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COMPOSITAE

TWO NEW β-DIKETONES FROM *HELICHRYSUM ITALICUM*

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Helichrysum italicum G. Don (= *H. angustifolium* DC) (Compositae) is a shrub having a strong and unpleasant odor; it has a woody base with several white, tomentose stems 30–50 cm high and grows in arid, sandy and stony areas. It is native to Europe and its decotion enjoyed a great reputation in folk medicine as an expectorant, antitussive, cholerethic, anti-inflammatory and anti-allergic agent.[1] Recently, an extract of the plant was found to exert bacteriostatic effects on many microorganisms *in vitro*.[2–5]

Helichrysum italicum has been reported to contain (+)-α-pinene,[6–8] (—)-β-pinene,[9] nerol and neryl acetate,[9,10,15] linalool,[11,18] sesquiterpenes,[6,8,12] eugenol,[12] β-diketones,[13] hentriacontane,[11,14,16] caprylic acid,[12] caffeic acid,[2,3] ursolic acid[16] and lactone,[21–23] β-sitosterol,[11] α-amyrin,[21–23] uvaol,[21–23] 5-methoxy-7-hydroxyphthalide and 5,7-dimethoxy-

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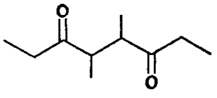
phthalide,[29] flavonoids,[20] and other unidentified compounds.[17] None of the foregoing compounds appear to be responsible for the strong and distinctive odor of the stems of *H. italicum*, and the present investigation was undertaken to identify the odorous principle.

RESULTS AND DISCUSSION

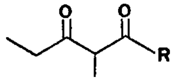
Helichrysum italicum was collected in the Ligurian mountains before flowering in April. Its stems, when steam distilled, gave an essential oil whose gas chromatogram showed four peaks *A*, *B*, *C*, and *D*, in order of increasing retention time; their relative intensity was $C \gg D > B > A$. Peak *D* appeared to be a mixture of compounds with MWs 202 and 204, probably sesquiterpene hydrocarbons. Peak *C* was found to be nerol, as proved by a comparison of the retention time and the mass spectrum. In contrast to other authors,[11,18] we did not find linalool in the essential oil.

The MS of compound *B* exhibited a molecular ion at *m/e* 170 and a fragmentation pattern consistent with an acyclic structure which could be one of four possible isomers, namely I, II, III and IV. The ratio of *m/e* 58 to *m/e* 57 indicated that both ions $C_4H_9^+$ and $C_3H_5O^+$ contributed to the most abundant peak of the spectrum at *m/e* 57;[24] further, the peak at *m/e* 86 could be explained as due, at least in part, to an ion such as V, arising from a McLafferty rearrangement.[24]

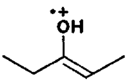
The presence and the position of the second carbonyl group in the molecule resulted from a number of facts; (i) its fragmentation pattern did not agree with an alkyl moiety containing eight carbon atoms,[25] (ii) the presence of a CH_3CO— group could be ruled out because the MS would have shown a much more intense peak at *m/e* 43, and (iii) the structure of 4-methylnonane-3,7-dione was excluded by the absence of a peak at *m/e* 72 expected from a McLafferty rearrangement involving the carbonyl group at the 7 position.



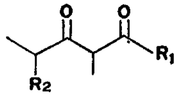
(I)



(II) $R = (CH_2)_3Me$
(III) $R = CH_2CHMe_2$
(IV) $R = CHMeEt$



m/e 86 (V)



	R_1	R_2
(IV)	$-CHMeEt$	H
(VI)	$-CHMe_2$	H
(VII)	$-Et$	$-CH_2CH=CMe_2$
(VIII)	$-CHMe_2$	$-CH_2CH=CMe_2$
(IX)	$-CHMeEt$	$-CH_2CH=CMe_2$

In order to distinguish between structures I–IV, all four isomeric diketones were synthesized. 4,5-Dimethyloctane-3,6-dione (I) was prepared through oxidative dimerization of diethyl ketone by means of benzoyl peroxide,[26] whereas the synthesis of the three β-diketones was achieved by acylation of diethyl ketone with the appropriate aliphatic ester in the presence of sodium amide.[27] A comparison of the retention times and the MS of the synthetic diketones with those of peak *B* showed structure IV to be the correct one.

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Structure VI was deduced for the compound corresponding to peak *A* on the basis of its fragmentation behaviour, bearing in mind the foregoing considerations. This assignment was confirmed by the synthesis of 2,4-dimethylheptane-3,5-dione (VI) by the methods described above. After pure IV and VI were obtained, it was apparent that the characteristic unpleasant odor of the stems of *H. italicum* is largely due to these two minor components.

From a biogenetic point of view, the occurrence of IV and VI as well as VII, VIII and IX previously reported[13] can be best explained assuming a common polyketide origin for all these β-diketones. Differences between them would arise only from the 'starter acid' ($R_1COSCoA$) in the process of chain assembly and from the extent of alkylation of the active —CH_2— groups.[28]

EXPERIMENTAL

GLC. A 180-cm glass column with Carbowax 20M (20%) on acid-washed Chromosorb W (80–100 mesh) at 170° with nitrogen was used. Samples were injected free from solvent.

GLC–MS. Mass spectra were determined using a LKB 9000 single focusing gas chromatograph–mass spectrometer, fitted with a 3 m × 4 mm column packed with 20% Carbowax 20M coated on 80–100 mesh acid-washed Chromosorb W. Inlet temp. 260°, ionization voltage, 70 eV, ion source temp. 290°, column temp. 175°; the carrier gas was He.

Spectroscopic measurements. The NMR spectra were recorded using diluted $CDCl_3$ solutions and TMS as internal standard. UV spectra were determined in MeOH and IR spectra in $CHCl_3$.

Isolation of volatile material and identification of its constituents. The freshly collected stems of *Helichrysum italicum* G. Don were steam distilled in a glass apparatus to yield 0·04% volatile oil (n_D^{20} 1·477). Nerol, 3,5-dimethyloctane-4,6-dione (IV) and 2,4-dimethylheptane-3,5-dione (VI) were identified by MS, GLC retention times and co-chromatography with authentic samples.

4,5-*Dimethyloctane*-3,6-*dione* (I). This compound was prepared according to Seebach.[26] Retention time 230 sec.

Synthesis of β-diketones of the type $CH_3CH_2COCH(CH_3)COR$. *General procedure.* To a stirred suspension of $NaNH_2$ (from 15·2 g Na) in Et_2O, was added during 5–10 min a solution of 51·6 g of Et_2CO in 50 ml Et_2O. After 5 min the calculated amount (0·3 mol) of ester in 50 ml Et_2O was added, and the stirring continued for 4 hr at 0°. The mixture was poured into 300 ml H_2O, neutralized (HCl) and extracted with Et_2O. The solvent was distilled and the residue fractionated *in vacuo* (20 mm Hg) through a 30-cm Vigreux column. Each fraction was examined by GLC; similar fractions were pooled, redistilled, if necessary, and characterized after checking their purity by GLC.

4-*Methylnonane*-3,5-*dione* (II). Yield 30%; b.p. 114–115°/20 mm Hg; n_D^{20} 1·452. (Found: C, 70·28; H, 10·90. Calc. for $C_{10}H_{18}O_2$: C, 70·54; H, 10·66%.) Retention time 292 sec. UV: λ_{max} 248 (1670), 290 (1120) nm; IR: ν_{max} 3500 (w, broad), 1730 (sh.), 1700 (s), 1650 (w), 1595 (w) cm^{-1}; NMR: quartet at δ 3·72 (0·50 H, J = 7 Hz) for —$COC\underline{H}(CH_3)CO$—; singlet at δ 1 86 (1·5 H) for —$C(OH)=C(C\underline{H}_3)CO$—; doublet at δ 1·31 (J = 7 Hz) for —$COCH(C\underline{H}_3)CO$—.

2,5-*Dimethyloctane*-4,6-*dione* (III). Yield 24%; b.p. 112–113°/20 mm Hg; n_D^{20} 1·445. (Found: C, 70·73; H, 10·98. Calc. for $C_{10}H_{18}O_2$: C, 70·54; H, 10·66%.) Retention time 230 sec. UV: λ_{max} 248 (2225), 290 (1180) nm; IR: ν_{max} 3690 (w), 3500 (w, broad), 1725 (sh.), 1700 (s), 1650 (w), 1600 (w) cm^{-1}; NMR: quartet at δ 3·70 (0·55 H, J = 7 Hz) for —$COC\underline{H}(CH_3)CO$—; singlet at δ 1·86 (1·35 H) for —$C(OH)=C(C\underline{H}_3)CO$—; doublet at δ 1·31 (J = 7 Hz) for —$COCH(C\underline{H}_3)CO$—.

3,5-*Dimethyloctane*-4,6-*dione* (IV). Yield 18%; b.p. 114–115°/20 mm Hg; n_D^{20} 1·443. (Found: C, 70·72; H, 11·00. Calc. for $C_{10}H_{18}O_2$: C, 70·54; H, 10·66%.) Retention time 230 sec. UV: λ_{max} 248 (2180), 290 (950) nm; IR: ν_{max} 3690 (w), 3520 (w), 3400 (w), 1725 (sh.), 1700 (s), 1655 (m), 1610 (w) cm^{-1}; NMR: quartet at δ 3·86 (0·8 H. J = 7 Hz) for —$COC\underline{H}(CH_3)CO$—; singlet at δ 1·86 (0·6 H) for —$C(OH)=C(C\underline{H}_3)CO$—; doublet at δ 1·31 (J = 7 Hz) for —$COCH(C\underline{H}_3)CO$—.

2,4-*Dimethylheptane*-3,5-*dione* (VI). Yield 20%; b.p. 117–118°/25 mm Hg; n_D^{20}, 1·442. (Found: C, 68·81; H, 10·16. Calc. for $C_9H_{16}O_2$: C, 69·19; H, 10·32%.) Retention time 167 sec. UV: λ_{max} 247 (980), 290 (1020) nm; IR: ν_{max} 3690 (w), 3540 (w), 3400 (w), 1730 (s), 1700 (s,sharp), 1650 (sh.), 1600 (w) cm^{-1}; NMR: quartet at δ 3·86 (0·78 H, J = 7 Hz) for —$COC\underline{H}(CH_3)CO$—; singlet at δ 1·86 (0·66 H) for —$C(OH)=C(C\underline{H}_3)CO$—; doublet at δ 1·30 (J = 7 Hz) for —$COCH(C\underline{H}_3)CO$—; doublet at δ 1·10 (J = 7 Hz) for $(C\underline{H}_3)_2CH$—.

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Key Word Index—Helichrysum italicum; Compositae; terpenes; nerol; C-10-β-diketones.