Phytochemistry, 1973, Vol. 12, pp. 2721 to 2723. Pergamon Press. Printed in England.

NEW DITERPENES FROM *SIDERITIS CANDICANS**

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(*Received* 8 *May* 1973. *Accepted* 22 *June* 1973)

Key Word Index—*Sideritis candicans*; Labiatae; chahorra; ent-kaurene diterpenes.

Abstract—The three new diterpenes candol-*A* (ent-16-kauren-7α-ol, I), candol-*B* (ent-16-kauren-18-ol, III) and epicandicandiol 7β-monoacetate (ent-7α-acetoxy-16-kauren-18-ol, V) as well as epicandicandiol (VII) have been isolated from *Sideritis candicans*.

INTRODUCTION

THE GENUS *Sideritis* (Labiatae) is widely dispersed on the Canary Isles, specially in the western part of the archipelago. In the literature consulted[1–4] there seems to be confusion about the botanical classification of its species. The aim of the present phytochemical study on this genus is to clarify the discrepancies. Previous communications[5–7] described the isolation of the three new diterpenes candicandiol (ent-16-kauren-7β,18-diol), epicandicandiol (ent-16-kauren-7α,18-diol) and candidiol (ent-16-kauren-15β,18-diol) from *Sideritis candicans* Ait. *var. eriocephala*. From *Sideritis canariensis* Ait. we obtained seven new diterpenes.[8–11] The present work reports our results on an un-classified variety of *Sideritis candicans*.

RESULTS

Candol-*A* (I), $C_{20}H_{32}O$, has IR absorptions of hydroxyl, exocyclic double bond and *gem*-dimethyl groups. The NMR spectrum shows signals for a methylene group (5·16 τ, 2H), a proton geminal to a secondary axial OH (6·34 τ, 1H, *t*, $W_{1/2}$ 6 Hz) and three methyl groups. On the basis of the spectroscopic data, candol A must be a diterpene with a kaurene skeleton and an axial hydroxyl at position 3 or 7. Mild acetylation of I gave II which proved to be identical (m.m.p., IR, NMR) with the dehydration product of powerol monoacetate (ent-7α-acetoxy-kauren-16β-ol);[10] hence, I must be ent-16-kauren-7α-ol.

* Part XVII in the series "Constituents of Labiatae". For Part XVI see Ref. 11.

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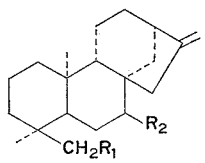
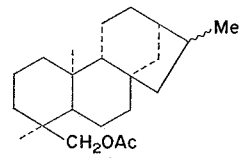
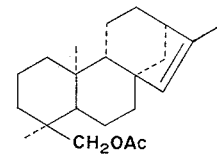
The IR spectrum of the second diterpene, candol-*B* (III), $C_{20}H_{32}O$, is similar to that of I but lacks the *gem*-dimethyl absorption. The NMR spectrum indicates the presence of a methylene and two methyl groups and a primary hydroxyl (6·80 τ, 2H, J 12 Hz) which must be equatorial as inferred from the chemical shift of the hydroxymethylene group in III and its acetate (IV).[12] The structure of III was confirmed by synthesizing it from epicandicandiol (VII) as follows: VII was partially acetylated to give a mixture which on dry column chromatography afforded compounds VI, V, VIII and starting material. Oxidation of VIII with Jones reagent to IX and subsequent Huang–Minlon reduction gave a mixture of three alcohols which was acetylated and separated by dry column chromatography on silica gel with $AgNO_3$, thus affording IV and, in minor quantities, X and XI. IV was identical in all respects with candol-*B* acetate. The isomerization of the double bond from position 16–17 to 15–16 as observed in XI was reported previously by us[10] and the reverse one by Fujita *et al.*[13]

	R_1	R_2
(I)	H	OH
(II)	H	OAc
(III)	OH	H
(IV)	OAc	H
(V)	OH	OAc
(VI)	OAc	OAc
(VII)	OH	OH
(VIII)	OAc	OH
(IX)	OAc	O





(X)



(XI)

The IR bands of the third new diterpene isolated from this species, epicandicandiol 7β-monoacetate (V), are indicative of hydroxyl and ester functions and an exocyclic double bond. The NMR spectrum presents signals for a hydroxymethylene, an acetate group, a proton geminal to the acetate and two angular methyl groups. Acetylation of V gave VI, identical (m.m.p., IR, NMR) with the diacetate prepared from epicandicandiol (VII). On the other hand, V proved to be identical with the 7β-monoacetate obtained by partial acetylation of VII; hence, it must be ent-7α-acetoxy-16-kauren-18-ol.

Epicandicandiol and a mixture of ursolic and oleanolic acids were also isolated from this species.

DISCUSSION

From *Sideritis candicans* Ait. var. *eriocephala* candicandiol was obtained as major product and epicandicandiol and candidiol in minor yield. In the variety of *Sideritis candicans* studied in the present work we could not trace any candicandiol, isolating epicandicandiol and its 7β-monoacetate as major components and as minor ones the new diterpenes candol-*A* and -*B*. On the basis of these findings it seems likely that the variety studied by us is different from *Sideritis candicans* Ait. *var. eriocephala.*

EXPERIMENTAL

The m.ps, determined on a Kofler block, are uncorrected. Solvent used for recrystallized compounds was MeOH except as noted. Optical activities and IR spectra were measured in $CHCl_3$, NMR spectra on a 60 MHz instrument in $CDCl_3$ with TMS as internal standard. Column chromatography was performed on silica gel 0·2–0·5 mm and dry column chromatography on silica gel 0·063–0·2 mm. Unless otherwise stated, acetates were prepared with Ac_2O in pyridine at room temp. overnight.

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Isolation of the diterpenes. The air-dried aerial part of the plant (7 kg), collected on the Monte de Vilaflor (Tenerife) beside the road C-821 at km 63·6 in May, was chopped and extracted several times with EtOH in a Soxhlet. The cooled extract was filtered concentrated *in vacuo* and chromatographed on a column. C_6H_6, C_6H_6–EtOAc and EtOAc eluted several mixtures of products which were rechromatographed on dry columns yielding the following compounds in order of elution: candol-*A* (I); a pentacyclic triterpene and candol-*B* (III), separated by dry column chromatography of the acetates on silica gel with 20% $AgNO_3$; a mixture of sterols, epicandicandiol 7β-monoacetate (V); ursolic and oleanolic acid; and finally epicandicandiol (VII).

Candol-A (ent-16-kauren-7α-ol) I (160 mg), m.p. 136–137·5°, $[\alpha]_D$-31° (*c* 0·54). (Found: C, 83·30; H, 11·18. $C_{20}H_{32}O$ requires: C, 83·27; H, 11·18%.) IR: 3610, 3090, 1640, 1400, 1390, 890 cm^{-1}. NMR: τ 5·16 (2H, *s*, $W_{1/2}$ 6 Hz, $=CH_2$), 6·36 (1H, *t*, $W_{1/2}$ 6 Hz, $>C\underline{H}OH$), 8·94, 9·14 and 9·17 (each 3H, *s*, 3Me). *7β-Acetate* II, m.p. 100–101°, $[\alpha]_D$-25° (*c* 0·63). (Found: C, 80·03; H, 10·57. $C_{22}H_{34}O_2$ requires: C, 79·95; H, 10·37%). IR: 3080, 1720, 1660, 1400, 1390, 1260, 880 cm^{-1}. NMR: τ 5·16 (3H, complex signal; $=CH_2$, $>C\underline{H}OAc$), 7·93 (3H, *s*, OAc), 9·85 (3H, *s*, Me) 9·21 (6H, *s*, 2Me).

Candol-B (ent-16-kauren-18-ol) III (270 mg), m.p. 107–108°, $[\alpha]_D$ −75° (*c* 1·01). (Found: C, 82·98; H, 11·36. $C_{20}H_{32}O$ requires: C, 83·27; H, 11·18%). IR: 3620, 3080, 1660, 1470, 1450, 1040, 880 cm^{-1}. NMR: τ 5·20 (2H, *s*, $W_{1/2}$ 6 Hz, $=CH_2$), 6·80 (2H, *q*, *J* 12 Hz, $-C\underline{H}_2OH$), 8·92 and 9·22 (each 3H, *s*, 2Me). *Acetate* IV, m.p. 121–122°, $[\alpha]_D$ −90° (*c* 0·86). (Found: C, 79·81; H, 10·60. $C_{22}H_{34}O_2$ requires: C, 79·95; H, 10·37%). IR: 3070, 1720, 1670, 1470, 1390, 1260, 880 cm^{-1}. NMR: τ 5·20 (2H, *s*, $=CH_2$), 6·20 (2H, *q*, *J* 12 Hz, $-C\underline{H}_2OAc$), 7·95 (3H, *s*, OAc), 8·95 and 9·17 (each 3H, *s*, 2Me).

7β-Acetoxy-epicandicandiol (ent-7α-acetoxy-16-kauren-18-ol) V (1·4 g), m.p. 139–140° (light petrol.), $[\alpha]_D$ −28° (*c* 0·90). (Found: C, 76·37; H, 9·78. $C_{22}H_{34}O_3$ requires: C, 76·26; H, 9·89%). MS: *m/e* (%) 286 (M^+-60; 100), 268 (19), 256 (23), 255 (79), 239 (15), 206 (13), 187 (16), 185 (16), 173 (16), 145 (15), 130 (18), 121 (15), 118 (16). IR: 3630, 3080, 1720, 1460, 1380, 1260, 880 cm^{-1}. NMR: τ 5·22 (3H, complex signal; $=CH_2$, $>C\underline{H}OAc$), 6·85 (2H, *q*, *J* 12 Hz, $-C\underline{H}_2OH$), 7·95 (3H, *s*, OAc), 8·92 and 9·30 (each 3H, *s*, 2Me). *Epicandicandiol diacetate* VI, m.p. 122–124° (lit.,[5] 120–121°). (Found: C, 74·21; H, 9·36. Calc. for $C_{24}H_{36}O_4$: C, 74·19; H, 9·34%). NMR: τ 5·24 (3H, complex signal; $=CH_2$, $>C\underline{H}OAc$), 6·36 (2H, *q*, *J* 12 Hz, $-C\underline{H}_2OAc$), 8·93 and 9·18 (each 3H, *s*, 2Me).

Epicandicandiol (ent-16-kauren-7α,18-diol) VII (3·2 g), m.p. 143–144°, $[\alpha]_D$ −40° (lit.[5] m.p. 141°, $[\alpha]_D$ −39·5°).

Partial acetylation of epicandicandiol VII. To a soln. of VII (1·4 g) in pyridine (28 ml) cold Ac_2O (10 ml) was added at 0° and the mixture left at this temp. for 10 min. Dry column chromatography (C_6H_6–EtOAc, 9:1) of the residue gave diacetate VI (40 mg), 18-monoacetate VIII (510 mg), 7β-monoacetate V (260 mg) and starting material (630 mg).

ent-18-Acetoxy-16-kauren-7α-ol VIII, m.p. 114–115° (light petrol.), $[\alpha]_D$ −44° (*c* 0·77). (Found: C, 74·29; H, 9·57. $C_{22}H_{34}O_3$ requires: C, 76·26; H, 9·89%). IR: 3610, 3070, 1720, 1670, 1390, 1050, 890 cm^{-1}. NMR: τ 5·20 (2H, *s*, $W_{1/2}$ 6 Hz, $=CH_2$), 6·30 (2H, *q*, *J* 12 Hz, $-CH_2OAc$), 6·42 (1H, *s*, $>C\underline{H}OH$), 7·95 (3H, *s*, OAc), 8·90 and 9·16 (each 3H, *s*, 2Me).

ent-18-Acetoxy-16-kauren-7-one IX. A soln of VIII (430 mg) in Me_2CO (minimum quantity) was treated dropwise with a slight excess of Jones reagent and left at room temp. for 5 min, when MeOH was added to destroy the excess reagent. The mixture was poured into H_2O and worked up, yielding the ketone IX (370 mg) which would not crystallize. NMR: τ 5·15 (2H, *s*, $=CH_2$), 6·32 (2H, *s*, $-C\underline{H}_2OAc$), 7·95 (3H, *s*, OAc), 8·82 and 9·10 (each 3H, *s*, 2Me).

Huang-Minlon reduction of IX. To a soln of IX (260 mg) in diethyleneglycol (13 ml) $N_2H_4.H_2O$ (3 ml) was added and the mixture refluxed for 2 hr (temp. 130°). After addition of KOH pellets (0·5 g) refluxing was continued for 45 min. Then the temp. raised to 200° and refluxing continued for 3 hr. TLC (20% $AgNO_3$) showed the resulting product (190 mg) to consist of three compounds. The mixture was acetylated and chromatographed on a dry column with silica gel–20% $AgNO_3$, light petrol.–C_6H_6 (1:4) eluting X (15 mg), IV (175 mg) and XI (24 mg). IV proved to be identical with candol-*B* acetate (m.m.p., IR, NMR).

ent-18-Acetoxy-kaurane X, m.p. 92–96°. NMR: τ 6·20 (2H, *g*, *J* 12 Hz, $-C\underline{H}_2OAc$), 7·96 (3H, *s*, OAc), 8·95 (3H, *s*, Me), 9·10 (3H, *d*, *J* 6 Hz, Me), 9·18 (3H, *s*, Me).

ent-18-Acetoxy-15-kaurene XI, m.p. 115–116°. NMR: τ 4·92 (1H, broad *s*, $-CH=C<$), 6·22 (2H, *q*, *J* 12 Hz $-C\underline{H}_2OAc$), 7·94 (3H, *s*, OAc), 8·30 (3H, *d*, *J* 2 Hz, $-CH{\equiv}C\underline{Me}$), 8·94 and 9·18 (each 3H, *s*, 2Me).

Acknowledgements—We thank Dr. W. Wildpret (Department of Botany, University of La Laguna) for identifying the plant and for his interest in this work. One of us (J.G.L.) thanks the Ministerio de Educación y Ciencia for a fellowship 'Formación de Personal Investigador'. This work forms part of the Programme 1971 conceded by the Foundation 'Juan March'.