Phytochemistry, 1981, Vol. 20, pp. 481–483. © Pergamon Press Ltd. Printed in England. 0031-9422/81/030481-03 $02.00/0

TRITERPENOIDS FROM *SALVIA PHLOMOIDES*, THREE NEW LUPANE DERIVATIVES

MARÍA C. GARCÍA-ALVAREZ,* GIUSEPPE SAVONA† and BENJAMÍN RODRÍGUEZ*

*Instituto de Química Orgánica, CSIC, Juan de la Cierva, 3, Madrid-6, Spain; †Istituto di Chimica Organica, Archirafi, 20, 90123-Palermo, Italy

(*Received* 12 *June* 1980)

Key Word Index—*Salvia phlomoides*; Labiatae; lupane-3β,11α,20-triol; 3β-acetoxy-lupane-11α,20-diol; 3-keto-lupane-11α,20-diol.

Abstract—Three new triterpenoids have been isolated from the aerial parts of *Salvia phlomoides*. Their structures have been established by chemical and spectroscopic means and by correlation with known products as lupane-3β,11α,20-triol, 3β-acetoxy-lupane-11α,20-diol and 3-keto-lupane-11α,20-diol.

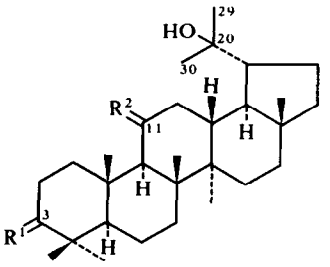
INTRODUCTION

In a previous study the presence of lupeol and lup-20(29)-ene-2α,3β-diol in the acetone extract of *Salvia phlomoides* was described [1]. A further investigation of the plant has led to the isolation of three new triterpenoids whose structures are reported here.

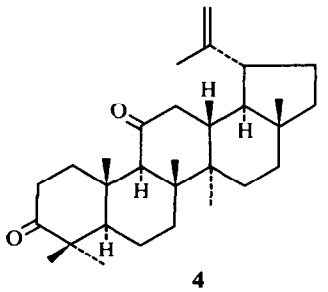
RESULTS AND DISCUSSION

The first of the new triterpenoids (**1**), $C_{30}H_{52}O_3$, had an IR spectrum which showed hydroxyl absorption and no CO bands. Compound **1** on acetylation gave a diacetate (**2**), the IR spectrum of which showed residual OH absorption (3530 cm^{-1}), thus establishing the hydroxylic nature of the three oxygen atoms of the molecule of the triterpenoid and suggesting a tertiary nature for the unreactive alcohol. The ^1H NMR spectrum of compound **1** showed signals for eight C–Me singlets at δ 1.23 (3H), 1.15 (3H), 1.10 (6H), 1.01 (3H), 0.99 (3H), 0.85 (3H) and 0.80 (3H) and for two hydroxymethyne groups, one of which must be equatorial and placed between a tetrasubstituted sp^3 carbon atom and a methylene grouping (δ 3.17, *q*, $J_{aa'} = 10$, $J_{ae'} = 6.5$ Hz) and the other one which must also be equatorial and placed between a methyne and a methylene groups (δ 3.91, six lines, $J_{aa'} = J_{aa''} = 10.5$, $J_{ae'} = 5.5$ Hz).

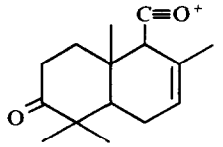
All the above data suggested a pentacyclic triterpenic structure for compound **1** with two secondary (and equatorial) and one tertiary hydroxyl groups. One of the secondary hydroxyl groups must be placed at the C-3 position, whereas the other one may be attached to the C-11 position, because the ^1H NMR spectrum of **1** showed a



	R^1	R^2
1	HO, H	H, HO
2	AcO, O	H, AcO
3	O	O
5	AcO, H	H, HO
6	O	H, HO
7	O	H, AcO



4



Ion A, *m/e* 233

clear one-proton doublet of quartets at δ 2.67 ($J_{gem} = 14.5$, $J_{ee'} = J_{ea'} = 3.5$ Hz) which must be attributed to the equatorial C-1 proton in a C-11 equatorially hydroxylated triterpene structure [2]. Jones oxidation of compound **1** yielded the hydroxy-diketone **3**, the MS of which showed an ion fragment at *m/e* 233 (ion A, 77%), also indicative of the presence of a ketone in the C-11 position [3].

On the other hand, dehydration of compound **3** yielded 3,11-diketo-lup-20(29)-ene (**4**), previously described [4], and thus compound **1** was lupane-3β,11α,20-triol.

A C-3 monoacetate of the triterpene **1** was also present in *S. phlomoides*. The ^{1}H NMR spectrum of this compound (**5**) was identical to the spectrum of **1**, except for the presence of an additional signal due to the acetyl group (δ 2.05, 3H, *s*) and the paramagnetic shift showed by the C-3 axial proton (δ 4.51, *q*). Treatment of compound **5** with Ac_2O–pyridine gave a substance identical in all respects to compound **2**.

The last triterpenoid (**6**) isolated from *S. phlomoides* had the molecular formula $C_{30}H_{50}O_3$ and its IR spectrum showed hydroxyl (3470 cm^{-1}) and ketone (1690 cm^{-1}) absorptions. On acetylation compound **6** gave a monoacetate (**7**), the IR spectrum of which showed residual OH absorption (3470 cm^{-1}). The ^{1}H NMR spectrum of this triterpenoid (**6**) (see Experimental) suggested a structure closely related to compound **1**, but lacking the C-3 hydroxyl group which was substituted by a ketone function. In fact, Jones oxidation of triterpenoid **6** yielded a compound identical in all respect to the hydroxy-diketone **3** obtained from **1**. Thus, compound **6** was 3-keto-lupane-11α,20-diol.

EXPERIMENTAL

Mps were determined in a Kofler apparatus o are uncorr. The ^{1}H NMR spectra were measured at 90 MHz in $CDCl_3$ or CD_3OD soln with TMS as int. standard. Elemental analyses were carried out in this laboratory (Madrid) with the help of an automatic analyser. Plant materials were collected in June 1979 near Molina de Aragón (Guadalajara, Spain) and voucher specimens are deposited in the Herbarium of the Faculty of Pharmacy (Madrid 'Complutense' University).

Extraction and isolation of the triterpenoids. Dried and finely powdered *S. phlomoides* aerial parts (585 g) were extracted 2 × with Me_2CO (4 l.) at room temp for 24 hr. The extracts were evapd to dryness under red. pres. and low temp (35°). The residue (25 g) was chromatographed on a Si gel (Merck, 7734, deactivated with 15% H_2O) column (350 g). Elution with *n*-hexane–EtOAc mixtures gave the following compounds in order of elution: lupeol (170 mg), lup-20(29)-ene-2α,3β-diol (1.2 g), 3β-acetoxy-lupane-11α,20-diol (**5**, 380 mg), 3-keto-lupane-11α,20-diol (**6**, 290 mg) and lupane-3β,11α,20-triol (**1**, 630 mg). The previously known triterpenoids were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (IR, ^{1}H NMR, MS) data and by preparation of some of their derivatives [1].

Lupane-3β-11α,20-triol (**1**). Mp 245–247° ($CHCl_3$–*n*-hexane), $[\alpha]_D^{17}$ − 3.4° (*c*, 0,.35, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3360, 2970, 2940, 2910, 2880, 1460, 1385, 1365, 1180, 1045, 1005, 953. ^{1}H NMR (CD_3OD): see Discussion. MS (75 eV, direct inlet) *m/e* (rel. int.): M^+ absent, 442 (M^+ − 18, 18), 427 (9), 424 (61), 409 (22), 237 (29), 217 (30), 216 (29), 207 (28), 205 (27), 204 (26), 203 (27), 189 (45), 149 (45), 135 (61), 121 (62), 107 (65), 95 (90), 81 (85), 69 (100), 55 (90). [Found: C, 78.32; H, 11.21. $C_{30}H_{52}O_3$ requires: C, 78.20; H, 11.38%.]

3β,11α-Diacetoxy-lupan-20-ol (**2**). Treatment of compound **1** (40 mg) with Ac_2O–pyridine at room temp. for 16 hr yielded the diacetate **2** (40 mg), mp 161–163° (MeOH), $[\alpha]_D^{20}$ + 10.0° (*c* 0.62, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3530 (OH), 1730, 1710, 1250 (-OAc). ^{1}H NMR ($CDCl_3$): δ 5.,21 (1H, *sextet*, $J_{aa'} = J_{aa''} = 10.5$, $J_{ae'} = 6$ Hz, H-11), 4.49 (1H, *q*, $J_{aa'} = 9$ Hz, $J_{ae'} = 7$ Hz, H-3), 2.05 and 1.97 (3H each, *s*, two -OAc), C-Me singlets at 1.21 (3H), 1.11 (6H), 1.00 (3H), 0.98 (3H), 0.87 (6H) and 0.80 (3H). MS (10 eV, direct inlet) *m/e* (rel. int.): M^+ absent, 526 (M^+ − 18, 1.5), 511 (0.7), 466 (100), 451 (17), 406 (10), 255 (16), 216 (22), 203 (40), 189 (22), 135 (19). [Found: C, 74.62; H, 10.55. $C_{34}H_{56}O_5$ requires: C, 74.95; H, 10.36%.]

3,11-Diketo-lupan-20-ol (**3**). Compound **1** (150 mg), treated with Jones reagent (room temp., 1 hr), yielded the hydroxy-diketone **3** (140 mg), mp 296–297° (EtOAc–*n*-hexane), $[\alpha]_D^{20}$ + 7.9° (*c* 0.40, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3510 (OH), 1690 (ketones), 1175, 947. ^{1}H NMR ($CDCl_3$): C-Me singlets at δ 1.39 (3H), 1.25 (3H), 1.20 (3H), 1.11 (3H), 1.08 (3H), 1.05 (6H) and 0.81 (3H). MS (75 eV, direct inlet) *m/e* (rel. int.): 456 (M^+, 6), 438 (62), 423 (10), 410 (9), 398 (28), 370 (12), 299 (34), 286 (14), 273 (21), 233 (77), 207 (38), 205 (23), 189 (63), 95 (100), 81 (77). [Found: C, 78.81; H, 10.75. $C_{30}H_{48}O_3$ requires: C, 78.89; H, 10.59%.]

3,11-Diketo-lup-20(29)-ene (**4**). To a soln of compound **3** (42 mg) in EtOH (10 ml), 1.5 ml conc. HCl were added and the soln refluxed for 18 hr. Work-up in the usual manner yielded compound **4** (32 mg after crystallization from Me_2CO–*n*-hexane, pure substance on Si gel plus $AgNO_3$ TLC plates), mp 263–265°, $[\alpha]_D^{19}$ + 24.7° (*c* 0.39, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3080, 1645, 880 (>C=CH$_2$), 1705 (ketones). UV λ_{max}^{EtOH} nm (ε): 290 (100). ^{1}H NMR ($CDCl_3$): δ 4.77 and 4.65 (1H each, *m*, $W_{\frac{1}{2}} = 4$ Hz, $J_{gem} = 2.2$, $J_{allylic} = 0.6$ Hz, measured by double resonance experiments, 2H-29), 1.70 (3H, *q*, $J_{allylic} = 0.6$ Hz, 3H-30), C-Me singlets at 1.39 (3H), 1.21 (3H), 1.10 (3H), 1.08 (6H) and 0.81 (3H). MS (12 eV, direct inlet) *m/e* (rel. int.): 438 (M^+, 100), 423 (12), 370 (15), 299 (36), 286 (10), 273 (9), 233 (57), 207 (24), 205 (15), 189 (45), 121 (36), 107 (39), 95 (54). [Found: C, 82.20; H, 10.71. Calc. for $C_{30}H_{46}O_2$: C, 82.13; H, 10.57%.] Identical in all respects to the product previously described [4]: mp 262°, $[\alpha]_D$ + 19°.

3-Acetoxy-lupane-11α,20-diol (**5**). Mp 175–176° (EtOAc–*n*-hexane), $[\alpha]_D^{20}$ + 9.2° (*c* 0.505, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3470, 3380 (OH), 1730, 1255 (-OAc). ^{1}H NMR ($CDCl_3$): δ 4.51 (1H, *q*, $J_{aa'} = 8$, $J_{ae'} = 7$ Hz, H-3), 3.98 (1H, *sextet*, $J_{aa'} = J_{aa''} = 10.5$, $J_{ae'} = 6$ Hz, H-11), 2.70 (1H, *dq*, $J_{gem} = 14$, $J_{ea'} = J_{ee'} = 3$ Hz, equatorial H-1), 2.05 (3H, *s*, -OAc), C-Me singlets at 1.23 (3H), 1.11 (3H), 1.07 (3H), 1.05 (3H), 0.96 (3H), 0.86 (6H) and 0.79 (3H). MS (12 eV, direct inlet) *m/e* (rel. int.): M^+ absent, 484 (M^+ − 18, 20), 469 (14), 466 (60), 451 (13), 442 (7), 441 (8), 424 (33), 409 (20), 406 (83), 391 (30), 279 (77), 217 (56), 216 (66), 203 (80), 189 (100), 162 (63), 149 (50), 134 (77), 123 (56), 109 (47). [Found: C, 76.53; H, 11.01. $C_{32}H_{54}O_4$ requires: C, 76.44; H, 10.83%.]

Acetylation of compound **5** *to yield compound* **2**. Ac_2O–pyridine treatment of **5**, as previously described for **1**, yielded a compound identical in all respects to **2** (mp, mmp, $[\alpha]_D$, IR, ^{1}H NMR, MS).

3-Keto-lupane-11α,20-diol (**6**). Mp 225–227° (Me_2CO), $[\alpha]_D^{20}$ + 46.1° (*c* 0.63, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3470 (OH), 1690 (ketone), 1260, 1215, 990, 903. UV λ_{max}^{EtOH} nm (ε): 289 (30). ^{1}H NMR ($CDCl_3$): δ 3.90 (1H, *sextet*, $J_{aa'} = J_{aa''} = 10.5$, $J_{ae'} = 6$ Hz, H-11), C-Me singlets at 1.23 (3H), 1.10 (3H), 1.08 (6H), 1.07 (3H), 1.05 (3H), 0.97 (3H) and 0.80 (3H). MS (75 eV, direct inlet) *m/e* (rel. int.): M^+ absent, 440 (M^+ − 18, 20), 425 (11), 422 (59), 407 (20), 382 (7), 379 (7), 235 (25), 232 (18), 217 (31), 216 (30), 204 (36), 203 (48), 189 (40), 121 (63), 109 (77), 95 (87), 81 (85), 69 (88), 55 (100). [Found: C, 78.54; H, 11.18. $C_{30}H_{50}O_3$ requires: C, 78.55; H, 10.99%.]

11α-*Acetoxy*-3-*keto-lupan*-20-*ol* (**7**). Treatment of compound **6** (32 mg) with Ac_2O–pyridine as previously described yielded the monoacetate **7** (32 mg), mp 165–168° (aq. MeOH), $[\alpha]_D^{20}$ + 36.8° (*c* 0.62, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3470 (OH), 1733, 1240 (-OAc), 1715 (ketone). ^1H NMR ($CDCl_3$): δ 5.15 (1H, *sextet*, $J_{aa'} = J_{aa''} = 10.5$, $J_{ae'} = 5.5$ Hz, H-11), 1.99 (3H, *s*, -OAc), C-Me singlets at 1.23 (3H), 1.15 (3H), 1.11 (6H), 1.05 (3H), 1.02 (3H), 0.92 (3H) and 0.81 (3H). MS (75 eV, direct inlet) *m/e* (rel. int.): M^+ absent, 482 (M^+ − 18, 2), 422 (78), 407 (23), 382 (6), 379 (10), 339 (12), 318 (22), 269 (10), 255 (12), 216 (12), 203 (34), 195 (38), 189 (14), 123 (100).

Oxidation of compound **6** *to yield compound* **3**. Jones oxidation of compound **6** (36 mg) yielded a hydroxy-diketone (30 mg) identical in all respects (mp, mmp, $[\alpha]_D$, IR, ^1H NMR, MS) to compound **3** obtained from triterpenoid **1**.

Acknowledgements—We thank Dr. J. Borja, Botany Department, Faculty of Pharmacy, Madrid, for the botanical classification of plant materials; Mr. J. Prieto for elemental analysis and Miss M. D. Casado and Miss M. Plaza for recording the ^1H NMR spectra. One of us (G. S.) thanks the Italian C.N.R. and the Spanish C.S.I.C. for grants for the work at the Instituto de Química Orgánica (Madrid).

REFERENCES

1. Savona, G. and Rodriguez, B. (1980) *An. Quim.* **76**, 187.
2. Williams, D. H., Bhacca, N. S. and Djerassi, C. (1963) *J. Am. Chem. Soc.* **85**, 2810.
3. Jolad, S. D. and Steelink, C. (1969) *J. Org. Chem.* **34**, 1367.
4. Ghisalberti, E. L., Jefferies, P. R. and Sefton, M. A. (1973) *Phytochemistry* **12**, 1125.