account of the influence of the carbonyl groups.

The decoupling experiments further established some other interesting long-range proton interactions. Thus, irradiation of H-5 converted the signals of the Me-12 and Me-15 protons into sharp doublets (J = 1.5 Hz); irradiation of Me-13 and Me-14 sharpened the signal of the Me-15 protons, while irradiation of the Me-12 group sharpened the signals of both Me-15 and H-5. Furthermore, irradiation of the Me-15 group influenced the signals of all closely located protons: both doublets of the Me-12 group produced two additional doublets (J = 1.5 Hz) and the signals of the protons at C-1, C-3–C-5, C-9 and C-11 were sharpened.

According to the carbon skeleton of **1**, the diketone was the sesquiterpene analogue of pinocamphone (**2**, *trans*) or of its epimer isopinocamphone (**2a**, *cis*). It was well-known that **2** was the more stable isomer and that epimerization either of **2** or of **2a** with sodium ethoxide yielded an equilibrated mixture of **2** and **2a** in the ratio 3:1 [2]. Similar treatment of **1** with sodium ethoxide at ambient temperature for 24 hr produced the epimer **1a** containing, according to its ^{1}H NMR spectrum, less than 10% of **1**. Since the Me-15 group in **1a** was deshielded (δ 0.96, *s*) due to the decrease of the anisotropic influence of the C-2 carbonyl group on Me-15 it followed that **1** was an analogue of isopinocamphone, **2a** and **1a** was an analogue of pinocamphone, **2**.

The diketone, **1**, and its C-3 epimer, **1a**, have a relatively high molecular symmetry regarding the plane through C-2, C-5, C-6, C-9, C-10 and C-15. Hence, the optical activity of **1** and **1a** (the same is valid for **2** and **2a**) is nominated mainly by the chiral centre, C-3. This made possible the determination of the absolute stereochemistry of **1** and **1a** by comparison of their CD spectra with those [3] of (+)-pinocamphone (**2**) and of (+)-isopinocamphone (**2a**), compounds of known absolute stereochemistry. The good agreement of λ_{max} and $\Delta\varepsilon$-values (Table 1) determined the absolute stereochemistry of **1** as (3*R*, 4*R*, 5*R*, 10*S*, 11*R*) and of **1a** as (3*S*, 4*R*, 5*R*, 10*S*, 11*R*).

Table 1. CD data of (+)-*cis*-longipinane-2,7-dione (**1**) (+)-*trans*-longipinane-2,7-dione (**1a**), (+)-pinocamphone, (**2**) [3] and (+)-isopinocamphone (**2a**) [3].

λ_{max}	**1**	**1a**	**2**	**2a**
314	—	−0.29	—	—
310	+0.37	—	—	+0.25
305	—	−0.52	−0.19	—
300	+0.52	—	—	+0.42
294	—	−0.55	−0.23	—
291	+0.48	—	—	+0.43
285	—	−0.42	−0.17	—
283	+0.35 sh	—	—	+0.35
278	—	−0.27	−0.11	—

The ^{13}C NMR spectra of **1** and **1a** contained signals of the following species of carbon atoms: 4Me, 3CH$_2$, 4CH, 2C and 2CO. The assignment of the atoms, listed in the experimental, was carried out by comparison with the carbon shifts in nopinone [4], isoverbenone [4], vulgarone-B [5], longipinane-3-ol and β-longipinane-2-one [6].

The structure and the relative stereochemistry of **1** was confirmed by X-ray analysis. Figure 1 presents a computerized drawing of the (3*S*, 4*S*, 5*S*, 10*R*, 11*S*) enantiomer of **1**, i.e. of (−)-*cis*-longipinane-2,7-dione, and the experimentally determined bond lengths in Å. The co-ordinates of the atoms with s.d.s, and the bond and torsional angles are deposited with the Cambridge Crystallographic Data Centre. The central structural element of **1** is the four membered ring, C-4, C-5, C-10, C-11 with a puckered conformation as a result of the bridges at C-4–C-11 and C-5–C-10, respectively. The dihedral angle between the planes of C-4, C-10, C-11/C-4, C-5, C-11 is 145.0° and between those of C-5, C-11, C-10/C-5, C-4, C-10 is 144.1°. The torsional angles have values of 24.2–29.8°. Both partial ring systems C-1–C-4, C-11 and C-5–C-10 linked by the four-membered ring have an almost perpendicular orientation of 93.6°. Both cyclohexanone moieties C-1–C-5, C-11 and C-1–C-4, C-10, C-11 adopt a modified chair and boat conformation, respectively. The planes through C-1–C-3, C-4, C-5, C-11 and C-4, C-10, C-11, show inclination angles of +9.7°, −75.0° and +70.1° against the central plane formed by the atoms C-1, C-3, C-4, C-11. The inclination angle of the first plane is very small because of the short transannular contacts between C-2 and the methyl group C-15 of C-15 (C-2 . . . C-15, 2.988; C-2 . . . H-15, 2.37 Å). The expected inclination would be in the opposite (i.e. in a(+)) direction, where no methyl

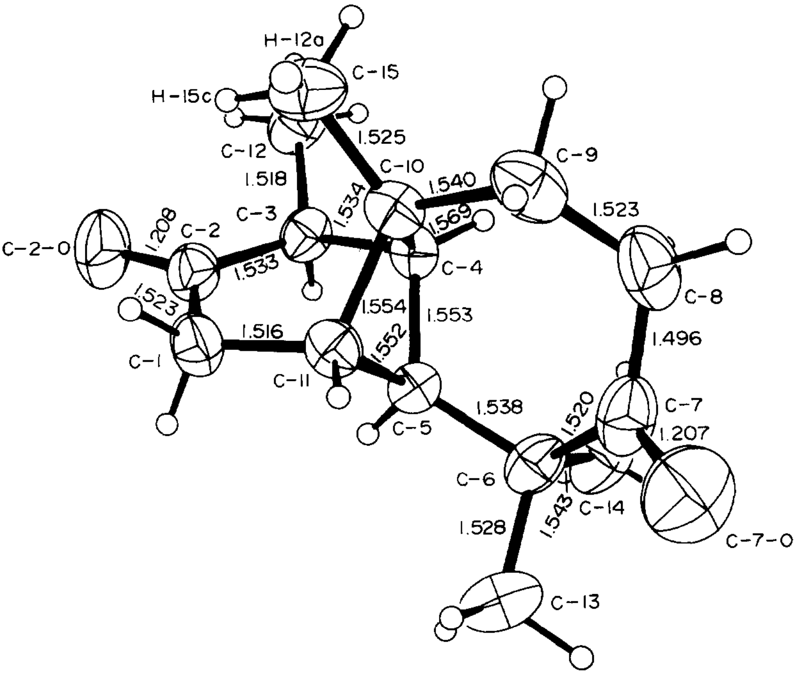


Fig. 1. Bond lengths (Å) of *cis*-longipinane-2,7-dione (**1**) with s.d.s of 0.002–0.003 A.

group interferes, but this conformational change would rotate the C-12 methyl group from an equatorial into an axial position and against C-15. This flapping is prevented by the already short contacts between both methyl groups C-12 and C-15 (C-12 ... C-15, 3.334; C-15 ... H-12, 2.70 Å). The same repulsive forces are also responsible for the comparatively long bonds C-4–C-10 (1.569 Å) and C-3–C-4 (1.534 Å). Corresponding enlargements of bond angles are also observed. Both seven-membered rings C-4–C-10 and C-5–C-11 have a twisted-chair conformation. The lengthening of the C-6–C-7 bond (1.520 Å) compared to the neighbouring C-7–C-8 bond (1.496 Å) is caused by the repulsive forces between C-13 and O-7 (C-13 ... O-7 2.718 Å). Therefore, the related bond angles C-6–C-7–O-7 and C-7–C-6–C-13 are greater than the complementary angles C-8–C-7–O-7 and C-5–C-6–C-13.

α-Longipinene-1-one and some derivatives with hydroxyls in the seven-membered ring have been found in *T. tanacetoides* [7], in two *Stevia* species [8] and in *Polyptoris texans* [9]; the latter plant also contains the saturated 7,8,9-trihydroxy-*cis*-longipinane-1-one and 8,9-diangeloyl-*cis*-longipinane-1,7-dione [9]. Vulgarone-B (α-longipinene-1-one) has been isolated from the underground parts of *T. vulgare* of European origin but cultivated in Japan [5]. While higher plants contain derivatives of *cis*-longipinane, *trans* compounds have been found in liverwort species [6, 10].

EXPERIMENTAL

Mps were taken on a Kofler hot-stage microscope and are uncorr.

cis-*Longipinane*-2,7-*dione* (**1**). Air-dried flowers of *T. vulgare* (6.600 kg), collected in 1978 near Sofia, were extracted with $CHCl_3$ for 24 hr at ambient temp. (3 × 15 l.). After evaporation of the solvent the residue (370 g) was taken-up at 50° with 50% aq. EtOH (3 × 1 l.) and the extract washed with petrol (3 × 200 ml). The concd petrol washings deposited **1** (1.85 g) as colourless crystals, mp 113.5–114.5° (petrol–Et_2O, 1:1) $[\phi]_D + 41.0°$. MS *m/z* (rel. int.): 234 (33), 219 (12), 166 (25), 96 (86), 82 (100); UV λ_{max} nm: see Results and Discussion; IR ν_{max}^{KBr} cm^{-1}: 1715, 1705, 1460, 1419, 1380, 1325, 1115, 1092, 1035, 910; ^1H NMR (300 MHz, $CDCl_3$, TMS as int. standard): δ2.49 (*q* H-3ax), 2.54 (*dd*, H-1eq, clearly visible by irradiation of H-9eq), 2.72 (*d*, H-1ax), 2.20 [sharp *m*, collapsing to 2.19 (*d*, H-4eq) and 2.21 (*d*, H-11eq) by irradiation of H-1eq], 1.44 (*s*, H-5), 2.66 [*br m*, H_2-8, on irradiation of H_2-8 it collapses to 1.79 (*d*, H-9eq) and 1.75 (*d*, H-9ax)], 1.20 (*d*, Me-12), 1.10 (*s*, Me-13), 1.08 (*s*, Me-14), 0.88 (*s*, Me-15) [*J* (Hz): 3ax, 12 = 7, 1ax, 11 = 3ax, 4 = 4, 5 = 5, 11 = 0, 1eq, 11 = 1.5, 1ax, 1eq = 20, 4, 11 = 7, 8ax, 8eq = 14, 9ax, 9eq = 15]; ^{13}C NMR (35 MHz, TMS as int. standard): δ22.7 (*q*, C-12), 23.5 and 23.6 (*q*, C-13 and C-14), 17.0 (*q*, C-15), 46.7 (*t*, C-1), 37.6 (*t*, C-8), 36.8 (*t*, C-9), 59.0 (*d*, C-3), 38.1 (*d*, C-4), 53.6 (*d*, C-5), 44.7 (*d*, C-11), 47.0 (*s*, C-6), 213 and 215 (C-2 and C-7), 41.0 (s, C-10).

trans-*Longipinane*-2,7-*dione* (**1a**). Compound **1** (0.3 g) dissolved in EtOH (5.0 ml with 0.25 g NaOH) afforded after 24 hr at ambient temp. a colourless viscous liquid (0.28 g), $[\phi]_D + 19.2°$; UV λ_{max} nm: 206, 225, 253; IR ν_{max}^{film} cm^{-1}: 1715, 1705, 1460, 1415, 1400, 1365, 1274, 1105, 1080, 1030, 980, 905; MS *m/z*: overlapping with those of **1**; ^1H NMR: see Results and Discussion.

X-ray experiments. Crystallographic constants of **1**: $a = 8.882$ (1); $b = 12.704$ (3); 11.673 (2) Å; space group: $P2_12_12_1$; $V = 1317.0$ Å^3; $d_x = 1.18$ g/cm^3 for $Z = 4$. The cell dimensions were derived by means of a least squares program from 26 high order ($2\theta > 40°$) reflections measured with *MoKα* radiation on a diffractometer. An independent set of 1829 intensities was recorded for $\sin\theta/\lambda \leqslant 0.664$ Å^{-1} with *MoKα* radiation on a computer controlled diffractometer (Siemens AED, graphite monochromator). 224 reflections were treated as unobserved,

$$F_{obs}^4/[\sigma(F_{obs}^2)]^2 < 7.$$

Lorentz and polarization corrections were applied; absorption and extinction effects were neglected.

The crystal structure was solved by direct methods with the MULTAN program [11]. The positions of the hydrogen atoms were calculated according to geometrical requirements or were found by difference Fourier synthesis. After several least squares refinement cycles in the full matrix procedure with isotropic temp. parameters for the hydrogen atoms and anisotropic temp. parameters for the carbon and oxygen atoms were obtained a final *R*-value of 0.038 (excluding unobserved reflections) and 0.042 (unobserved reflections included)

$$R = \sum(kF_0 - |F_c|)/\sum kF_0.$$

In the last refinement cycle, 116 unobserved reflections were included ($|F_c| > KF_0$). Ten of the strongest reflections affected by extinction were assigned zero weight. The scattering factors were obtained from ref. [12]. The computations were carried out in the Computer Centre (IBM 370/168), University of Heidelberg.

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